

Cost-effectiveness modelling for benefit-risk assessment

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Abstract

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Introduction and aims

Benefit-risk assessment is important for summarising the effectiveness and safety profile of an intervention. Current methods for benefit-risk assessment are based upon flawed clinical trial data. For biosimilars, regulatory approval is given on the basis of extrapolated evidence assessed in qualitative benefit-risk frameworks, leading to uncertainties. This thesis aimed to investigate methods for assessing the benefit-risk balance of therapies, including identifying harms data and developing a quantitative framework for assessing whether the cost savings of biosimilars justify the increased uncertainties regarding efficacy and safety.

Methods

This thesis reports a novel systematic review of the efficacy and harm outcomes reported in Crohn's disease (CD) randomised clinical trials (RCTs) to 2015. Extracted outcomes and adverse events data were categorised and the results benchmarked against a core outcome set (COS) for inflammatory bowel disease and the commonly used outcome measurement tools in CD RCTs. Summaries of Product Characteristics (SPCs) were investigated as a source of harms data with the use of standardised MedDRA (Medical Dictionary for Regulatory Activities) queries (SMQs). Finally, this thesis presents a one-year decision analytic model of biosimilar versus originator infliximab (IFX) to test the limits of biosimilarity and the value-based price needed to compensate for increasing risks.

Results

The systematic review yielded 181 studies, 96.1% of which reported primary or secondary endpoints (median five per trial). The reporting of clinical and objective markers of inflammation, patient reported outcomes and safety outcomes as primary and secondary endpoints all increased over time, but with a lack of standardised definitions. Within the outcome hierarchy, the efficacy outcomes matched to 35 domains, split equally into physical manifestations and the impacts of the health condition. Adverse events matched to a greater number of domains (46), but most were physiological manifestations with few reported life impact adverse events. Key literature for IFX identified five uncertain categories of harms, which matched to six SMQs. Each SMQ included adverse events reported in the SPC but not reported in clinical trials, 28 of which allowed an estimate of risk. Immunogenicity is a key concern for the IFX biosimilar, and was an important variable in the decision analytic model. The base-case analysis predicted annual QALYs of 0.803 for each biologic, and costs of £18,087 and £19,176 for biosimilar and originator, respectively. The incremental net health benefit of 0.04 (95% Central Range 0.00-0.09) favoured the biosimilar. Two-way sensitivity analyses suggested that even at high immunogenicity, the value-based price would exceed the current market price.

Conclusions

The results of the systematic review provide a comprehensive inventory of benefit and harm outcomes reported in the literature and could form the basis of a COS development process. Use of additional SPC harms data requires a strong theoretical approach to reduce the "noise" in the data. Categorising outcomes is useful in lieu of the development and widespread use of a COS and the results presented here should support the development of much needed new outcome measurement tools for Crohn's disease. The study presents a novel framework for the quantitative benefit-risk assessment of biosimilars, which could be used at the point of health technology assessment to trade off the price paid for a biosimilar against the uncertainty in effect and risk of the therapy.

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Abbreviations

5-ASA	5-aminosalicylates
ADA	Adalimumab
ADR	Adverse drug reaction
AE	Adverse event
AS	Ankylosing spondylitis
ATI	Antibodies to infliximab, anti-drug antibodies
ATI_I	Antibodies to infliximab for Inflectra
ATI_R	Antibodies to infliximab for Remicade
BNF	British National Formulary
BRA	Benefit-risk assessment
CAM	Complementary and alternative medicines
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CGP	Clinical good practice
CHMP	Committee for Health and Medicinal Products
COMET	Core Outcomes Measurement in Effectiveness Trials initiative
COS	Core outcome set
DH	Department of Health
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EVPI	Expected value of perfect information
EVPII	Expected value of perfect parameter information
FDA	Food and Drug Administration
HBI	Harvey Bradshaw Index
HLGT	High-level group term
HLT	High-level term
HTA	Health technology assessment

IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental Cost-effectiveness ratio
ICF	International Classification of Functioning, Disability and Health
ICH	International Conference on Harmonisation
IFX	Infliximab
IMI	Innovative Medicines Initiative
INHB	Incremental net health benefit
INMB	Incremental net monetary benefit
IQR	Inter-quartile range
IR	Infusion reaction
LLT	Lowest level term
LOR	Loss of response
MCDA	Multi-criteria decision analysis
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Regulatory Agency
NEC	Not elsewhere classified
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMB	Net monetary benefit
OMERACT	Outcomes Measurement in Rheumatology initiative
PD	Pharmacodynamic
PDAI	Perianal Disease Activity Index
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medicinal Devices Agency
PRO	Patient reported outcome
PROM	Patient reported outcome measure
PSA	Probability sensitivity analysis
PSM	Probability sensitivity methods
PT	Preferred term

QALY	Quality-adjusted life-year
RA	Rheumatoid arthritis
SMQ	Standardised MedDRA query
SPC	Summary of product characteristics

Initials of PhD researcher and supervisors:

DH	Dyfrig Hughes
HC	Heather Catt
JJK	Jamie Kirkham
KB	Keith Bodger

Publications and presentations of work in this thesis

Chapter 2 and 3

An early version of the work in Chapter 2 and Chapter 3 was presented at the following conferences:

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Chapter 5

An early model was presented at the following conference:

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Chapter 1: Introduction to benefit-risk assessment and cost-effectiveness modelling

Any health-related intervention has the potential to cause harm alongside any benefit. The assessment of benefit and harm (more often labelled as “risk”) of a medicine takes place from the early development of a drug, to regulatory approval for marketing, and beyond into the post-marketing period. Post-marketing assessment of benefit and risk includes health-care payers’ decisions on whether to authorise a drug for funding, through to clinical decisions on prescribing for individual patients. Benefit-risk assessment (BRA) should take place at all parts in the life cycle of a drug to capture the changes in the benefit-risk balance, which occur over time as new data emerges for this and comparator drugs¹⁻⁴. BRA is comparative in nature and considers the benefits and risks of one intervention against those of a comparator or comparators. As such, changes in the benefit and risk data for a comparator drug will affect the benefit-risk balance of the intervention of interest.

This chapter introduces this thesis beginning with a discussion of BRA, cost-effectiveness modelling and outcomes in Section 1.1. Section 1.2 introduces Crohn’s disease, which is the clinical motivation of the thesis. Section 1.3 introduces the case study for this thesis, in the form of biosimilars used in Crohn’s disease, which are an area of particular challenge for BRA that has required a significant response from all decision makers involved. Finally, the thesis objective and structure are explained in Section 1.4.

1.1. Introduction to benefit risk assessment and cost-effectiveness modelling

1.1.1. Benefit-risk assessment

Essentially BRA has two stages – identify the benefits and risks of the intervention and then compare them to decide whether the benefits outweigh the risks at an acceptable level for the target population. The first step is an objective evaluation, whereas the second requires value judgements in the form of whether to trade-off some risk against benefits⁵. The assessment of

benefit and risk is not without challenges. One key challenge is balancing the need to allow patients access to medicines in the shortest possible timeframe to extend life or halt the progress of a disease, whilst ensuring that they go through an appropriately robust process for assurance that they are safe to use or that the harms do not outweigh the benefits. Failure to ensure an adequate benefit-risk balance could result in harm to patients and products being withdrawn after authorisation⁴. The benefit-risk balance of a pharmaceutical product will vary by indication for which it is prescribed and will vary over time, as it will be possible to characterise the benefits and the risks more fully once the drug is available to a large population. Data from multiple sources may be used for the assessment of the benefit-risk balance, which increases the complexity of analysis and the potential for bias in the results. Section 1.1.1.1 to Section 1.1.1.4 provides further discussion of benefit-risk assessment.

1.1.1.1. Concepts in benefit-risk assessment

A number of concepts underpin the process of BRA as described in Mt-Isa et al (2011)¹. Given that BRA takes place over the life cycle of a drug, there are numerous decision makers. First, the drug company decides whether to develop a drug, followed by regulators in numerous jurisdictions deciding whether to approve the drug for marketing, and the health technology assessor (HTA) deciding whether it should be prescribed based on its cost-effectiveness (discussed further in section 1.1.2.1). At a more micro level the healthcare provider decides if they will offer it to patients, and the patient decides whether to take (and keep taking) the drug.

At each point, each decision-maker assesses the benefit-risk balance and each earlier assessment affects the ability of later agents to make decisions. For example, if the HTA decides not to approve the drug as cost-effective, then clinicians cannot decide to prescribe it and patients cannot technically decide whether to take it. However, patients can influence further up the channel by, for example, requesting earlier access to potentially life extending drugs, or for the reinstatement of drugs that have had regulatory approval removed on the basis of their

willingness to accept higher than expected risk (discussed further in section 1.1.1.2). Within the UK NHS, the prescriber is usually the agent requesting access to drugs not approved by NICE and this is through a system of individual funding requests (IFR).

Possible actions is a further, simpler, concept: does the patient take the drug or not, does the regulator or the HTA approve the drug? Uncertain consequences are a feature of benefit-risk assessment and these differ by decision maker. For the patient, these will be clinical and personal outcomes, for example, whilst for health care providers, the consequences include the health outcomes of the population, as well as the budget and the opportunity cost of spending on this drug (the lost health gain that could have been achieved by spending the money on alternative drugs)¹. The sources of data used by all decision makers are likely to be the same and will primarily be evidence from clinical trials. However, patients may also consider anecdotal or very early phase trial data, and will particularly pay regard to their own personal experience. A patient experiencing an event that they perceive as related to the drug may decide to stop taking it.

Utility assessments are a key concept in some forms of benefit-risk assessment, although other methods do not consider utility, as described in section 1.1.1.3. Essentially utility values are the preferences of the decision maker, and these are likely to vary substantially by decision maker (discussed further in section 1.1.1.2). Patients will weigh up the seriousness of potential individual consequences to them in terms of harm they could face and the improvement in disease that they may experience. Regulators face the additional consideration of how much certainty in the evidence matters in the interest of public health¹.

1.1.1.2. Perceptions of benefits and risks

The interpretation of the benefit-risk balance depends upon the perspective that is adopted for the assessment⁶. The perceptions of benefit and risk will vary by context, for example, very different levels of risk are likely to be accepted for treatments for serious cancers than for a simple headache. Similarly, there is likely to be a degree of myopia in risk assessment with patients willing

to trade an uncertain risk at some point in the future for benefit now. Further complications arise when patients are asked to trade-off risk or harm in the present for the promise of potential benefit in the future. This is particularly relevant for public health interventions such as vaccines and screening where patients experience harm in order to prevent something that may well not have occurred anyway in the absence of the intervention. A patient and clinician will weigh up the likely benefits and risks against clinical history, whilst regulatory agencies evaluate evidence from trials on benefits and risks when deciding whether to approve a drug for marketing¹.

The cost of the drug will not be a factor for a regulator, nor is it likely to be of concern for a patient in a health care system such as the National Health Service (NHS) in the UK where patients do not pay directly for treatment. However, the cost will be a factor for the health-care payer (including patients in health care systems requiring direct payment or co-payment), who will wish to maximise the health improvement they can achieve within a fixed healthcare budget and will therefore compare the cost of health gained between treatments. Similarly, an NHS prescriber may consider cost if a drug with similar efficacy is available at a cheaper price.

Therapeutic benefit-risk balances may involve benefits and risks at the margin, which can be interpreted differently by the manufacturer, regulator, clinician and patient. Patients, particularly those with chronic diseases or late stage diseases, may be more willing to trade the adverse events of drugs with the possibility of disease improvement than other decision makers, regulators especially, are prepared to do^{2,5}. Surveys of patients with chronic diseases have found them willing to accept a small probability of life-threatening risks in exchange for significant improvements in disease-related health outcomes^{5,7,8}. The drug natalizumab provides a good case study of the differences in risk-preference as it was withdrawn from the market by the FDA following identification of a risk of fatal degenerative neurological disease PML, but then reinstated following pressure from patients who were willing to accept the risks against the significant benefits that they perceived⁹.

The evidence supplied for benefits and risks is likely to be limited, especially in the pre-marketing stages of BRA. Regulators must decide how much uncertainty in the evidence matters in the interest of public health¹. Regulators seek to guarantee adequate processes are in place to ensure the efficacy and safety of drugs, but they are often challenged by patients groups demanding early access to health care technologies, and they must balance the two arguments⁴. Patients should be involved in assessments of how much risk a target population will accept as their attitudes to risk may differ so much from those of the general public, with greater focus on benefits and less on risk-aversion⁵. Research is ongoing into patient involvement in benefit-risk assessment with the recognition of the need to involve affected patients to supplement data and the development of a framework to incorporate patient preferences into benefit-risk processes¹⁰⁻¹². The inclusion of the patient perspective in benefit-risk assessment is supported by the International Conference on Harmonisation (ICH), an international collaboration to improve drug efficacy, safety and quality (discussed further in section 1.1.1.3)¹³.

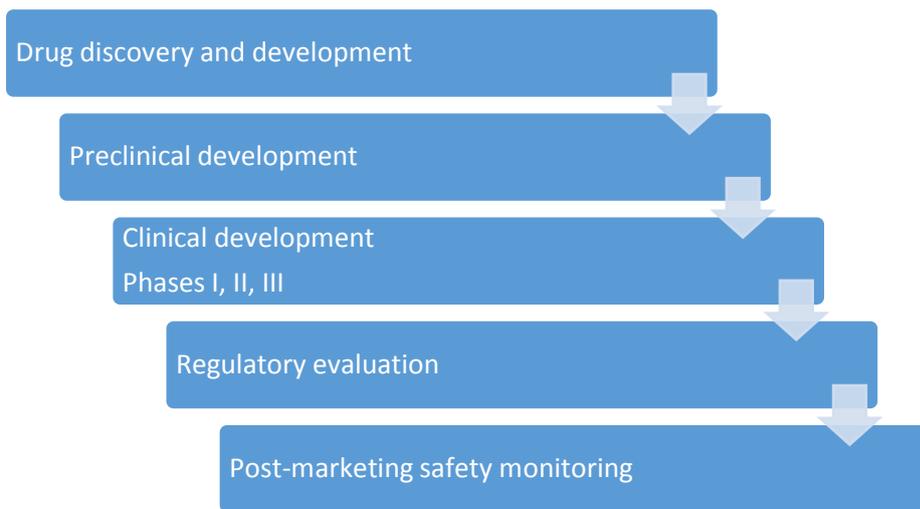
1.1.1.3. Benefit-risk assessment in the regulatory framework

Numerous regulatory bodies operate across the world who receive applications from drug manufacturers for approval for new pharmaceuticals. In Europe, regulation is the remit of the European Medicines Agency (EMA), specifically within the Committee for Medicinal Products for Human Use (CHMP) who assess the benefits and risks of medicines. In the United States it falls within the remit of the Food and Drug Administration (FDA), who established the Drug Safety and Risk Management Advisory Committee to evaluate the safety, efficacy and abuse potential of drugs and deal with risk management and risk communication³.

Other international regulators include Health Canada, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan and the Therapeutics Goods Administration (TGA) in Australia. The International Conference on Harmonisation (ICH) provides guidelines on technical requirements for quality, safety and efficacy of drugs¹⁴. The guidelines aim to ensure consistency in the data

shared across the jurisdictions for decisions on marketing approval of drugs, thereby streamlining the processes internationally. Figure 1 shows the typical regulatory process for a new drug. It starts with drug discovery by researchers who identify active ingredients that offer potential benefit. Preclinical development will include animal studies to determine whether the drug is likely to cause harm (toxicity)^{15,16}.

Figure 1: Example regulatory process¹⁶



Early clinical testing involves pharmacokinetics (PK) and pharmacodynamics (PD) modelling studies to establish, amongst other things, how the drug will impact and be dispersed within a body and the likely dose-response relationship^{15,16}. Clinical research then takes place on humans in three phases of trials. Phase one trials take place in a small number of usually healthy volunteers and aim to ensure the drug is safe to use in humans and at what dose. Phase two trials involve larger groups of people with the indicated disease and consider whether the drug works (efficacy) and whether it has any common dose-related side effects. Phase three trials involve larger groups who receive the drugs over longer periods and are primarily concerned with efficacy, but do monitor safety outcomes that occur during the course of the trial (adverse events). Once phase three trials have taken place, the drug should be comprehensively characterised in terms of its pharmacology, safety and efficacy and the drug company may submit an application for regulatory approval to allow it to market the drug.

BRA takes place at each point and is a necessary component of the regulatory evaluation. It should be noted, however, that up to this point the assessments are done on the basis of incomplete data on both benefits and risks, which can provide a result at the margin². This can result in differences in decisions between regulators. Once a drug receives regulatory approval, monitoring continues for any safety (risk) signals. As more safety data are gathered in the post-marketing period, reassessment of the benefit-risk balance may change significantly, especially in the case of a marginal result where the real-world benefit (effectiveness) is less than the trial efficacy or the risk is greater than expected².

A detailed BRA takes place at the point of regulatory evaluation, where the drug company submit all their evidence and the regulator determines whether the drug has a positive benefit-risk profile. Historically, this process has been qualitative, with the regulators taking an overall view of the data and considering, on balance, whether there is enough evidence to support a positive benefit-risk profile. Where there are uncertainties, the regulator may place conditions on the approval. The EMA require that a summary of product characteristics (SPC) document is produced by the manufacturer to obtain marketing approval¹⁵. Additional conditions of marketing, for example periodic safety update reports, a risk management plan and any additional risk minimisation measures, must be published in the SPC.

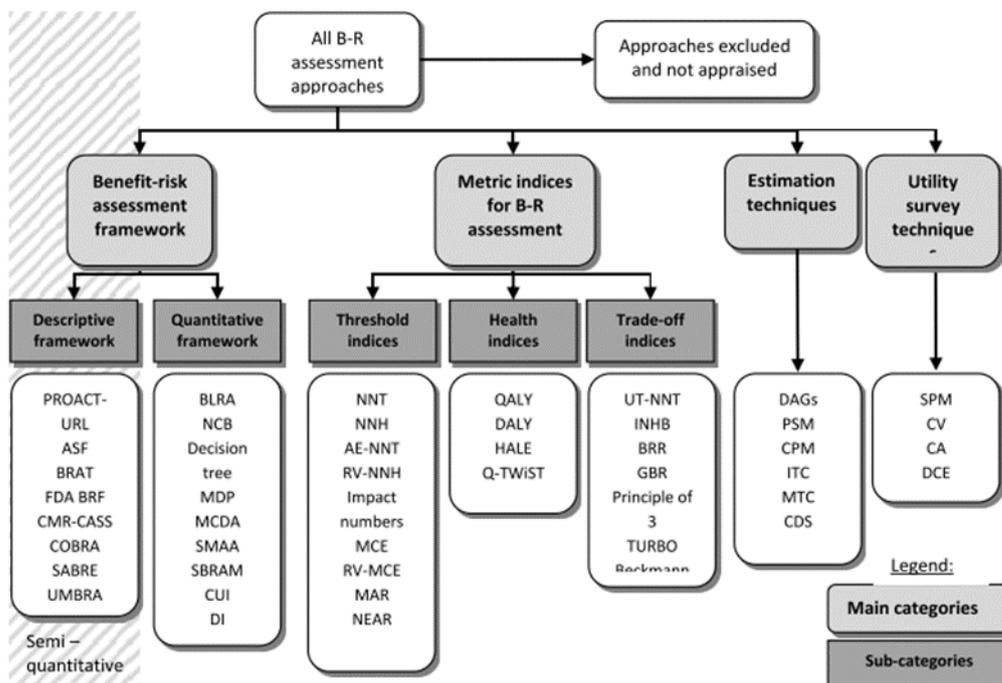
1.1.1.4. Methods and models of benefit-risk assessment

The methods and models here focus on those used for regulatory decision-making, as this is the stage of most formal BRA. Other methods and models may be more appropriate in different contexts of BRA. Past reviews have found that BRA by regulators tended to be performed in an ad-hoc, informal, variable and qualitative way⁵. In response, much research has focused on improving the quality and consistency of assessments by creating frameworks and tools for analysing and presenting complex information⁵. Numerous benefit-risk methodologies are

available and the factors taken into account in choosing one method over another will vary greatly, depending on the perspective of the assessor¹.

A 2014 systematic review identified 47 methodologies for benefit-risk assessment, which were classified into four categories (Figure 2, full list in Appendix 1): frameworks, metrics, estimation techniques and utility survey techniques¹⁷. The systematic review was conducted as part of the Innovative Medicines initiative (IMI) project that aims to “strengthen the monitoring of the benefit-risk balance of medicines in Europe” – Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT)^{6,18}. The vast majority of the methodologies are quantitative with only eight qualitative methods included, all within the frameworks category.

Figure 2: Classification of benefit-risk methodologies¹⁷



FRAMEWORKS

BRA frameworks are structured, stepwise methodologies and provide guidance for the whole process¹⁸. Descriptive (qualitative) frameworks use structured stepwise questions to identify all

elements of the benefit-risk balance, which provides transparency and communicability and allow for an overall assessment¹⁷.

Quantitative frameworks are similarly structured but provide explicit methods for measuring benefits and risks¹⁷. They break decisions down into elements to be quantified and aggregated to provide an overall picture of the benefit-risk balance. Sensitivity analysis and incorporation of value judgements are key aspects of these frameworks¹⁸ and are discussed further in Section 1.1.3.3.

METRICS

Metric indices offer numerical representations of benefits and risks¹⁸. Threshold indices provide measures of either benefit or risk, but not both, health indices characterise health outcomes and implicitly trade off benefits and risks, and trade-off indices explicitly trade off quantified benefits and risks into a single metric to indicate whether a treatment option is favourable or unfavourable^{17,18}. Metric indices are primarily what decision-makers will use to judge the right decision, but they cannot be used on their own and must be nested within a broader framework¹⁸.

ESTIMATION TECHNIQUES

Estimation techniques include general statistical techniques that can be useful in synthesising benefit-risk evidence from multiple sources and handling statistical uncertainties within a model¹⁷. As with metric indices, they are best applied within a broader framework, specifically quantitative frameworks¹⁸.

UTILITY SURVEY TECHNIQUES

Utility survey techniques provide the value judgements of stakeholders that are necessary for regulatory BRA^{17,18}. One example is the time-trade off method, where patients are given two options: experience a chronic health for a period of time (remaining life expectancy), followed by death, or experience a period of perfect health, followed by death¹⁹. The period of time in perfect health in the second option is varied (shortened) until the respondent is indifferent between the

two options. At this point, a preference score is calculated based upon a ratio of the healthy life expectancy in option 2 and the life expectancy with chronic disease in option 1. These techniques elicit and collect value preferences of various outcomes and help to increase the transparency of decisions.

QUALITATIVE VERSUS QUANTITATIVE BENEFIT-RISK ASSESSMENT

Most available frameworks and tools for benefit-risk assessment are quantitative⁵. Despite this, research by Phillips et al (2011) found that no regulatory agency employs quantitative modelling of the data in applications to obtain a yes or no answer to the assessment of benefit and risk²⁰. Regulatory agencies tend to prefer descriptive frameworks: PrOACT-URL is the framework adopted by the EMA, but similar ones are used by other regulatory agencies, such as the US FDA Benefit-Risk Framework (FDA BRF)^{6,17,18}. Even where a safety signal is detected in the post-marketing period, the new data are considered with all previous evidence in a qualitative process and the committee takes a decision. The process does not produce an explicit, transparent quantification of risk and lacks clarity on the factors involved³.

The US FDA see the need for a structured approach to benefit-risk assessment, but argue in favour of qualitative approaches. Uncertainty in available information, especially for risk, creates the need for judgement, which can lead to different conclusions. They argue that qualitative approaches lay down these value judgements clearly, making them more transparent. Conversely, the FDA claim that a quantitative approach *“requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgements that are at best debatable and at worst arbitrary”*⁹.

The EMA argue that structured processes, both qualitative and quantitative, could further improve the transparency, communicability, auditability, quality, speed of decision-making, and have included quantitative methods in the regulatory agenda^{3,21}. Mid-way between the EMA and the FDA are the ICH, who propose that qualitative approaches are sufficient for regulatory

applications. They suggest that quantitative methods can be presented, but applicants are encouraged to think carefully about the *“utility, complexity, the extent to which the method is established and the ease of interpretation of the results”*¹³.

Whilst qualitative methods use implicit utilities, formal quantitative processes will make these utilities explicit, making the decisions more transparent¹. Quantitative frameworks may be of most value when the benefit-risk balance is unclear or contentious, for example by highlighting the impact of different factors or disparities in the value judgements of different assessors. Even if quantitative frameworks are not desired in and of themselves, multiple methods of risk-benefit assessment can be used to bound the risk-benefit profile³, thereby identifying a likely range of the benefit-risk balance, which could be useful in the presence of uncertainty.

IMI-PROTECT BENEFIT-RISK GROUP

IMI-PROTECT suggest that no single method will provide a full assessment of benefit and risk and as the complexity of the problem increases, so will the need to supplement a BRA framework with other quantitative methods⁶. In particular, whilst descriptive frameworks allow for the framing of the decision problem, the inclusion of quantitative models allows for the exploration of trade-offs between benefits and risks and the consideration of uncertainty^{6,17}. Quantitative decision models aim to both frame the decision problem and incorporate quantitative measures of the benefit risk balance.

IMI-PROTECT recommend thirteen methodologies of benefit-risk assessment for further research^{6,17,18}. Two descriptive frameworks are recommended for further research:

1. ProACT-URL framework. This qualitative framework uses eight steps to assess the benefit-risk balance: problems, objectives, alternatives, consequences, trade-offs, uncertainty, risk attitudes and linked decisions. The framework addresses all the important elements of decision problems but was criticised for failing to capture the importance of identifying appropriate evidence and parties to be involved.

2. Benefit Risk Action Team (BRAT) framework. This framework proposes keeping benefits and risks assessment separate to make it accessible and transparent. However, it is criticised for using odds ratios for assessment of the benefit-risk balance as they can be misleading and do not approximate the relative risk very well.

To assess the benefit risk balance and quantify trade-offs, IMI-PROTECT recommend the following quantitative frameworks for further research:

3. Multi-Criteria Decision Analysis (MCDA). This quantitative framework follows the stepwise system of ProACT-URL. It identifies and values the options, and weights the values of separate effects, using the preferences of the decision-makers, to allow benefits and risks to be compared on a common scale^{20,21}. It is able to capture multiple objectives simultaneously and integrate them into a common measure which is transparent and conceptually simple¹. However, it relies on clinical trials data, which can make it problematic in certain situations, especially post-marketing.
4. Stochastic Multi-Criteria Acceptability Analysis (SMAA). This is an extension of MCDA, which can account for sampling variation due to variability in study designs and missing utility values. It is more complex, however, which may reduce its usefulness.

Metric indices are useful for summarising evidence numerically and communicate to a general audience. IMI-PROTECT recommend the following threshold indices (5 and 6), health indices (7 and 8) and trade-off indices (9 and 10) for further research:

5. Number Needed to Treat (NNT) and Number Needed to Harm (NNH). These metrics estimate the number of patients that need to receive treatment for one to experience the benefit (NNT) or the risk (NNH)²¹. They are recommended as they are simple to use and understand, but with a warning that they should be used to support modelling rather than in place of it.

6. Impact numbers. These are an extension of NNT/NNH and indicate the number of people affected by the medical condition and treatment¹⁸. They are therefore useful in providing an indication of the public health burden of disease and the potential impact of treatment. They are intuitive and may make the results of a BRA more accessible to a wider audience.
7. Quality Adjusted Life Years (QALY). This metric provides a measure of the remaining length of life adjusted for the quality of that life within each health state across the lifespan. This metric provides a trade-off of time against quality of life and it is a well-established metric in chronic disease where time is important in the assessment of benefit and risks. It is discussed further in Section 1.1.2.2 and is used in Chapter 5.
8. Quality Adjusted Time Without Symptoms and Toxicity (Q-Twist). This metric is an extension of the QALY with health states specific to cancer and can aid cancer patients in decisions.
9. Incremental Net Health Benefit (INHB). This metric builds upon the QALY and is advantageous as it trades off the extra benefits and extra risks of a treatment over an alternative, which is directly applicable to benefit-risk assessment. It is discussed further in Section 1.1.2.2 and is used in Chapter 5.
10. Benefit Risk Ratio (BRR). These metrics are easy to understand as the benefits and risks are valued on the same scale and compared. However, IMI-PROTECT suggest it should only be used with careful consideration of weighting to bring them onto the same scale, alongside baseline values, and with high quality data and statistical modelling.

IMI-PROTECT recommend the following estimation techniques may be of use where evidence synthesis and complex benefit-risk modelling is needed to address a more complex decision problem:

11. Probabilistic Simulation Method (PSM). PSM is an estimation technique that uses probability distributions to propagate the uncertainty in input variables throughout a

decision model. This method is valued because of the potential to deal with a range of uncertainties under different assumptions. However, it does rely upon good quality data to maximise its potential, in line with the adage 'garbage in, garbage out'. It is discussed further in Section 1.1.2.2 and is used in Chapter 5.

12. Mixed Treatment Comparison (MTC). This method is recommended in place of PSM where little direct evidence is available. It is considered the most flexible and is capable of dealing with a range of biases and the combining of a mix of evidence.

To incorporate stakeholder preferences into benefit-risk assessments, IMI-PROTECT recommend the following utility survey technique should be researched further:

13. Discrete Choice Experiments (DCE). This is considered the most comprehensive and well-constructed method and therefore should provide the most valid results on stakeholder utility. However, DCE is resource consuming so there is a need for alternatives.

EMA BENEFIT-RISK METHODOLOGY PROJECT

The EMA has conducted a benefit-risk methodology project to identify quantitative approaches that might be useful to guide the regulatory process. A necessary first step to measuring benefit and risk in a quantitative framework is defining benefit and risk. A survey of European regulatory bodies by Phillips et al (2011) identified consensus in the definitions of benefit (providing a clinically meaningful improvement) but large heterogeneity in risk with more than 50 definitions, many conflicting²⁰. This is intuitively possible, since there are a number of potential risks from taking a drug – including the risk of worsening of a disease, a risk that the drug does not work and risk of side effects from taking that drug. Phillips et al (2011) applied decision theory, which splits consequences and their value from uncertainties about the consequences, and proposed a four-fold model for defining benefit and risk, which has been adopted by the EMA²¹.

Figure 3: European Medicine Agency's four-fold model of 'benefits' and 'risks'²¹

Favourable effects	Uncertainty of favourable effects
Unfavourable effects	Uncertainty of unfavourable effects

Favourable effects are defined as *“any beneficial effects for the target population (often referred to as “benefits” or “clinical benefits”) associated with the product”*²¹. Unfavourable effects are defined as *“any detrimental effects (which may be referred to as risks, harms, hazards both known and unknown) that can be attributed to the product or are otherwise of concern for their undesirable effect on patients’ health, public health or the environment”*. Uncertainties about both types of effects arise from various sources including variation, bias, methodological flaws and limitations of the dataset. These issues are discussed further in Section 1.1.3.

The EMA identify key features needed for any quantitative method²²:

1. Data for favourable and unfavourable effects
2. Uncertainties about those effects
3. Clinical judgements about the desirability, severity and relevance of the effects.

In practice, this means that the risks and benefits are weighted according to their relative importance and the strength of evidence available. To this end, the EMA suggest that only decision theory provides a comprehensive approach as it allows for all effects to be related to preference (utility) values and uncertainty of the effects captured from prevalence and incidence data.

RECOMMENDATIONS OF THE EMA BENEFIT-RISK METHODOLOGY PROJECT

Many of the conclusions under work package 2 of the benefit-risk methodology project²¹, which assessed the applicability of tools and processes for regulatory benefit-risk assessment, confirmed those of the IMI-PROTECT project. Specifically, they agreed that decision theory is the most appropriate basis for a quantitative framework and that MCDA is an appropriate method to represent the benefit-risk balance numerically. A particular role was seen for developing a MCDA model, which could be passed onto HTAs who could add costs and QALY data²². This would help to harmonise BRA across regulatory and HTA processes.

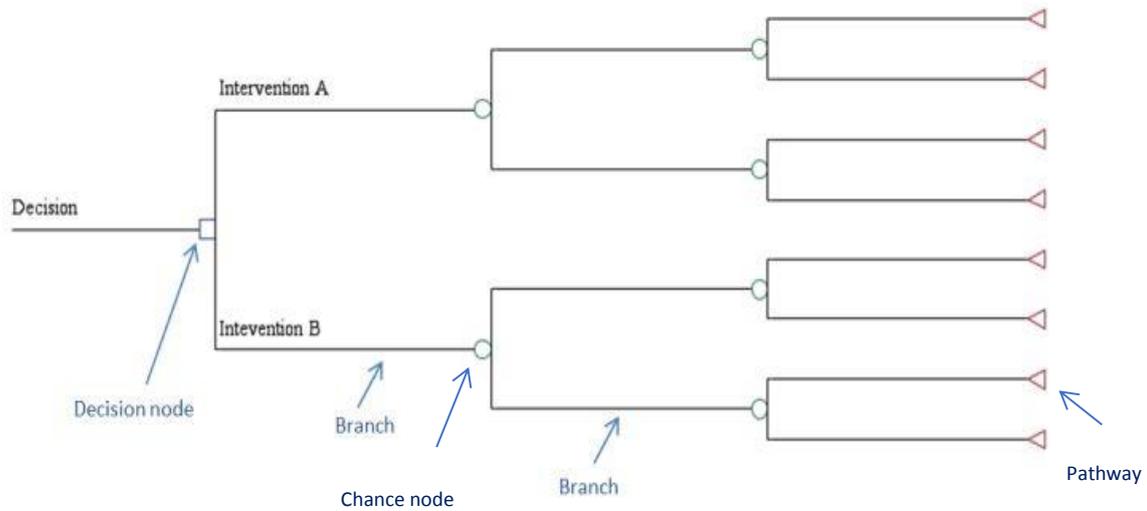
The use of QALYs and conjoint analysis (such as discrete choice experiments) is supported for particular cases: modelling multiple health outcomes in the former and examining trade-offs, particularly in eliciting patient preferences, in the latter. Further, they reach the same conclusion as IMI-PROTECT, that combinations of approaches will be useful in different situations and that BRAs do not make the decision, but are instead aids to decision-making²¹.

In addition, the EMA recommend the use of Bayesian statistics and decision analytic models with a role for Kaplan Meier estimators and Markov processes as supporting approaches when there is uncertainty in the decision.

Bayesian statistics provide methods for allowing inferences to be made from evidence. Bayes' theory allows for the updating of "prior" probabilities of events with additional data as they becomes available to create "posterior" probabilities. In other words, if we have knowledge of conditions that might be related to an event we might be able to obtain the probability of that event occurring. It is the basis of significance tests and methods such as value of information analysis, discussed further in Section 1.1.3.3.

Decision analytic models are a commonly used model in medical literature^{21,23} and present possible outcomes following an intervention as individual pathways. The model starts with a node indicating the decision being taken within the model, as shown in Figure 4.

Figure 4: Example decision analytic model²⁴



In the case of an application of regulatory approval of a new drug, this is likely to be whether to give a patient the new drug, or an existing treatment. Chance nodes indicate the potential pathways from that decision (which could be benefits or risks) and branch probabilities indicate the likelihood of each of those events.

Moving from left to right, further chance nodes show the likelihood of further uncertain (favourable or unfavourable) events. The combinations of each of the branches provides a pathway, each of which is mutually exclusive. Once patients enter one pathway, they cannot enter another. The probability of a patient following each pathway is a conditional probability, that is, it is the result of the multiplication of each probability along the pathway. All pathways are exhaustive and must add to 1 so that the model represents all potential events and pathways. Utility values can be elicited and applied to each pathway. Multiplying the utility values by the probability of each pathway results in the overall expected utility from the model. Comparing the expected utility between the treatments included in the model forms the basis of an understanding of the benefit-risk balance. Decision models have limitations, including the tendency for them to become very large, very quickly, especially for a chronic disease where patients may experience multiple health states and adverse events from treatment over time.

They also time consuming to programme and analyse²³. However, they are logical and can incorporate data from numerous sources²¹. A decision-analytic model is developed in Chapter 5.

Markov processes can be seen as addressing some of the limitations of decision models as they capture the dynamic processes of disease progression over time, which makes them useful in chronic disease²³. Markov models incorporate disease states that patients can occupy over periods of time. Each disease state is associated with a utility value and therefore an overall expected utility can be calculated by measuring the time spent in that state. Transitions between states are governed by a series of transition probabilities, which are taken from the literature. They can be seen as an extension of decision trees and should, in fact, arrive at the same conclusions as decision trees, but with greater efficiency²¹. Limitations of Markov models include the lack of memory, meaning that the prior events of patients in a disease state are not considered and they are all treated equivalently, which is not clinically realistic²³. For example, patients with Crohn's disease in post-surgical remission following a first resection are likely to experience a different future disease course to patients who have had multiple resections. A Markov will not consider this unless it is built into the structure of the model, but this can make a model unwieldy.

Kaplan Meier estimates enable the display of survival data and can be used to display the results of a Markov model²¹. At any point, the difference between two curves representing two treatments can show the differences in outcomes between the patients. It is limited to a single favourable or unfavourable effect, but has the advantage of showing the effects over time. The Q-TWIST trade off metric (discussed earlier) is an extension of this method.

Challenges to developing a quantitative methodology for BRA include the heterogeneity and multiplicity of benefits and risks, uncertainty in attribution to a particular treatment, temporality of exposure and effect and the paucity of drug exposure and outcome data³. These issues are discussed further in section 1.1.3.

1.1.2. Cost-effectiveness modelling

It is not only regulators who seek to understand the benefit-risk balance and involve the views of patients. As the price of modern medicines has increased in excess of the growth of health care budgets, the assessment of clinical and cost effectiveness has become more important². Scientific evaluation of clinical trial data is used to compare a new drug to existing therapies as part of the Health Technology Assessment (HTA) process to support decision-making on price and reimbursement²⁵. HTA makes judgements about the benefits of a product in the context of its safety risks to determine the reimbursement decisions, but also make cost-benefit decisions to determine the price of the product⁵. As such, HTA deals with benefit and risk but also focuses on economic outcomes, which are excluded from traditional benefit-risk approaches due to the regulatory perspective¹⁷.

Given the significant overlap in BRA and HTA processes, there is growing international interest in optimising the interface between regulatory approval and reimbursement decisions^{5,25}. Work began in the European Union to improve the data contained in the European Public Assessment Report (EPAR), which is the regulatory report supporting the licensing of medicines in Europe, so that it might contribute to HTA²⁵. Further areas of collaboration are being explored, including information exchange, specifically the timely provision of the outcome of regulatory assessment to support joint production of rapid economic assessments (REA)²⁶.

1.1.2.1. *Cost-effectiveness modelling in health technology assessment*

Given the focus on cost-effectiveness, drugs that have proven clinical effectiveness may be rejected for use because the additional health gain is simply too costly. The opportunity cost of such drugs is too high as the same money could be spent elsewhere to obtain greater health gain. The role of assessing whether a drug is cost effective and should be available for reimbursement, and at what price, is determined by HTA agencies at national level²⁵.

In the UK, the National Institute for Health and Clinical Excellence (NICE) is one such agency that performs HTA. The purpose of a NICE technology appraisal is *“to appraise the health benefits and the costs of those technologies...and to make recommendations to the NHS in England and Wales”*²⁷. NICE considers evidence on the clinical effectiveness of the intervention being assessed and economic effectiveness in terms of whether it represents value for money for the NHS²⁸. Both types of evidence will come from the drug manufacturer and the economic appraisal is likely to be in the form of an economic model. Prior to the start of the HTA, NICE will meet with the drug company to discuss the scope of the decision problem and how the problem is to be modelled, including the types of evidence to be used and how the model will deal with uncertainty²⁸.

In addition to forming the basis of a decision as to whether a drug is cost-effective or not and should be reimbursed, HTA can support pricing decisions²⁵. This may be directly, or it may be in the form of risk sharing arrangements between the drug manufacturer and the health care payer. Risk-sharing helps to reduce the financial risk of a drug by linking pricing and reimbursement decisions to real world effectiveness or utilisation²⁹. These agreements may take many forms and help to overcome uncertainty in outcomes and therefore improve the cost-effectiveness of a drug. Cost-effectiveness modelling can help support discussions about risk sharing through pricing.

1.1.2.2. Methods of economic evaluation

A number of economic methods are available for use in HTA, with the choice informed by the decision to be made. All involve the comparison of the costs and consequences of an intervention against those of the next best treatment or intervention. In BRA for HTA purposes, the comparison is of the costs of the interventions against the benefits and risks of the interventions included in the analysis. Four types of economic evaluation are described below: cost-benefit, cost-effectiveness, cost-utility and cost-minimisation.

COST-BENEFIT ANALYSIS

In simple terms, cost-benefit analysis (CBA) involves comparing the costs of interventions against the benefits, which have been valued monetarily. An intervention is considered worthwhile if there is a social benefit, that is, if the monetary benefits exceed the monetary costs. More precisely, CBA involves comparing the discounted future incremental benefits against incremental costs, with the difference between the two representing the net benefit to society³⁰.

One major benefit of CBA is the ability to compare interventions across different sectors because all consequences are converted into money. This helps with decision making in the broadest sense, in terms of allocating budgets across all possible programmes and allows for the net benefit to society to be maximised by investing in the most worthwhile programmes. The achievement of “allocative efficiency” is possible through CBA, but not other forms of economic evaluation²³. Historically, the act of valuing health states has been considered controversial, but methods described earlier in section 1.1.1.3 have become more popular in health care for this purpose, specifically conjoint analysis and discrete choice experiments³⁰.

COST-EFFECTIVENESS ANALYSIS

Cost effectiveness analysis (CEA) is another method of comparing the costs and consequences of treatments. However, only one effectiveness measure is used and it is a measurement in natural units, for example, heart attacks prevented, reduction in tumour growth or years of life gained. Typically this approach is used when a decision maker is interested in maximising the measurement of interest within a fixed budget^{31,32}. An advantage of CEA is its simplicity, but this is also its downfall as it is not possible to consider a range of outcomes that are likely to define a health condition or disease. Further, as this method tends to be about maximising health gain within a budget it does not consider wider societal impacts and whether programmes are worthwhile, based upon the preferences of society. That is, it addresses technical efficiency but not allocative efficiency. Further weaknesses are that it is not possible to compare treatments

with different objectives and that it might not be clear how the chosen outcome measure relates to health, particularly when using a biological marker such as tumour response^{31,32}.

COST-MINIMISATION ANALYSIS

Cost-minimisation analysis (CMA) is a form of CEA that can be applied where two treatments are equivalent in terms of efficacy and safety, and therefore the one with lower cost is chosen. Critics argue that it is not a useful type of economic evaluation as it is very unlikely that effectiveness would be equivalent^{31,32}. However, the growth of new drugs called biosimilars has seen a return in the implicit use of CMA by NICE and the NHS^{33,34}. CMA is discussed further in Section 1.3.3.1.

COST-UTILITY ANALYSIS

Cost-utility analysis (CUA) overcomes some of the limitations of CEA by utilising a standard measure of health outcome, the quality-adjusted life-year (QALY). The QALY allows for the capture of information on both length of life gained and the quality of that life. The QALY is a measure of utility or patient preferences and is accepted as the standard unit of measurement for economic evaluation by NICE^{27,32}. Societal preferences are elicited for particular health states and these data are combined with survival data to generate a QALY. The value of a QALY typically ranges from one, which is equivalent to a year in perfect health, to zero, which is death. Negative QALYs are possible in the case of health states that are considered worse than death. Also of note is that one QALY gained in one patient is considered equivalent to 0.01 QALYs gained in 100 patients, and that a QALY gained in one population is equal in value to a QALY gained in another patient population.

Using CUA allows for the comparison of a range of different health care interventions due to the consequences taking a common value. It overcomes the limitation of CEA that stems from the inability to consider whether a programme or intervention is worthwhile rather than simply maximising health gain, and therefore helps decisions concerning allocative efficiency. It is very useful in the comparison of treatments for chronic conditions because it considers the wider

quality of life. However, it is limited to the comparison of health care interventions unlike CBA. CUA is a special case of CEA due to the use of QALYs, but is frequently referred to as CEA^{32,35}.

INCREMENTAL COST-EFFECTIVENESS RATIOS

Like CEA, CUA compares the incremental costs and consequences of treatments. With QALYs, the result is an incremental cost effectiveness ratio (ICER). The ICER is the ratio of the incremental costs between a new treatment in comparison with the next best alternative, divided by the incremental effectiveness (QALYs). The ICER can indicate whether a treatment is cost-effective and is calculated as shown in Equation 1.

Equation 1: Incremental cost-effectiveness ratio formula

$$ICER = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E}$$

Where C_1 and E_1 are the costs and effectiveness of the intervention of interest and C_0 and E_0 are the costs and effectiveness of the comparator intervention. The costs include the total management of the intervention, which may include drug costs, resource use for delivering the intervention and the costs of consequences from the intervention, which may include harms.

The incremental costs and incremental benefits versus a comparator treatment can be plotted on a cost-effectiveness plane as shown in Figure 5. An intervention in the North West quadrant has higher costs and lower QALYs and is dominated by the comparator, which is the more cost-effective option. An intervention with coordinates in the South East quadrant has lower costs and higher QALYs and is the cost-effective option as it dominates the comparator treatment. Points in the North West and South East quadrants will both be negative ICERs. Results in the North East quadrant, with higher costs and QALYs, and the South West quadrant, with lower costs and QALYs, both result in positive ICERs but their interpretation is less clear.

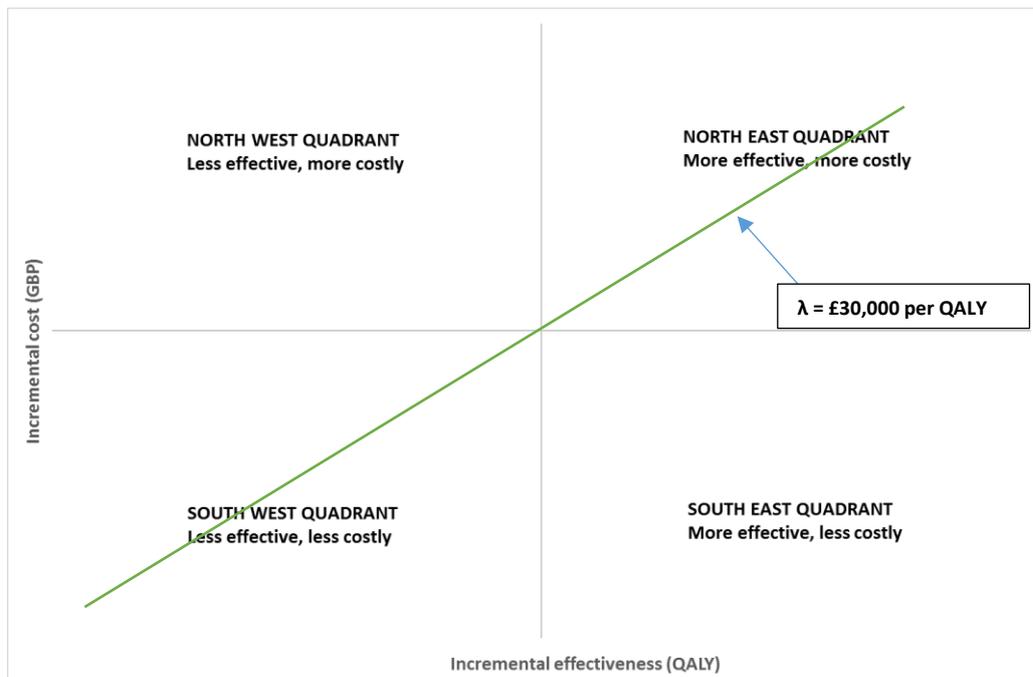
Where there is a positive ICER there are trade-offs between cost and effectiveness to consider³².

In these cases, reference is made to a cost-effectiveness threshold, often denoted as lambda (λ).

This is the opportunity cost of investing in this option, as it represents the value that could be

gained from other options. If the new option is in the North East quadrant, with higher costs and higher QALYs, the decision rule is that if $ICER < \lambda$, the activity is cost-effective, and vice versa. For options in the South West quadrant, the decision rule is reversed so that if $ICER > \lambda$ then the activity is cost-effective.

Figure 5: Example cost-effectiveness plane



NICE traditionally operates with an acceptable cost-effectiveness threshold (λ) of $\text{£}20,000$ to $\text{£}30,000$ per QALY²⁷, as indicated by the green line in Figure 5. Treatments that cost more per QALY are not deemed cost-effective and are unlikely to be approved for use on the NHS. However, this is no longer a strict threshold. A number of schemes have been created by NICE which allow for varying thresholds, such as $\text{£}50,000$ per QALY for end of life treatments and $\text{£}100,000$ to $\text{£}300,000$ for 'very rare diseases'³⁶. In addition, processes have been created for certain drug categories, including a cancer drug fund allowing earlier access to experimental treatments, and an expedited review for drugs costing less than $\text{£}10,000$ per QALY. Whilst NICE operates with transparency in these approaches, it has been argued that these changes are implicitly inequitable as different values are being placed on different conditions³⁶.

INCREMENTAL NET BENEFIT APPROACHES

The QALY is, in effect, a measure of the net benefit of a treatment, weighted by societal preferences for benefits and harms. Whilst the ICER has benefits in being relatively intuitive and allowing direct comparison of interventions, it can be difficult to use as it has no meaningful interpretation without the context of the cost-effectiveness plane quadrant and the cost-effectiveness threshold (λ)³⁷. Net benefit approaches offer an alternative as they result in a meaningful statistic that can be directly interpreted as the additional benefit from a treatment. It is possible to consider either net health benefit (NHB) or net monetary benefit (NMB) as shown in Equation 2 and Equation 3:

Equation 2: Net health benefit

$$NHB = E_i - C_i/\lambda$$

Equation 3: Net monetary benefit

$$NMB = E_i\lambda - C_i$$

Where E_i is the effectiveness of intervention i , C_i is the cost of intervention i and λ is the cost-effectiveness threshold, as previously defined³⁷. NMB converts the effectiveness into a monetary unit and defines the results in terms of currency, whilst NHB converts the costs into health units³². Either approach can be used to compare a new treatment against a comparator, resulting in incremental net health benefit (INHB) and incremental net monetary benefit (INMB). If the resulting INHB or INMB is positive, the new treatment delivers a net benefit and is the cost-effective option. INHB is discussed further and applied in the model in Chapter 5.

1.1.2.3. Cost-effectiveness modelling

Whichever methods of economic evaluation and modelling are selected, there are a number of good practice principles that should be followed, from design to reporting³⁸⁻⁴². These include that the model should be structured to answer the decision problem being addressed and should be transparent, internally consistent and reproducible. The model should be consistent with

available knowledge of the health condition and evidence regarding causal linkages in variables, as well as exploring all forms of uncertainty^{38,39}.

Models should incorporate important factors and health states should not be excluded because of a lack of evidence, for example adverse events not observed in clinical trials. Instead, health states can be included where they are coherent with the theory of the condition³⁹. At the same time, however, models should not be unnecessarily complex and should only include variables that are important to the decision problem³⁸. Typically, models in the literature focus more on benefits of therapies and fail to capture the adverse events. A systematic review of model-based economic evaluations of anti-TNF therapies in rheumatoid arthritis found that models have not routinely considered the direct costs or consequences of adverse events, which can bias the estimates of relative cost-effectiveness and affect the validity of associated recommendations.⁴³ There are numerous reasons behind this, which are discussed in section 1.1.3.2.

1.1.3. Outcomes

When considering the benefit-risk balance of an intervention, it is necessary to be able to draw from the evidence base on outcomes. All forms of evaluation and modelling require good quality data on health outcomes. Health outcomes are defined by the International Committee of Medical Journal Editors (ICMJE) as any biomedical or health-related measures, including pharmacokinetic measures (such as how long the drug takes to be absorbed or how it is distributed) and adverse events⁴⁴.

The RCT is the gold standard for determining efficacy and safety, but they have some well-known flaws including cost and time requirements, and the assessment of efficacy under perfect conditions meaning the results do not necessarily translate in clinical practice⁴. Uncertainty in BRA stems from the uncertainty in the component benefits and risks. Uncertainty about efficacy can result from bias and errors, whilst uncertainty about safety outcomes is likely to be greater due to the fact that studies are powered for efficacy⁴. Uncertainty in the benefits and risks of a

product may be highest at the point of marketing authorisation, once it begins to be marketed to a wider population who are using the treatment in a less-controlled manner than in clinical trials⁵. Post-marketing research is useful to detect safety signals, but can also provide evidence on the effectiveness of a drug, which also informs the benefit-risk balance⁴.

Benefits and risks may be considered as absolute values, such as the percentage of patients who experience an improvement in disease or who avoid an adverse event from taking a drug. They may also be considered as relative benefits and risks, where they are compared to the outcomes of other therapies. Relative risks may be used to assess the improvement in condition or reduction in the occurrence of an adverse event, for example, patients taking the intervention of interest experienced a relative risk reduction of 10% compared to patients on the alternative therapy. Economic evaluation methods consider comparative risks and benefits, but it is important to also monitor the absolute values of risks and benefits. As way of example, a treatment may lead to a 50% increase in the risk of an adverse event, which appears large and concerning. However, if the absolute increase is from 0.4% to 0.6%, the actual risk remains very low and the increase may not be considered clinically significant, especially if accompanied by an improvement in disease activity. Conversely, a treatment may result in a 10% improvement in the number of patients achieving a benefit, which may seem relatively small, but may mean that 88% of patients achieve an outcome, instead of 80% and could result in considerable improvement in population health. If this is balanced against no increased risks, or small increased risks, it is an even more positive result.

1.1.3.1. Benefits

Assessment of benefit is important for all BRAs and the considerations are likely to be similar for all decision makers – essentially, will this treatment make the patient's condition improve? This type of information will come from clinical trials, usually RCTs. RCTs are considered the gold standard method for assessing benefit of a therapy because of the randomisation of patients

between treatment arms, which should ensure that any additional benefit is the result of the treatment and no other differences. Generally, the benefit, or efficacy, of an intervention is tested in the primary and secondary endpoints of a trial. These endpoints are pre-specified in the trial protocol as an aide to ensure transparency in trial reporting to support the collection and publication of best evidence and prevent outcome reporting bias. The International Committee of Medical Journal Editors (ICMJE):

“requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication”⁴⁴.

Clinical trial endpoints incorporate the outcome to be measured, the outcome measurement and the outcome measurement tool. For example, 2006 EMA guidelines recommended the measurement of the proportion of patients achieving remission (CDAI<150) within four to six weeks to demonstrate short-term efficacy. In this endpoint, the outcome is remission, the measurement is CDAI <150 and the outcome measurement tool is the CDAI.

The International Conference on Harmonisation (ICH) guidelines on clinical trial data suggest how key benefits should be identified for inclusion in a BRA¹³. Key benefits are defined as favourable effects that are assessed by primary and other clinically important endpoints. The clinical importance of the benefit is a stressed requirement, which should include consideration of the magnitude of the difference in effect between treatment populations. Further, the guidelines highlight that other findings might be used in the BRA beyond primary endpoints, including secondary and exploratory endpoints.

However, RCTs are very expensive to run and tend to take place over the short term, which can reduce their ability to assess efficacy over the longer term. This is problematic for chronic conditions, where therapy may be received for years or decades to keep a disease under control. Further, clinical trials monitor efficacy of a drug, which can be summarised as what a drug could

do in a patient population. However, there is often a gap between this and what a drug actually does do in the patient population, which is known as effectiveness⁴.

Intention-to-treat can help to identify the effectiveness of a treatment, rather than the efficacy. Intention-to-treat (ITT) is the method of analysing patients in their original randomised group, which aims to maintain the original sample size and the split of prognostic factors between the groups, irrespective of study withdrawals, missing data and non-adherence to therapy^{45,46}. If ITT analysis is used in the reporting of studies, patients who have withdrawn due to adverse events should be followed up and are still included in the analysis. This might not be the case in per-protocol analysis, where patients are analysed in terms of the treatment they receive. Where per-protocol analysis is used, it can bias the results, creating a more optimistic view of the benefits of a drug than can be achieved in reality^{45,46}. ITT analysis was previously required by the CONSORT statement and the 2010 version offers clarity for trialists that analysis should be done by the original groups with complete follow up of patients to preserve randomisation⁴⁷.

CORE OUTCOME SETS

The multitude of outcomes that can be measured for a condition make it difficult to synthesise data and establish more precise estimates of benefits and risks from treatment. Core outcome sets (COS) are one method for resolving this issue. A COS is a standardised set of outcome measures that should be reported in research^{48,49}. It is not an exhaustive list, and researchers may measure additional outcomes of their choosing. The intention is that all trials should measure and report the core set as a minimum requirement so that it is possible to produce precise outcomes that allow for the comparison of benefit and risk within and across treatments. Ideally, the COS should also be used in clinical practice to further add to the evidence base of effectiveness and longer-term outcomes⁴⁹.

The Core Outcomes Measurement in Effectiveness Trials (COMET) initiative⁵⁰ is a leading contributor to the research field of COS, but COS groups also operate for individual conditions. A

key example is the Outcomes Measurement in Rheumatology (OMERACT)⁵¹ initiative which advocates the use of COS in rheumatology trials. Key to the development of COS is the use of consensus methods, which means that the final outcomes selected for inclusion are agreed by all stakeholders, including patients⁴⁹. Core outcome sets are discussed further in Chapter 2 and Chapter 3.

1.1.3.2. Risks

Regulatory agencies use a number of methods to identify risks: RCTs, observational studies, automated databases linking drugs and disease, spontaneous reporting systems and patient registries³. The system as a whole is called pharmacovigilance and is designed to ensure that drugs are safe, and the benefits outweigh the risks, at all points in the life cycle.

Understanding the risks of treatments tends to be more complicated than benefits because trials are powered for efficacy rather than safety endpoints, but also because the assignment of causation is more complicated. Clinical Good Practice (CGP) requires that all adverse events occurring during clinical trials should be recorded¹³. Adverse events are then assessed as being serious or not, and treatment-related or not. The ICH recommends that this information should be presented in the application for regulatory approval, but also suggest that the analysis of common adverse events should be on the total number, regardless of causation, because *“evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related”*¹³. This subjective nature of causality assessment is problematic in various ways, and is discussed in Chapter 4 on the consideration of methods for capturing long-term harms from drugs.

Further, whilst harms would ideally be identified in the controlled environment of clinical trials, the cost and time requirements, and safety database required to detect small safety signals of rare harms, and small increases in common events, makes this unfeasible^{4,9}. As such, the true safety profile of a drug is unavailable at the time of approval and post-marketing monitoring is a

necessary component of the regulatory process. To this end, the EMA requires that sponsors must submit detailed risk-management plans with an application for market authorisation, which contains:

- *“the identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively of further studies (‘safety specification’);*
- *The planning of pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions (the ‘pharmacovigilance plan’);*
- *The planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the ‘risk minimisation plan’)”⁵²*

The pharmacovigilance plan contains information on the collection of additional data on harms from the drug to inform the benefit-risk balance. It contains sections for routine pharmacovigilance activities and for additional pharmacovigilance activities that are not considered routine⁵². Long term follow up studies of clinical trial patients or cohort studies of patients receiving the drug over a long period, are examples of potential additional activities.

Traditional forms of pharmacovigilance rely upon the spontaneous reporting of adverse reactions. Whilst the lack of denominator and controls makes it difficult to distinguish signals from background noise, important drug safety issues can, and are, identified through such systems⁴ (see further discussion in Chapter 4). Rarely, drugs may be withdrawn because serious safety signals are identified in the post-marketing phases and this should be viewed as a success of the pharmacovigilance mandated by regulatory processes⁴.

DEFINITIONS

Many terms are used to describe risks of drugs and this section provides a summary of some of the main classification systems.

INTERNATIONAL CONFERENCE ON HARMONISATION (ICH)

ICH guidance on clinical safety data management⁵³ define adverse events (AEs) as:

“any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”⁵³.

Adverse drug reactions (ADRs) are defined according to whether they occur in a pre-approval or post-approval setting. In a pre-approval setting, they are defined as:

“all noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions”.

In a post-approval setting, they are described as:

“a response to a drug which is noxious and unintended and which occurs at doses normally used in man...”⁵³.

Unexpected adverse drug reactions are described as:

“an adverse reaction, the nature or severity of which is not consistent with the applicable product information”⁵³.

Further defined are serious adverse events or reactions:

“a serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent of significant disability /incapacity, or is a congenital anomaly / birth defect”⁵³.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

The MHRA is the UK regulatory agency for medicines and medical devices. The MHRA operate the UK’s spontaneous reporting scheme for adverse events, the Yellow Card scheme⁵⁴. Suspected adverse reactions are reported to the MHRA and statistical methods are used to identify potential signals of harm. The processes and methods are discussed in more detail in Chapter 4. Once causality is established, and events are determined to be adverse drug reactions, the MHRA classifies them into different types⁵⁵.

Type A and type B reactions are the most common. Type A reactions are related to the mechanism of action of the drug, and are usually (though not exclusively) an exaggeration of the normal

pharmacological response. Type B reactions are unexpected reactions that could not be predicted from what is known about the drug. Whilst Type A reactions are likely to be identified in clinical trials, type B may only be discovered once the drug has been marketed⁵⁵. Three other reaction types are identified. Type C reactions are related to continued use of a drug over time, for example, osteoporosis with extended steroid use. Type D reactions are delayed reactions where the harm occurs sometime after the exposure, even if the medicine has been discontinued since. For example, the thalidomide effects on unborn foetuses. Type E reactions are related to withdrawal of a medicine, for example withdrawal syndrome with antidepressants. A further type of reaction, type F, reported by Aronson (2002) in Aronson and Ferner (2003)⁵⁶ is failure of therapy.

DOSE, TIME AND SUSCEPTIBILITY CLASSIFICATION SYSTEM

The system outlined by MHRA to classifying adverse drug reactions is based upon dose response, and this has been criticised as simplistic and inadequate⁵⁶. Aronson and Ferner (2003)⁵⁶ propose a three-dimensional system that also incorporates the time course and patient susceptibility, known as DoTS, which stands for dose, time and susceptibility. The dose-relatedness component can be classified as 'toxic' effects, where the reaction occurred with excessive dose, 'collateral' with standard doses, and 'hyper-susceptibility' with sub-therapeutic doses. Time relatedness is classified as time-independent or time-dependent. Time-dependent effects are 'rapid reactions' when the drug is delivered too rapidly, 'early reactions', which occur early in treatment but the patient develops tolerance over time, 'intermediate reactions', which occur after some delay, 'late reactions', which occur with increasing risk with continued treatment, and 'delayed reactions', which appear after a delay even if the treatment has already been stopped. Sources of susceptibility to adverse drug reactions are classified as genetic, age, sex, physiology altered (such as pregnancy), exogenous factors (including drug interactions) and disease.

The range of definitions and classifications highlights some of the difficulties in identifying harm outcomes for all areas of BRA. These issues are discussed further in Chapter 4.

1.1.3.3. *Dealing with uncertainty*

Uncertainty in the benefit and risks inputs to any model are unavoidable, particularly when decisions are made early in the life cycle of a drug. As highlighted by the earlier discussion in section 1.1.2.3, uncertainty about input data is not an adequate reason to omit important variables from the model^{38,39}. Particularly when modelling complex decisions, speculation in input parameters may be necessary and this should be explicit⁵⁷. As such, any quantitative benefit-risk model needs to be able to explore the uncertainties and the impact on the benefit-risk balance²². Many sources of uncertainty exist in modelling but the most important ones for this thesis are those related to input data and model structure.

Probabilistic sensitivity methods (PSM) allow for the exploration of uncertainty around input data as described in section 1.1.1.4. By sampling values for input parameters from a distribution, it is possible to produce estimates of the benefits and risks, with precision estimates in the form of confidence intervals. An additional value of PSM is the ability to use the results to conduct a value of information analysis (VOI), which supports decision makers in their understanding of the value of delaying a decision to gather further information⁵⁸.

VOI methods expose the costs of uncertainty by quantifying the probability that the decision is wrong and the (cost) consequences if it is wrong⁵⁷. The expected costs that result from this process are known as the expected value of perfect information (EVPI) which highlights the value of additional information. If the cost of conducting further research is below the EVPI, then it is potentially cost-effective to conduct the research to reduce the decision uncertainty⁵⁷. Further, it is possible to calculate the expected value of perfect parameter information (EVPPI), which can help to inform decisions on which parameters to research and potentially which endpoints would be suitable⁵⁷. The VOI method has the potential to establish how much evidence is enough for a regulatory or HTA decision and to inform the requirements for post-marketing research⁵⁸.

Scenario analysis is used to address structural uncertainty in the model and future uncertainty²². This is especially useful for the crucial element of quantitative modelling – explicit statements of value judgements. Scenario analysis allows for underlying assumptions in the model to be altered and the impact explored and is considered a necessary part of quality models^{38–40,42}.

All these methods of dealing with uncertainty are applied in the quantitative model developed in Chapter 5.

1.2. Crohn's disease

Crohn's disease and ulcerative colitis are the two main types of Inflammatory Bowel Disease (IBD). Crohn's disease is a relapsing and remitting disease, which can cause inflammation and ulceration anywhere along the gastrointestinal tract and can impair the body's ability to digest food, absorb nutrients and eliminate waste. The presenting symptoms vary but tend to include diarrhoea (with or without blood and mucus), abdominal pain and weight loss, and potentially malaise (general feeling of being unwell), anorexia or fever⁵⁹. Crohn's disease is characterised by periods of active disease followed by time spent in remission. There is no known cure and the causes of the disease are unclear but are believed to be the result of an interplay between genetic susceptibility and environmental factors, and potentially linked to triggering events, such as gastroenteritis infections^{59–61}. An overactive immune response is believed to be at least partially responsible for the inflammation in the intestinal mucosa and is the basis of many new biological therapies (see section 1.3.3).

Crohn's disease is estimated to affect at least 115,000 people in the UK and can affect patients of any age⁶². Crohn's disease has a significant impact on patients' lives, affecting their education, work, family and social lives due to repeat hospitalisation, repeated operations and poor nutrition⁶¹. It is difficult to diagnose, associated with a range of complications and comorbidities and the treatments available are variable in their effectiveness and linked to risks of very serious adverse events. The disease is associated with high healthcare costs. Diagnostic techniques, new

biological treatments, hospitalisations and surgeries are all very costly, and the annual average cost of care per Crohn's disease patient in the UK has been estimated as £838⁶³.

1.2.1. Disease course

1.2.1.1. *Disease classification*

Crohn's disease is classified using the Montreal phenotype classification, which is advocated by the European Crohn's and Colitis Organisation (ECCO) in their evidence based consensus paper⁵⁹. The classification identifies the location and phenotype of Crohn's disease. A survey of adults with Crohn's disease by Thia et al (2010), reported in Baumgart and Sandborn (2012)⁶⁰, found Crohn's disease was located in the terminal ileum in 45%, colon in 32%, ileocolon in 19% and upper GI tract in 4%. The phenotype was inflammatory in 81%, structuring in 5% and penetrating (fistulising) in 14%. However, whilst location tends to remain the same, severity tends to progress over time and 51% of patients in the survey by Thia et al (2010) had moved to a more serious phenotype within 20 years of diagnosis^{59,60}.

1.2.1.2. *Disease severity*

Crohn's disease is commonly categorised based upon clinical symptoms and response to treatment. Disease activity indices such as the Crohn's Disease Activity Index (CDAI)⁶⁴, the Harvey-Bradshaw Index (HBI)⁶⁵ and the Perianal Disease Activity Index (PDAI)⁶⁶ are used extensively to define the severity of Crohn's disease and are discussed in detail in Chapter 2. All three indices record the severity of disease at a point in time, which is considered a flawed approach by some given the progressive nature of the disease⁶⁷.

ECCO consensus is that there are no precise definitions for mild, moderate and severe disease, but clinical trials tend to define active disease as CDAI>220⁵⁹. NICE defines severe disease as very poor health, with one of more symptoms of weight loss, fever, severe abdominal pain and frequent diarrhoea, corresponding to a CDAI score above 300 or a HBI score above 8⁶².

Remission is commonly measured by a CDAI score below 150, although as discussed in Chapter 2, there is an increasing movement towards objective measures of inflammation and patient-reported outcomes (PROMs)^{59,68}. Response is defined as a change in CDAI of at least 100 points, although an alternative endpoint of a 70-point change is also used. Relapse is defined as a CDAI score above 150 with an increase of more than 70 points⁵⁹. Relapse in clinical terms is a flare in symptoms following a period of remission, and ECCO recommend it should be confirmed by objective measures such as those discussed in section 1.2.3.1. Recurrence is a flare of disease following surgical remission and is defined in both clinical terms and objectively by the recurrence of ulcers.

Patients are defined as having steroid-refractory disease if they have active disease despite 4 weeks of steroid treatment. Steroid-dependent disease is defined where patients are unable to reduce steroids without recurrent active disease or who relapse within 3 months of stopping steroids⁵⁹.

Peyrin-Biroulet et al (2016)⁶⁷ have argued that none of the available systems for characterising the disease course are flexible enough in terms of measuring the disease course over time, and fail to account for the underlying inflammatory processes and wide impact of disease on patient's lives. The lack of availability of validated instruments for accurately measuring disease activity is discussed in the work in Chapter 2 and Chapter 3.

1.2.2. Complications and comorbidities of Crohn's disease

The irreversible damage caused by inflammation within the intestine can lead to a number of complications of Crohn's disease. Fistulas occur when inflammation leads to the development of connections between different parts of the intestine, from the intestine to other organs (for example, recto-vaginal) or from the intestine to outside the body (for example, to the stomach or the perianal area). The fistula tracts allow faecal matter to pass through, and can have significant negative impact on a patient's quality of life⁶⁹.

Strictures are a narrowing of the intestine and result from the build-up of scar tissue due to repeated inflammation. They can lead to abdominal obstruction in the intestine and carry a risk of perforation where severe, which can be life threatening. Intra-abdominal abscesses may also occur with Crohn's disease where the bowel is compromised and bacteria can enter. Control of these complications may necessitate surgery where they don't respond to medical therapy^{60,61}. As many as 80% of patients with Crohn's disease are expected to require a surgery at some point in their life for strictures, fistula, perforation or failure of medical therapy⁶².

Crohn's disease may be accompanied by extra-intestinal manifestations, such as mouth ulcers (aphthous mouth ulcers) or skin conditions that cause painful ulcers (pyoderma gangrenosum) or painful lumps followed by bruising (erythema nodosum). Joints can be affected by arthralgia and frank arthritis. Complications can also affect the eyes, with inflammation resulting in episcleritis, scleritis and uveitis. These extra intestinal manifestations were deemed important by physicians and researchers in the 1970s and were therefore included in the CDAI when it was designed⁶⁴. It is unclear whether these complications are important to patients and clinicians today, and this is discussed further in Chapter 3.

A number of other conditions are linked to Crohn's disease including osteoporosis, which can result from steroid use and reduced ability to absorb minerals, and iron deficiency anaemia, which can result from blood loss in the digestive tract and from poor absorption of iron⁶⁰⁻⁶². Crohn's disease patients face a higher risk of some cancers, which are related both to the condition and to the treatments, and fertility can be reduced, which is understood to be voluntary and due to mistaken beliefs about pregnancy outcomes⁶¹.

1.2.3. Diagnosis and treatments for Crohn's disease

Diagnosis is complex because of the variability of the disease, the difficulty of distinguishing it from other conditions like irritable bowel syndrome (IBS) and the lack of a gold standard method.

Instead, diagnosis is via a combination of clinical evaluation, endoscopic, histological, radiological and biochemical investigations^{59,61}.

1.2.3.1. Diagnosis

CLINICAL EVALUATION

Initial diagnosis by a clinician is based upon the presentation of symptoms related to Crohn's, which may be initially in the form of extra-intestinal manifestations.

LABORATORY INVESTIGATIONS

Laboratory tests can include C-reactive protein, erythrocyte sedimentation rate and full blood count, which are markers of inflammation^{59-61,70}. Faecal calprotectin correlates well with inflammation and is a useful measure, recommended by NICE, to differentiate IBD from irritable bowel syndrome without the need for invasive endoscopy^{59-61,70}. Genetic studies have been successful in identifying a number of loci that infer susceptibility to Crohn's disease, however, none has enough sensitivity or specificity to help in diagnosis and no genetic tests are currently recommended^{59,71}.

ENDOSCOPIC AND HISTOLOGICAL INVESTIGATIONS

Where Crohn's disease is suspected, endoscopy with biopsies is considered the first line method for diagnosis in secondary care^{59,70}. A colonoscopy can examine the entire colon, but is considered a risk for bowel perforation when a patient has severe disease. In this case it is recommended to use flexible sigmoidoscopy and return to colonoscopy when the clinical condition has improved⁵⁹. Where there are no signs indicative of Crohn's disease from colonoscopy (and radiological investigations) or if there is concern about the small bowel, camera endoscopy can be used^{59,70}. Endoscopies are also used for monitoring purposes due to the higher risk of colorectal cancers in patients with Crohn's.

Endoscopic investigations look for particular features to identify Crohn's including patchy distribution of inflammation, cobblestone appearance and rectal sparing. However, a number of

characteristic features of Crohn's disease cannot be identified with endoscopy and microscopic examination is required of histological samples. A reliable diagnosis requires multiple biopsies throughout the colon and the identification of multiple microscopic features of Crohn's disease⁵⁹. Whilst mucosal biopsies can identify mucosal inflammation, they are criticised for being unable to represent the bowel-thickness inflammation (transmural) characteristic of Crohn's disease⁷².

A number of endoscopic and histologic scoring systems are used to help diagnose Crohn's disease and assess the impact of treatment, which are discussed in Chapter 2.

RADIOLOGICAL INVESTIGATIONS

Radiological investigations are recommended as complementary tools to endoscopy as they can be used when disease is suspected to be out of reach of an endoscope, and can help to assess the stage and extent of disease, including complications like fistula and abscesses⁵⁹. Magnetic resonance imaging (MRI) and computed tomography enterography (CT) are used for imaging. CT is more widely available and less time-consuming, but involves exposure to radiation, which may be repeated many times over the lifetime of a Crohn's disease patient; consequently, MRI is preferred⁵⁹. Trans-abdominal ultrasonography (US) also allows for the assessment of the extent of the disease by assessing the increased bowel wall thickness and has the benefit of being non-invasive, not involving radiation and being well tolerated by patients⁵⁹. Endoscopic anorectal ultrasound (EUS) is also recommended for diagnosis of perianal disease and is necessary to support surgical drainage of complicated fistula⁷³. Barium X-rays can be used for imaging where a barium solution is swallowed to line the gut and give a clearer view. However, barium X-rays expose patients to radiation and have low sensitivity in identifying Crohn's disease so MRI, CT and US are preferred, all of which have high sensitivity and specificity⁵⁹.

1.2.3.2. Treatment

Crohn's disease treatment focuses on inducing and maintaining remission. Treatment aims are to reduce symptoms and improve quality of life whilst minimising toxicity over the short and long

term. Further, treatments aim to halt the progression of disease and minimise the damage that leads to intestinal failure and complications such as fistula, strictures and abscesses⁶⁰.

Patient perceptions of benefit and risk are an important point in the treatment process. NICE promotes patient-centred care, where patients should be supplied with appropriate evidence-based information so that they can make informed decisions⁶². Research shows that Crohn's disease patients are willing to trade-off risk against therapeutic effects, but that risk tolerance is not homogenous across the population⁷. This must be factored into decisions about treatment, especially the pursuit of top-down approaches using more aggressive therapies earlier, or the use of less established therapies. The lack of adequate tools for measuring the course and severity of disease has implications for patients who may benefit from more intensive treatment but may not be identified as having severe disease using currently classification systems⁷⁴.

Treatments for Crohn's disease include glucocorticosteroids, 5-aminosalicylates, antibiotics, immunosuppressives, biologics, nutritional therapy and surgery. The appropriate treatment will be dependent upon the type of Crohn's disease, the extent of the disease, the presence of complications, and the patient's preferences for risk. Individual therapies carry some serious risks such as the risk of infections in immunosuppressive therapy, including anti-TNF agents, increased risks of malignancy with combination immunosuppressive therapy (steroids, thiopurines and anti-TNF agents) and infusion and anaphylactic reactions with anti-TNF agents⁵⁹. Such risks must be balanced against the benefits, and with consideration to the views of the patient and their clinical profile.

The following sections on induction and maintenance therapy present the recommendations of the ECCO consensus statements for diagnosis and medical management⁵⁹ and surgical management⁷³ and the NICE clinical guideline for managing Crohn's disease⁶².

INDUCTION

Glucocorticosteroids are recommended by NICE to induce remission with those first presenting with Crohn's disease, with budesonide offered as an option for those who cannot tolerate conventional glucocorticosteroids⁶². 5-aminosalicylates can be used for patients who cannot tolerate glucocorticosteroids treatment. If systems persist, azathioprine or mercaptopurine immunomodulators can be added as second-line treatments. Methotrexate can be used if azathioprine or mercaptopurine are not tolerated.

For patients who present with severe disease (defined in section 1.2.1.2) and who have failed or are intolerant to the described conventional treatment, anti-TNF α agents can be prescribed. Adalimumab and infliximab are the options and patients start on the cheapest drug. The ECCO consensus is that patients with clinical features suggesting a poor prognosis and high disease activity should be considered for early introduction of anti-TNF in a 'top-down' approach, rather than the standard 'step up', although the potential for toxicity from treatments must be considered⁵⁹. Two new biological therapies, vedolizumab and ustekinumab, have also been approved by NICE for use by patients with severe disease that has not responded to anti-TNF therapy^{75,76}.

Patients with fistulising disease may require a different treatment package which starts with antibiotics to treat infection, drainage (through the placement of setons, which are threads passed through the fistula that allow it to heal), and immunosuppressive treatments^{73,77}. Infliximab or adalimumab may be prescribed to patients with active fistulising disease if they do not respond to conventional treatment. Where these treatments fail, surgical options are available dependant on the location and extent of the fistula. A fistulotomy is used for an anal fistula and involves cutting the fistula to lay it flat and allow it to heal and is a recommended option from simple anal fistula⁷³. Surgical treatments for perianal fistula carry a risk of leaving a patient incontinent.

Surgical treatments in inflammatory Crohn's disease are intended to be curative by removing the section of intestine that is affected. Surgery might be considered as an alternative to medical treatment in early disease course for patients with disease limited to the distal ileum^{62,73}. Surgery is generally an option when patients fail all medical treatment, but carries a risk of short bowel syndrome where a lot of bowel is removed as absorption of nutrients and medications is compromised. Surgery may involve a resection resulting in an anastomosis, where sections are reconnected. Surgery may also result in a colectomy or partial colectomy, where the healthy remainder of the intestine is brought out as a stoma and a bag is fit. This can be a permanent stoma or a temporary one to allow a section of bowel to heal.

Simple strictures should be managed by balloon dilation, where a balloon is used to widen and reshape the section of intestine, guided by colonoscopy⁶². Surgical back up should be available should there be complications or the dilation fails⁷³. Strictureplasty is the surgical procedure that involves opening up, reshaping and sewing together a narrowed section.

MAINTENANCE

Choice of maintenance therapy depends upon the treatment that induced remission and on the preferences of the patient. Where remission was achieved with glucocorticosteroids, azathioprine or mercaptopurine should be offered to maintain remission, with methotrexate available for those who are intolerant or needed methotrexate to achieve remission⁶².

Infliximab or adalimumab may continue to be used to maintain remission until failure of the medication and the need for surgery, or until the treatment is received for one year, when it should be reviewed⁶². The same procedures apply to maintenance therapy with ustekinumab or vedolizumab^{75,78} and they are believed to have a lower adverse event profile than anti-TNF agents⁵⁹. Patients with fistulising disease who achieved remission medically may maintain remission with a combination of thiopurines, anti-TNFs and seton drainage⁷³.

For patients who achieved remission through surgery, 5-ASA treatment is recommended, with azathioprine or mercaptopurine recommended with patients who have had more than one resection or previously had complicated disease⁶². ECCO also recommends anti-TNF therapy in patients with risk factors for recurrence⁷³.

Where relapses occur, patients can “step up” therapy. Confirmed loss of response to anti-TNF agents should initially be managed by dose optimisation, which involves either shortening the interval between doses or increasing the dose. The measurement of levels of the drug and anti-drug antibodies in the blood are recommended to guide clinical decision making⁵⁹. Medical failure in patients with perianal fistulising disease may require an ostomy⁷³.

OTHER TREATMENTS

Nutritional therapy involves the use of enteral food, which allows the bowel to rest. It may be used following surgery to allow bowel rest, but is not recommended to maintain remission following surgery and is otherwise not recommended by NICE for treatment in adults⁶². However, ECCO see a role for nutritional therapy in support of conventional therapy, and for patients who decline conventional therapy for induction of remission. Further, parenteral nutrition, where nutrition is supplied intravenously and bypassing the gastrointestinal system entirely, is recommended in the case of complex fistulising disease⁵⁹.

The use of complementary and alternative methods is not considered part of conventional therapy.

[1.3. Benefit-risk challenges of biosimilars](#)

[1.3.1. Biosimilars](#)

As patents for biological therapies expire, biosimilars, which are near identical to the originator products, are changing the therapeutic landscape.⁷⁹ Biosimilars is the term given by the EMA to a biological drug that contains a version of the active substance of an authorised biological medical reference product (RMP). The EMA is the leading regulator in the field and consequently many

regulators have adopted the term. Both the Australian TGA⁸⁰ and the US FDA⁸¹ use the term biosimilar. Health Canada refers to such products as Subsequent Entry Biosimilars (SEBs) but acknowledges the equivalence of this term with biosimilar⁸². The Japanese PMDA uses both biosimilar and follow-on biologics for such drugs⁸³.

Biosimilars are generally less expensive, or prompt a reduction in the price of the RMP while achieving comparable health outcomes. Biosimilars offer the opportunity for less expensive treatment of chronic conditions, which allows for reduced expenditure on the therapies or the extension of treatment to allow more patients to benefit within the same budget. Regulators seek reassurance that they will offer efficacy and safety that is not different, in terms of clinical significance, to the RMP^{79–83}.

1.3.2. Regulatory processes for biosimilars

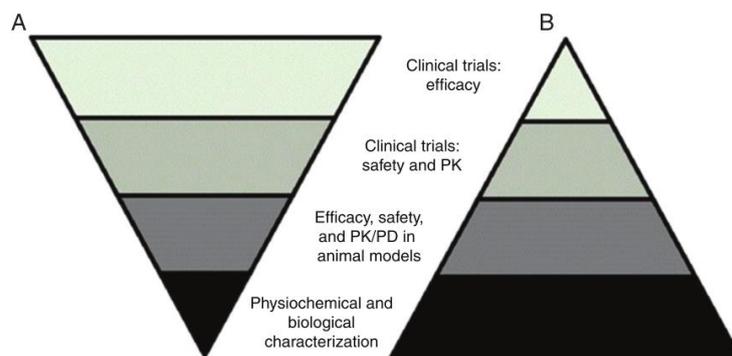
The EMA has been the leading regulator in the biosimilars approval process and have adopted a “totality of evidence” approach⁸⁴ to assessing the benefit-risk balance of a biosimilar, which has been adopted by regulators across the world^{80–83}. The EMA requires that product sponsors conduct a comprehensive comparability exercise to demonstrate similarity in terms of quality characteristics, biological activity, safety and efficacy. In practice, this requires a stepwise approach to conducting non-clinical and clinical studies. Key elements of the requirements include:

- The non-clinical studies should begin with physicochemical and biological characterisation studies before determining whether in vivo work in animal studies is required.
- The clinical studies should begin with PK and PD studies, followed by clinical trials to establish safety and efficacy.
- The clinical study population should be representative of the approved therapeutic indication and should be sensitive for detecting potential differences between the biosimilar and the reference products.

- The EMA allows for extrapolation to other indications as long as adequate scientific justification is provided, again based upon the totality of data.

Figure 6 shows how this approach differs from the typical approach for the development of a new drug⁸⁵. Drug development begins with some physicochemical and biological characterisation but the emphasis is placed upon clinical trials, especially to establish efficacy and safety. The emphasis in biosimilar development is to reverse engineer a product and then demonstrate similarity to the RMP⁸⁵. Regulatory agencies regard biosimilars as sufficiently similar to the originator that they can follow a shortened approval process³³.

Figure 6: Illustration of the differences in process development between biosimilar (B) and reference medical product (A)⁸⁵



1.3.3. Regulatory approval of infliximab biosimilars

The first Crohn's disease biological treatment patent to expire was for Remicade (Merck Sharp & Dohme Limited, Hertfordshire, UK), which is the brand name for the anti-TNF agent infliximab. The biosimilar developer selected rheumatoid arthritis (RA) and ankylosing spondylitis (AS) as sensitive populations for the clinical studies, which were used to demonstrate biosimilarity and justify extrapolation to Crohn's disease. The timeline of regulatory approvals for infliximab biosimilars (Inflectra, Pfizer Europe, Belgium, and Remsima, Biogen Idec Ltd, Maidenhead, UK), shown in Table 1, highlights the difficulties arising from the subjective nature of qualitative BRA, and extrapolation from evidence in other indications.

Table 1: Timeline of regulatory decisions for infliximab biosimilars

Date	Detail
June 2013	CHMP gave approval for Inflectra as a biosimilar for infliximab in all indications. Small differences in quality data, related to antibody-dependent cellular cytotoxicity (ADCC) were not determined to be clinically meaningful ⁸⁶ .
January 2014	Health Canada approves Inflectra as a biosimilar for limited indications. Extrapolation to Crohn’s disease and ulcerative colitis is not recommended due to differences that could potentially impact on clinical safety and efficacy in these indications ⁸⁷ .
July 2014	PMDA (Japan) approval given for Inflectra to be considered an infliximab biosimilar for all indications ⁸⁸ .
May 2015	FDA refuse approval of Inflectra as an infliximab biosimilar because of uncertainty in the observed differences in ADCC and what clinical impact it may have. This is especially important to IBD due to the potential mechanism of action of ADCC in IBD ⁸⁹ .
July 2015	TGA (Australia) approves the listing of Inflectra as a biosimilar infliximab for all indications ⁹⁰ .
August 2015	Health Canada determine a favourable benefit risk assessment for Inflectra in Crohn’s disease and ulcerative colitis based upon newly submitted physiochemical and biological data and observational clinical safety data for IBD patients. The issues related to ADCC are mitigated by sponsor provided rationales addressing the potential mechanisms of action and their relationships to clinical outcomes ⁹¹ .
April 2016	CHMP approve Flixabi as a biosimilar for infliximab for all indications. Small differences are detected in quality attributes that are determined not to translate to clinical meaningful differences. A divergent position statement is provided due to concerns over safety and efficacy differences ⁹² .
May 2016	The FDA approve Inflectra for all indications following submission of sponsor data from ongoing open-label marketing studies and registries and interim immunogenicity data from an ongoing, randomised controlled study in patients with Crohn’s disease ⁹³ .

STRAIGHTFORWARD APPROVALS

Some regulators have offered complete approval with extrapolation to all indications without any concerns, despite noting differences between the biosimilar and reference product in terms of quality data. The first such approval for an infliximab biosimilar was granted in the European Union in June 2013 when the CHMP approved Inflectra for all indications. Some differences were noted in the data provided, especially with regard to antibody-dependent cellular cytotoxicity (ADCC) and the number of adverse events reported, but the CHMP decided that the differences were not clinically meaningful. On balance, they determined that the benefit risk balance, based on qualitative assessment, was positive for all indications but would monitor long-term efficacy

and safety data from post-authorisation studies and registries, including IBD⁸⁶. Japan's PMDA followed with full approval in all indications in July 2014⁸⁸ and the Australian TGA in July 2015⁹⁰.

COMPLICATED REGULATORY DECISIONS

Other regulatory decisions have not been so straightforward. Health Canada approved Inflectra as a biosimilar in January 2014 but refused indication extrapolation to IBD as they felt the differences in the data could have an impact on safety and efficacy in these indications⁸⁷. A more favourable decision was given in July 2015 after consideration of new evidence supplied by the sponsor⁹¹. This new evidence included additional physicochemical and biological data and rationales addressing the various potential mechanisms of action and their relationship to IBD. On this basis, Health Canada approved the extrapolation of indications to IBD.

The US FDA refused the application for Inflectra to be an infliximab biosimilar on the basis of differences in ADCC in May 2015⁸⁹. The clinical reviewer interpreted that the differences not only meant that it would not be possible to extrapolate due to the potential role of ADCC as a mechanism of action in Crohn's disease, but that they also meant that the drug could not be considered biosimilar. The sponsor submitted additional data from ongoing post-marketing studies and registries and interim safety data from a trial in patients with Crohn's disease and full approval with extrapolation was given in May 2016⁹³.

The CHMP approved Flixabi as a biosimilar for infliximab in April 2016⁹². However, not all members of the committee agreed with the majority decision and a divergent position statement was issued. Some members felt that approval should not be given for the following reasons:

- A higher number of adverse events reported for the biosimilar than the reference;
- Lower efficacy in the RA trial for the biosimilar than the reference (although within the pre-specified equivalency margins).

- The use of immunosuppressives in the RA trial could have reduced the level of immunogenicity in these patients. The consequence on adverse events and efficacy in other indications is not understood.

1.3.3.1. Uncertainties

The approach of all the regulators has been one based on the “totality of evidence” to determine the benefit-risk balance. This is a subjective process and there remain numerous uncertainties. Many regulators identified differences in quality data related to ADCC but the interpretation has differed with some suggesting it could not be ruled out as a plausible mechanism of action in Crohn’s disease and therefore indication extrapolation could not be approved. Many of these decisions were later reversed but there remains uncertainty, as highlighted by the divergent position statement offered by the CHMP for Flixabi.

The main concern with biosimilars is the potential for developing anti-drug antibodies, something that the trials in RA are not able to rule out for Crohn’s disease due to the dampening effect of the concomitant use of methotrexate and AS trials cannot rule out as patients with the condition historically have lower risk of anti-drug antibodies than CD patients⁹⁴. The consequences of developing anti-drug antibodies are:

- Alterations in the drug pharmacokinetics and bioavailability;
- Reductions in drug efficacy;
- Cross reaction with endogenous proteins and inhibition of the latter’s physiological behaviour;
- Allergic drug reactions, such as infusion reactions.

Further uncertainty arises as immunogenicity results depend upon many factors including the time point of sampling, the technical protocols adhered to in taking and storing the samples, the treatment dosing and schedule and the different assays used⁹⁵.

Uncertainty can also be introduced with regards to the use of non-inferiority trials and the choice of non-inferiority margin, which is pre-specified in comparative trials for biosimilars^{96,97}. Traditional RCTs compare a new treatment against an existing one and aim to demonstrate superiority of the treatment, which is achieved with a point estimate for the difference in efficacy, supported by a 95% confidence interval to demonstrate statistical significance. A non-inferiority trial, however, is hoping to demonstrate that the new product is not worse than the existing product, with differences in efficacy allowed within a pre-specified margin, subject to an assessment of statistical significance through a 95% confidence interval⁹⁷. Non-inferiority trials are used for biosimilars because the interventions are assumed equally efficacious. In the RA trial used to demonstrate non-inferiority for Inflectra, the non-inferiority margin is set to $\pm 15\%$. Consequently, Inflectra can be deemed non-inferior with marginally lower efficacy evidenced in RA. In the context of BRA, where the focus is on incremental benefits and risks, a marginal difference may be significant. However, such uncertainties appear to be accepted in exchange for the cost-saving opportunities.

1.3.3.2. Uncertainties in decision modelling

The goal in decision modelling is to extend statistical analysis to include the effects of uncertainty and value judgements on the overall BRA of drugs²². Usually, decision modelling input uncertainty is primarily on harms. Efficacy of a treatment is reasonably certain where clinical trials are conducted as studies are powered to detect this with accuracy. However, in biosimilars, even the efficacy is uncertain, greatly adding to overall uncertainty in benefit-risk. The assumption of equivalent efficacy leads to the approval of biosimilars by the UK NHS on the basis of cost-minimisation³⁴. However, certainty of equivalent efficacy requires head to head trials, which are rarely available for biosimilars³³. It is therefore unclear whether cost-minimisation analysis is appropriate and whether the price reduction compensates enough for the increased uncertainty faced by the HTA agency. Due to the level of uncertainty, a modelling method is required with sensitivity analyses and scenario analyses to test the impact of the uncertainties on the decision

of the HTA. Indeed, this approach has been previously suggested by Stewart et al (2010)³³ who propose that HTA should use a model of cost-utility analysis, which makes use of efficacy, utility and cost data based on the originator drug and use threshold analysis of treatment efficacy to determine the point at which the willingness to pay threshold is exceeded.

1.4. Thesis objective and structure

BRA is a necessary process for summarising the effectiveness and safety profile of an intervention, to provide evidence that can be used by decision makers in a range of settings. Understanding and quantifying the harms from treatments is especially problematic, particularly those related to long-term treatment. As an example, in the field of Crohn's disease research, the motivating example of this thesis, outcome measurement tools have been developed over the years but are no longer considered valid, and there is a current shift away from clinical-composite outcome measures towards objective measures of inflammation alongside patient reported outcome measures. There is a need to understand what is being measured, what should be measured (and how) and how else we can capture the scale of benefits and harms to provide evidence to facilitate decision-making. Further uncertainty is present in decision-making related to biosimilars, stemming from the use of extrapolated evidence assessed in qualitative benefit-risk frameworks.

This thesis aims to investigate methods for assessing the benefit-risk balance of therapies, including identifying sources of harms data and developing a quantitative framework for assessing whether the cost savings of biosimilars justify the increased uncertainties regarding efficacy and safety.

Chapter 2 reports the pattern of endpoints and adverse events measured in randomised controlled trials (RCTs) of treatments to induce or maintain remission in adults with Crohn's disease. The results highlight the reliance upon outcome measurement tools that are now considered invalid for measuring disease status. There is a need for a core outcome set for Crohn's disease to standardise outcomes measurement, including harms, and reporting to ensure that

good quality data are available on benefits and risks of treatments. The trial endpoints were disaggregated into individual signs, symptoms and events and categorised into a framework in Chapter 3. In the absence of a core outcome set for Crohn's disease, the results were compared against a core set for IBD and the dominant outcome measurement tools used in Crohn's disease trials to highlight the gaps in measurement and provide a starting point for the development of a new outcome measurement tool.

Chapter 4 proposes a method to identify and quantify harms to attempt to fully characterise the safety profile of drugs, making use of the SPC documents that result from the regulatory process.

Chapter 5 uses some of the methods discussed here to develop a decision-analytic model to help regulators involved in HTA to quantify what price reduction is necessary to trade off for the increased uncertainty involved in biosimilar infliximab.

The final chapter, Chapter 6, summarises the findings of the previous chapters, reflects upon the implications for both clinical practice and research, and suggests areas for future research.

Chapter 2: A systematic review of outcomes and adverse events in randomised controlled trials in Crohn's disease

2.1. Introduction

Defining the key outcomes of therapeutic interventions and the best way to measure those outcomes is essential for clinical and regulatory decision-making. Due to the complexity of Crohn's disease and the multitude of treatment choices, many different measurements of outcomes have historically been reported in clinical trials, for example response (outcome), might be measured with the Crohn's Disease Activity Index (outcome measurement tool) as a 70 point score reduction (outcome measurement). The Crohn's literature is characterised by an array of instruments such as disease activity indices and quality of life questionnaires used by researchers to measure the variety of different outcomes^{98,99}. Clinical and regulatory decision making also relies on the availability of good information on the unintended effects, or harms, from treatments, which are reported as adverse events and study withdrawals in clinical trials. Accurate reporting of the outcomes from treatment enables the synthesis of data to establish more certain estimates of the effect of treatment and identify potential harms. This supports the assessment of the benefit-risk balance at the clinical level as well as at the regulator level and for the NHS.

Diversity in reported outcomes and measurement instruments may hinder the comparison of results within systematic reviews, due to heterogeneity in outcome measurement, but may also inhibit the meaningful interpretation of individual studies⁴⁸. One way to mitigate the problems is the introduction of an agreed minimum set of standardised outcomes, to be measured and reported in all trials for a particular disease or condition, referred to as a core outcome set (COS)^{48,49}. There is no COS for Crohn's disease, although a model has been proposed for classifying outcomes for inflammatory bowel disease (IBD) using the World Health Organisation (WHO) International Classification of Functioning, Disability and Health (ICF). The result is the ICF comprehensive core set for IBD and a brief core set for IBD, the latter known as the IBD disability

index.¹⁰⁰ In 2017, the International Consortium for Health Outcomes Measurement (ICHOM) developed a 'Standard Set' for IBD with recommendations for measuring outcomes in routine care to support benchmarking¹⁰¹. Also recently published are a study protocol for the development of a COS for IBD¹⁰² and a COS for fistulising Crohn's disease¹⁰³, indicating the importance of this research area. Future trial design and COS development for Crohn's disease would benefit from a systematic synthesis of outcome reporting across published clinical trials.

In this chapter, the literature was systematically reviewed to extract data on the outcomes and measurement instruments used (trial endpoints), and the adverse events and study withdrawals reported, in randomised clinical trials (RCTs) of treatments for Crohn's disease (CD). The aims were to explore the extent of heterogeneity among existing trials, to examine time trends in reporting and to generate insights to support future trial design and COS development. The results are supported by recently published literature in this research area^{103,104}.

2.2. Methods

2.2.1. Protocol and registration

A protocol with defined aims, objectives and methods was developed for the review. The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42016027656 <http://www.crd.york.ac.uk/PROSPERO>) and with the Core Outcome Measures in Effectiveness Trials (COMET) database (<http://www.comet-initiative.org/studies/details/867>). The protocol for the systematic review is in Appendix 2.

2.2.2. Information sources

A systematic electronic search was used to retrieve all RCTs conducted in an adult population using any treatments for Crohn's disease to 3rd November 2015. No date limits were placed on the searches. The following electronic databases were searched: Cochrane Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). It was possible to restrict the searches to adult only studies in all databases

except CENTRAL. The disease term 'Crohn's disease' and the key word 'outcome' was used. The detailed search strategies used for all databases are provided in Appendix 3.

2.2.3. Inclusion and exclusion criteria

The eligibility criteria were designed to maximise the data captured by the review. As discussed in Section 1.2.3.2, treatment options for patients with Crohn's are varied and patients tend to move through numerous treatment types during the course of their disease, often receiving a combination of treatments at any period in time. Ultimately, all interventions that aim to achieve remission, maintain remission or treat complications were included.

2.2.3.1. *Inclusion criteria*

- Adults (aged 18 years and over).
- Due to the overlap in outcomes with other inflammatory bowel diseases (IBD), the scope of the review included IBD, as long as outcomes were specified for Crohn's.
- Interventions including drug therapies (corticosteroids, 5-ASAs, immunosuppressants, biologics and antibiotics), surgery and non-drug therapies (enteral nutrition, complementary and alternative medicine (CAM), probiotics and prebiotics) and treatments for complications of Crohn's disease (strictures, fissures, abscesses and perforations). Innovative interventions such as granulocyte or monocyte apheresis were also included.
- All comparator interventions, such as placebo, alternative dose or standard treatment.
- All years of publication.
- Randomised controlled trials.
- English language.
- Full text available.

2.2.3.2. *Exclusion criteria*

- Patients aged less than 18 years. Children with Crohn's disease face a range of outcomes that are not relevant to adults (related to growth, for example), which leads to differences between the two groups in the outcomes that are considered important^{105,106}.
- Other specific forms of IBD, including ulcerative colitis, other forms of colitis such as microscopic, ischaemic, collagenous and lymphocytic, and other forms of bowel disease, such as diverticulitis, irritable bowel syndrome, colon cancer and intestinal.
- Treatments for common sequelae and comorbidities (commonly iron-deficiency anaemia, osteoporosis, vitamin B12 or folate deficiency anaemia, erythema nodosum, pyoderma gangrenosum, inflammation of the eyes, blood clots, primary sclerosing cholangitis and ankylosing spondylitis). Some methods used for therapy, such as endoscopy, when used only for diagnosis. Pre-surgery interventions, such as bowel preparation.
- Foreign language studies.
- Abstract only studies.
- Systematic reviews, non-randomised controlled trials, case series and case studies, letters, editorials, commentaries.

2.2.4. *Study selection*

The records retrieved from the search were exported to Microsoft Excel and combined. Duplicates were removed after a complete list of studies was identified from the searches. Two reviewers (HC and JJK) independently assessed a random sample of 100 studies resulting from the search against the screening criteria in the title screening and abstract screening stages. Discrepancies were resolved by discussion. Following good inter-rater reliability, HC screened the remaining papers independently with reference to JJK when uncertain of eligibility. Full copies were

obtained of all potentially eligible studies and reassessed independently by the primary researcher. Reference was made to JJK where needed.

A critique of the methodological quality of the studies was unnecessary, as this project did not involve synthesis of outcome data.

2.2.5. Data Collection process

A pilot data extraction template was developed and tested. JJK reviewed the template and offered feedback, which led to modifications such as the inclusion of the country of the study (or the lead author when the study was multi-centred). Data were extracted from the eligible studies with an initial sample of ten checked by JJK. Regular reporting to the PhD supervision team provided a check that all outcomes had been identified.

2.2.6. Demographic data items

The following demographic information was collected from each study:

1. Author(s).
2. Year and journal of publication.
3. Country of study / lead author.
4. Sample size.
5. Disease behaviour in study population.
6. Duration of follow up.
7. Intervention(s) under investigation.
8. Comparator intervention(s).

Trials were categorised as induction (of remission) where participants had active disease or maintenance (of remission) where patients were in remission. Some studies had patients with active disease entering but the study aimed to achieve remission and then maintain it, so followed up only those patients who achieved remission. Trials were sub-categorised as 'medical induction' when patients received medical therapies and had active disease; 'surgical induction' when

patients had active disease and received surgical therapy; 'maintenance of medically-induced remission' where patients received interventions to maintain remission achieved through medical interventions; and 'maintenance of surgically-induced remission' where patients received interventions to maintain remission achieved through surgery. Studies were flagged if they were of interventions to treat solely patients with fistulising disease to identify any differences in outcomes reporting.

The drug name and dosage instructions of the intervention under investigation was recorded and the interventions grouped into the main intervention types for Crohn's disease:

- **5-ASAs** or aminosalicylates to treat inflammation such as mesalazine and sulphasalazine.
- **Antibiotics** to treat infections such as metronidazole, ciprofloxacin and clarithromycin.
- **Biologics** to treat inflammation such as infliximab, adalimumab, certolizumab pegol and natalizumab.
- **Corticosteroids** to treat inflammation such as prednisolone, hydrocortisone and budesonide.
- **Dietary** treatments provide all required nutrition whilst allowing the bowel to rest. They are either liquid foods such as polymeric and elemental diets or parenteral diets, which are delivered intravenously. Interventions of this type can also be diets to reduce symptoms such as low micro particle diets, whole-wheat diets or low residue diets. Finally, they may also be interventions that involve dietary supplements such as omega 3 fish oils, oral glutamine and lactulose syrup.
- **Immunosuppressives** to treat inflammation such as azathioprine, mercaptopurine, methotrexate and cyclosporine.
- **Surgery** to remove severely inflamed sections of bowel or repair strictures or fistula.

- **Complementary and alternative medicines (CAM)** such as prebiotics and probiotics, acupuncture, cannabis, exercise, relaxation therapy, osteopathy, trichuris suis ova and plant extracts.

Other interventions were used which are not part of the standard therapies for Crohn's disease. Examples include novel treatments in the earliest stages of research, such as blood apheresis to remove cells involved in inflammation and spherical carbon adsorbent, which absorbs toxins that may be involved in inflammation so that they can be excreted through faeces. These were grouped together as 'other interventions'. Where trials examined combination therapies, they were classified as 'combination interventions'.

2.2.7. Outcomes data items

The following data on trial endpoints was extracted from each trial report:

1. The designation of the endpoint as primary, secondary or not specified.
2. The outcome.
3. The outcome measurement tool.
4. The outcome measurement.

The outcomes were categorised as follows^{106–108}:

- Biomarker and serologic outcomes, which are measurable characteristics indicating disease process. For Crohn's disease, this could include a blood test or faecal sample such as C-reactive protein or faecal calprotectin, which are indicators of intestinal inflammation.
- Clinical or composite-clinical outcomes, such as clinician assessment of symptoms or weight measurement or disease activity indices.
- Economic outcomes, including the cost of interventions and associated utility values.

- Endoscopic outcomes, which were measurements resulting from endoscopies and included scores and the presence or absence of ulcers in the intestine.
- Histologic outcomes, which were measurements based upon tissue samples taken from the intestine, frequently reported as scores.
- Patient reported outcomes (PROs), such as daily diary reporting of symptoms such as diarrhoea, blood in the stool or abdominal pain and quality of life questionnaires.
- Safety-related outcomes, which were pre-specified as trial endpoints in the methods sections of the paper.

2.2.8. Adverse event data items

Data were taken from tables reporting adverse events and the descriptive text, where present in the reports. Some papers reported the occurrence, or not, of pre-specified serious adverse events such as deaths. These were recorded as an adverse event report event if no events were observed in the study.

Adverse event reporting was recorded in specific categories: adverse events (AEs), serious AEs, treatment-related AEs, treatment-related serious AEs, study withdrawal, abnormal laboratory results and AEs by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA)¹⁰⁹.

The adverse events were recorded verbatim and standardised using the Medical Dictionary for Regulatory Activities (MedDRA) terminology web-based browser.¹¹⁰ MedDRA is an international medical terminology developed for biopharmaceutical regulatory purposes. It is structured in a hierarchy with five levels:

1. Lowest level terms (LLTs) are the lowest level and allow for the capture of different terms for the same medical concept, including abbreviations, different word order and slight variants.

2. Preferred terms (PTs) are a single medical concept for a symptom, sign, disease, diagnosis, therapeutic indication, investigation or medical or surgical procedure.
Many LLTs can link to a PT.
3. High-level terms (HLTs) are a grouping level for PTs. They link together PTs that are related by anatomy, pathology, physiology, aetiology or function,
4. High-level group terms (HLGTs) group together HLTs that are related by anatomy, pathology, physiology, aetiology or function.
5. System organ class (SOC) is the highest level and gives the broadest concept. SOCs may be based upon aetiology (e.g. infections and infestations), manifestation site (e.g. gastrointestinal disorders) or purpose (e.g. surgical and medical procedures).
PTs can be linked to more than one SOC but will only have one primary SOC.

Each level of the MedDRA hierarchy was recorded for every adverse event. Where a difference was noted between the SOC reported in the paper and that recorded as the primary SOC in MedDRA, the primary SOC was recorded.

2.2.9. Study withdrawals

Data were extracted on reports of participants who discontinued treatment. Study withdrawals were categorized as due to AEs, serious AEs, treatment-related AEs, treatment-related serious AEs, treatment failure (insufficient therapeutic effect, exacerbation of CD, development of complications or need for additional therapy, surgery or hospitalisation) or other reasons (protocol non-compliance, lost to follow-up, prohibited medicine use or withdrawal of consent).

2.2.10. Data presentation

A comprehensive record of efficacy and safety-related outcomes was generated and organised by outcome category as described in section 2.2.7. The main analysis of the efficacy outcomes focused on those designated as primary and secondary end-points in the papers. A similar approach was adopted for safety-related outcomes, which were specified as primary and

secondary endpoints. All reported data for AEs and study withdrawals were analysed. AE reporting was considered at two levels of the MedDRA hierarchy: SOC and HLT, the latter of which is considered a clinically relevant grouping of MedDRA preferred terms¹⁰⁹.

A secondary analysis considered the reporting of outcomes that were not specified as primary or secondary end-points. To mirror the increased focus on the importance of objective measures of inflammation and mucosal healing¹¹¹, the numbers of studies reporting any additional endoscopic or histologic outcomes or the faecal calprotectin biomarker was assessed.

The proportion of studies reporting each category of outcome (section 2.2.7) was calculated, by trial category as described in section 2.2.6. The results were stratified a priori into pre-2009 and 2009 onwards, to capture differences in the most recent trials. The changes over time in reporting was summarised in matrix form with outcome categories listed in rows and frequency of outcome reporting plotted in greyscale on a time axis¹⁰⁸.

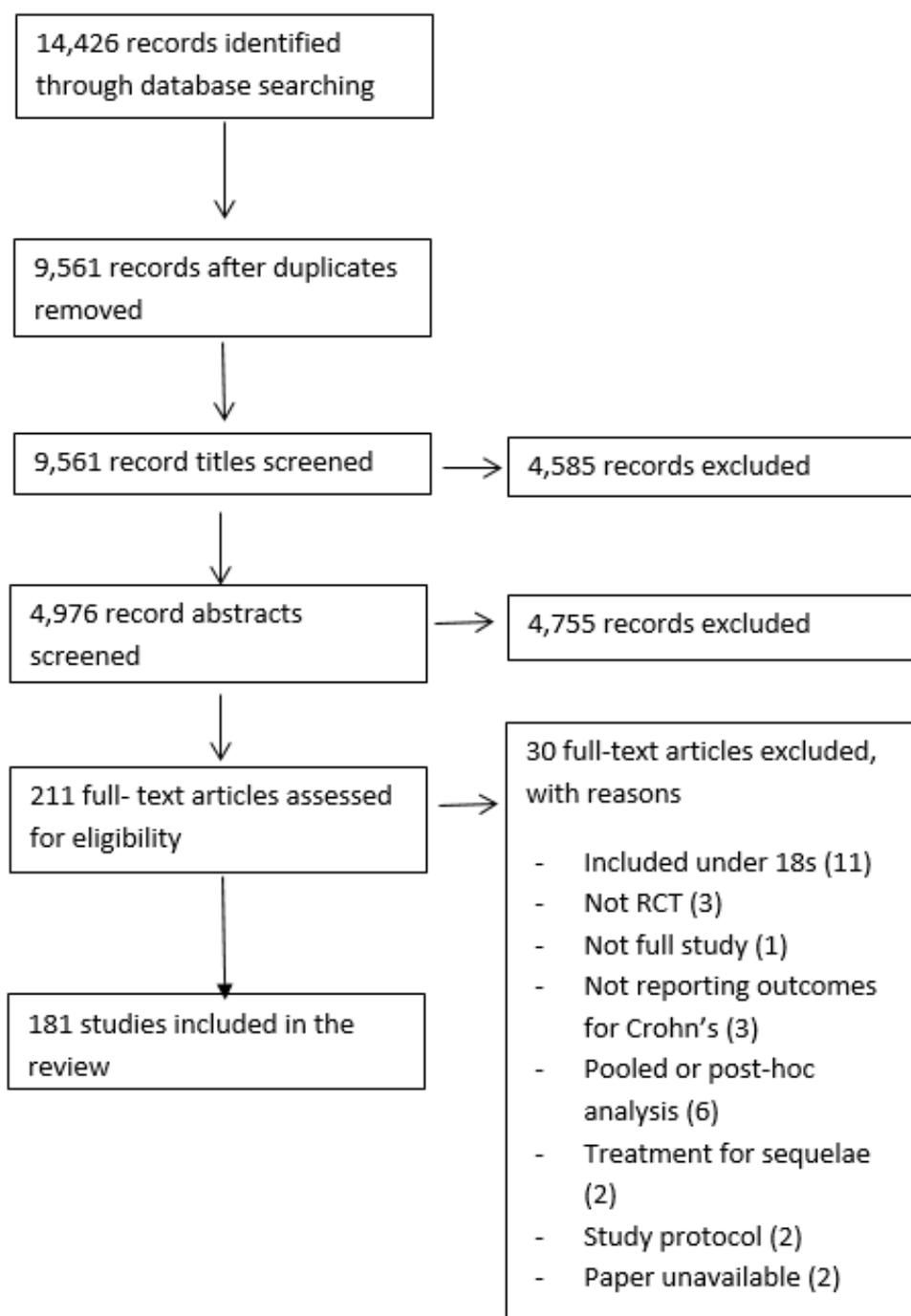
The review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and harms checklist^{112,113}.

2.3. Results

2.3.1. Study selection

The database searches yielded 9,561 records after duplicates were removed. Title screening excluded 4,585 records and abstract screening excluded a further 4,755. The results of the initial double screening were comparable, which allowed for the rest of the sample to be screened independently. The large number of exclusions is indicative of the broad nature of the search, which identified numerous records related to Crohn's disease and outcomes, but not to treatments for Crohn's disease. The full text reports were obtained for 211 records. Thirty of these were excluded upon full review due to the reasons indicated in Figure 7. The review considered the 181 records that met the criteria for inclusion.

Figure 7: PRISMA flow diagram



2.3.2. Study demographics

The review included 181 studies and a summary of their characteristics is shown in Table 2 (full list in Appendix table 6). Induction of remission was the focus of 110 studies: 104 (94.5%) through medical approaches^{114,115,124,214–217,125–133,116,134–143,117,144–153,118,154–163,119,164–173,120,174–183,121,184–193,122,194–203,123,204–213} and 6 (5.5%) through surgical approaches^{218–223}. Nine (of 110, 8.2%) induction

studies solely treated patients with fistula with medical ^{135,163,178,185,190,209,212} or surgical ^{218,219} therapies.

Maintenance of remission was the focus of 71 studies: 52 (73.2%) sought to maintain remission achieved through medical therapies ^{224,225,234–243,226,244–253,227,254–263,228,264–273,229,274,275,230–233} and 19 (26.8%) aimed to maintain surgically-induced remission ^{276,277,286–294,278–285}. One study aimed to maintain medically induced remission in patients with fistulising disease²⁴⁵.

Table 2: Characteristics of Randomised-Controlled Trials in Crohn's Disease

	Induction (n=110)	Maintenance (n=71)	Total (n=181)
Trial participants	13,153	10,697	23,850
Trial participants (median (IQR))	77 (36-169)	89 (56-167)	83 (40-168)
Trial year publication			
1979-2008	78 (70.1%)	47 (66.2%)	125 (69.1%)
2009-2015	32 (29.1%)	24 (33.8%)	56 (30.9%)
Country of lead author			
UK and Europe	61 (55.5%)	40 (56.3%)	101 (55.8%)
USA and Canada	39 (35.5%)	24 (33.8%)	63 (34.8%)
Rest of world	10 (9.1%)	7 (9.9%)	17 (9.4%)
Subgroup			
Medically induced	104 (94.5%)	52 (73.2%)	156 (86.2%)
Fistula	7 (6.4%)	1 (1.4%)	
Surgically induced	6 (5.5%)	19 (26.8%)	25 (13.8%)
Fistula	2 (1.8%)	0	
Intervention of interest			
5-ASAs	3 (2.7%)	8 (11.3%)	11 (6.1%)
Antibiotics	8 (7.3%)	3 (4.2%)	11 (6.1%)
Biologics	40 (36.4%)	15 (21.1%)	55 (30.4%)
Corticosteroids	9 (8.2%)	9 (12.7%)	18 (9.9%)
Immunosuppressants	7 (6.4%)	7 (9.9%)	14 (7.7%)
Surgery	6 (5.5%)	0	6 (3.3%)
Dietary	16 (14.5%)	5 (7.0%)	21 (11.6%)
CAM, prebiotics/probiotics	8 (7.3%)	15 (21.1%)	23 (12.7%)
Combination interventions	6 (5.5%)	8 (11.3%)	14 (7.7%)
Other	7 (6.4%)	1 (1.4%)	8 (4.4%)
Comparator intervention			
Placebo	66 (60.0%)	45 (63.4%)	111 (61.3%)
Active	44 (40.0%)	26 (36.6%)	70 (38.7%)
Follow up weeks (median (IQR))	16 (8.0-25.1)	52.0 (48.0-60.0)	25.1 (12.0-52.0)
Note: 5-ASAs – aminosalicylates; CAM – complementary and alternative medicine; IQR – interquartile range			

2.3.2.1. Year of publication

The earliest study included in the review was from 1979. Over 30% of studies were published after 2009 (56 of 181, 30.9%).

2.3.2.2. Country of research and journal of publication

Examination of the studies by the country of the research (or lead author in multi-centre studies), highlights a geographical concentration. 90.6% (164 of 181) of all studies either took place or had a lead author residing in Europe or North America. The vast majority, 74.6% (135/181), of the studies were either conducted in, or led from, one of six countries: the USA (45/181, 24.9%), Germany (24/182, 13.2%), the UK (22/181, 12.2%), Canada (18/181, 9.9%), Italy (15/181, 8.3%) and France (11/181, 6.1%).

Similarly, there is a concentration by journal of publication as 47.0% (85/181) of the included studies are published in one of three journals: Gastroenterology, Gut and Alimentary Pharmacology & Therapeutics. The remaining 53% of articles (96/181) are published in 36 journals.

2.3.2.3. Sample size and trial length

In total, 23,850 patients were involved in the studies, with median sample size of 77 (IQR: 36-169) in induction studies and 89 (IQR: 40-168) in maintenance studies. Follow up was a median 16 weeks (IQR: 8.0 - 25.1) in induction studies and 52 weeks (IQR: 48.0-60.0) in maintenance studies.

2.3.2.4. Intervention of interest and comparator

Over 90% of the studies considered a single therapy (167/181, 92.3%). Biologics were the intervention of interest in 33.7% studies (61 of 181), either as monotherapy or part of a combination therapy, demonstrating the level of research interest in this particular treatment. Induction trials were also common for dietary interventions (16/110, 14.5%) and corticosteroids (9/110, 8.2%). Maintenance trials were common for CAM therapies including prebiotics and probiotics (15/71, 21.1%) and corticosteroids 9/71 (12.7%).

Placebo treatments were the comparator in the majority of trials (111/181, 61.3%). Just over a third of studies (70/181, 38.7%) used an active comparator treatment. Active treatments include the use of standard medication, alternative therapies, alternative doses of the treatment of interest or tapering or withdrawal of a particular treatment. EMA guidance for Crohn's disease recommends that active treatments should be used for trials supporting a first line indication and placebo should be used as an add-on comparator for add-on treatments⁶⁸. This indicates that the majority of trials identified are for add-on treatments rather than first line.

2.3.3. Outcomes

Outcomes data were extracted from the 181 included studies. A median of nine outcomes were reported per paper (IQR: 6-11). Almost all the studies (174/181, 96.1%) reported primary or secondary outcomes, only seven studies (3.9%) did not specify either primary or secondary outcomes. 95.6% (173/181) of studies reported primary outcomes, with a median of one primary outcome per paper (IQR: 1-2). Three quarters (136/181, 75.1%) of studies reported secondary outcomes with a median of three outcomes reported per paper (IQR: 1-5). The reporting of outcomes not specified as primary or secondary endpoints was common (158/181, 87.3%) and was consistent across the time periods. A median of three outcomes per paper were reported that were not specified as primary or secondary endpoints (IQR: 2-6).

Table 3 shows a summary of the primary and secondary outcomes reported in CD RCTs by category and highlights the wide range of outcomes and outcome measures. The full detail of reported primary and secondary outcomes by outcome categories type are provided in Appendix table 7 to Appendix table 12.

Table 3: Primary and Secondary Efficacy Outcomes and Measurement Tools in Crohn's Disease Randomised Controlled Trials

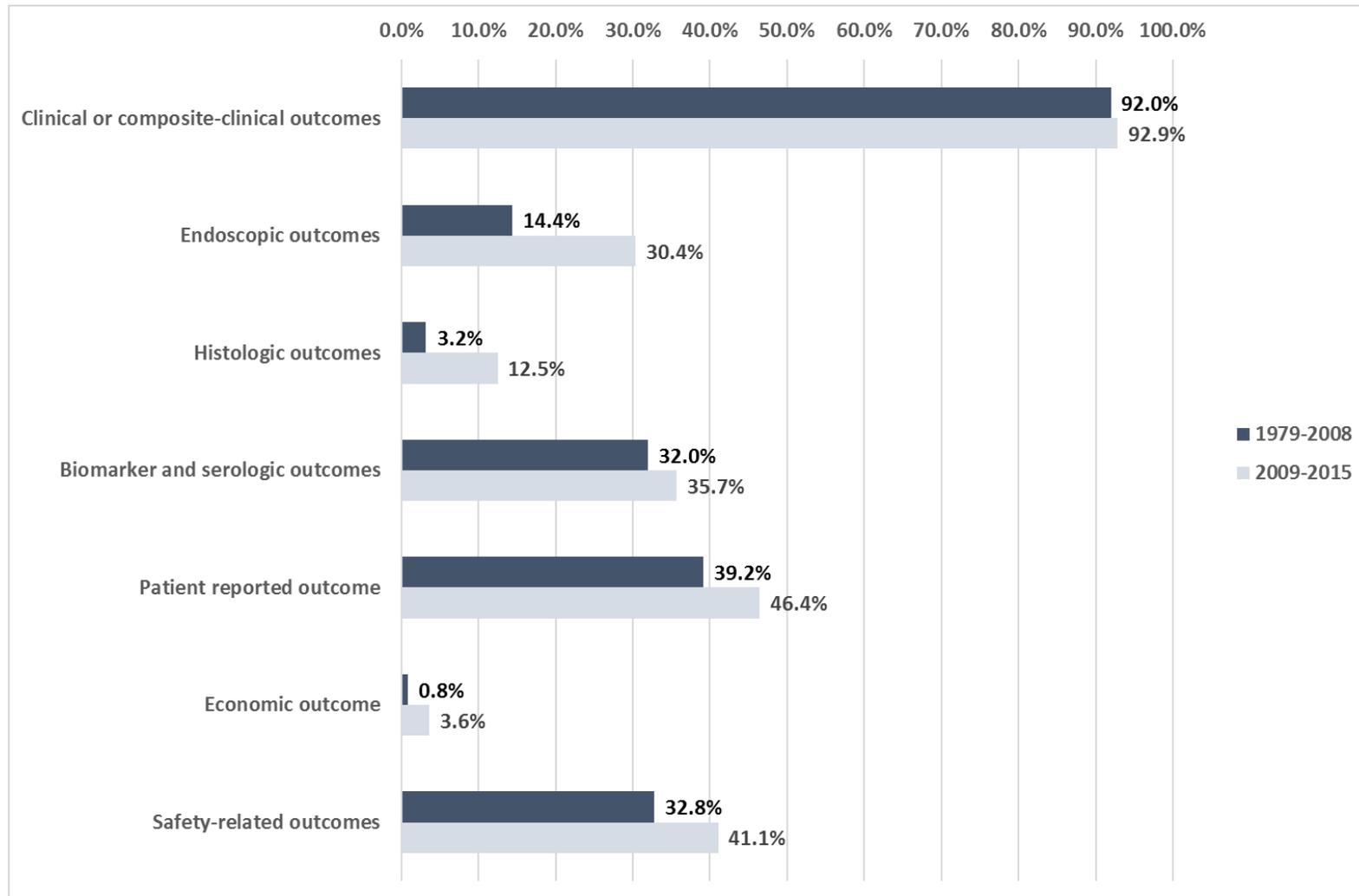
Outcome category	Primary or Secondary Outcomes	Other Outcomes	Measurement Tools
Clinical or composite-clinical outcomes	Clinical response Clinical remission Disease relapse or worsening Fistula remission / response Corticosteroid-free remission / response Recurrence Corticosteroid-sparing Sustained remission / response Change in individual sub score components Combined clinical and endoscopic remission / recurrence Post-operative recovery Sustained corticosteroid-free remission Sustained fistula remission Complete response Treatment compliance	Treatment acceptability	Crohn's Disease Activity Index Harvey Bradshaw Index Perianal Disease Activity Index Physician Global Assessment Van Hees Activity Index European Co-operative Crohn's Disease Study based ranking system Severity and Activity Index Clinical recurrence grading scale Dutch Index International Organisation of Inflammatory Bowel Disease (IOIBD) score Partial Harvey Bradshaw Index Present Score
Endoscopic outcomes	Endoscopic recurrence Endoscopic response Endoscopic mucosal healing Endoscopic remission		Rutgeerts endoscopic score Crohn's Disease Endoscopic Index of Severity Simple Endoscopic Score for Severity D'Haen's endoscopic categories Marteau endoscopic score Radiological grading scale
Histologic outcomes	Histologic recurrence Tissue cytokine, leukocyte, receptor or gene expression Histologic response Histologic remission	Tissue bacteria concentrations	Average Histology Score D'Haens-Geboes score Dieleman histological score Histological Activity Score Regueiro histology score
Biomarker and serologic outcomes	Serum C-reactive protein Serum erythrocyte sedimentation rate Serum full blood count and subsets Antidrug antibodies Drug concentration and pharmacokinetics Serum cortisol level Serum protein concentrations Intestinal permeability Serum albumin Autoantibodies Faecal calprotectin Serum lymphocyte count and subset expression Serum cytokine or immunoglobulin levels	Body mass Faecal bacteria concentrations Serum fatty acids Treatment compliance	
Economic outcomes	Cost of treatment Utility		Quality-Adjusted Life Years

Outcome category	Primary or Secondary Outcomes	Other Outcomes	Measurement Tools
Patient-reported outcomes	Quality of life Pain Defecation functions Bowel symptoms Treatment compliance Treatment acceptability		IBDQ SF-36 (and component sub scores) Patient Global Assessment Visual analogue scale Gastrointestinal Quality of Life Index Hamilton Depression Scale Short IBDQ Adapted Vaizey Faecal Incontinence Score Assessment of Quality of Life Questionnaire Beck's Depression Inventory Fatigue Impact Scale Hospital Anxiety and Depression Scale IBD Quality of Life Scale IBS Severity Scoring System IBD Self-Efficacy Scale IBD Stress Index Medical Adherence Scale Perceived Stress Questionnaire – Recent Psychiatric and Socio-communicative finding standardised clinical interview Quality of Life instrument SF-12 Short Health Scale State Trait Anxiety Inventory instrument
Safety-related outcomes	Adverse events Abnormal laboratory or ECG parameters Complications of surgery Death	Adverse events Treatment related adverse events Serious adverse events Treatment related serious adverse events Study withdrawal due to AEs, treatment failure and other reasons.	Medical Dictionary for Regulatory Activities Coding Symbols for a Thesaurus of Adverse Reactions Terms WHO Toxicity Grading Criteria

Note: AEs, adverse events; IBDQ, inflammatory bowel disease questionnaire; SF-36, Short-Form 36; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SF-12, Short-Form 12; ECG, electrocardiogram; WHO, World Health Organisation.

Figure 8 shows the evolution of primary and secondary outcomes reporting over the decades of Crohn's disease RCTs. In general, the reporting of all outcome categories has increased over time.

Figure 8: Proportion of Crohn's Disease RCTs reporting key primary and secondary outcome categories, stratified by decade of publication



2.3.4. Clinical or composite-clinical efficacy outcomes and definitions

As shown in Figure 8, clinical or composite-clinical efficacy outcomes were reported as primary or secondary endpoints in 92.3% of trials, which was consistent across the two time-periods. Table 4 shows the top nine reported clinical or composite-clinical efficacy outcomes. The full detail of the primary and secondary clinical or composite-clinical outcomes is shown in Appendix table 7.

Table 4: Clinical and composite-clinical primary and secondary outcomes reported and number of studies reporting, by trial category and sub-category

	Induction of remission				Maintenance of remission			
	Total	Medical	Surgical	Fistula	Total	Medically induced	Surgically induced	Fistula
Outcome	110 n(%)	104 n(%)	6 n(%)	9 n(%)	71 n(%)	52 n(%)	19 n(%)	1 n(%)
Clinical response	77 (70.0)	75 (72.1)	2 (33.3)	7 (77.8)	31 (43.7)	26 (50.0)	5 (26.3)	1 (100)
Clinical remission	72 (65.5)	72 (69.2)	0	0	14 (19.7)	14 (26.9)	0	0
Disease relapse or worsening	14 (12.7)	13 (12.5)	1 (16.7)	0	38 (53.5)	38 (73.1)	0	1 (100)
Recurrence	1 (0.9)	0	1 (16.7)	0	14 (19.7)	0	14 (73.7)	0
Fistula response	14 (12.7)	12 (10.5)	2 (33.3)	9 (100)	1 (1.4)	1 (1.9)	0	0
Fistula remission	10 (9.1)	9 (7.9)	1 (16.7)	6 (66.7)	2 (3.8)	2 (2.8)	0	0
Corticosteroid sparing	11 (10.0)	11 (10.6)	0	0	3 (4.2)	3 (5.8)	0	0
Corticosteroid-free remission	8 (7.3)	8 (7.7)	0	0	4 (5.6)	4 (7.7)	0	0
Sustained remission	4 (3.6)	4 (3.8)	0	0	7 (9.9)	7 (13.5)	1 (5.3)	0

NB: percentages are calculated from the number of studies in the top line of each column.

Clinical response was reported by 70.0% (77 of 110) induction studies; 75 (of 104, 72.1%) medical^{117,118,140–149,120,150–152,155,157–162,121,163–167,169–173,128,176–180,182–184,186,187,129,188–195,197,198,131,199–206,208,210,135,211–216,136,139} and two (of six, 33.3%) surgical^{218,219} interventions. Clinical response was reported less frequently in maintenance trials (31 of 71, 43.7%) and was more commonly reported in studies of maintenance of remission from medical interventions (26, 50%)^{224,227,253–256,259–}

262,264,266,230,267,268,270–272,275,234,239,241,245,248–250 than from surgical interventions (5, 26.3%)^{278,279,288,291,293}. Clinical response was an outcome in 80% of studies that included only patients with fistulae (seven of nine induction and one maintenance)^{135,163,178,190,212,218,219,245}.

Clinical remission was reported in 65.5% of induction studies (72 of 110)^{115,117,132,136,137,139,140,142,143,146,147,149,118,150–154,157–161,119,162,164–172,120,173,174,176,177,179,182–184,186,188,121,189,191,192,195–200,202,123,203–206,210,211,213–216,124,217,125,127} and 19.7% of maintenance studies (14 of 71)^{224,230,260,264,268,270,240,242,246,252–255,257}, all of which examined medical therapies (69.2% of medical induction and 26.9% of maintenance of medically induced remission studies). Clinical remission was not reported as a primary or secondary outcome in any surgical studies nor those focused on patients with fistulae.

Disease relapse or worsening was a primary or secondary outcome in 12.7% of induction studies (13 medical^{114,121,202,211,217,124,141,148,151,170,177,187,188} and one surgical²²³) and 38 (53.5%) studies of maintenance of medically induced remission^{224,225,235–244,227,245,247–252,257,259,260,228,261,262,265–267,271,272,275,229–234}. Recurrence was an outcome reported in 73.7% of maintenance studies of surgery-induced remission (14 of 19)^{278,280,289,290,292,294,281–288} and one surgical induction study²²².

Fistula response and remission were commonly reported in medical induction studies for patients with fistulae (nine of nine^{135,163,178,185,190,209,212,218,219} and six of nine^{135,185,190,209,212,218}, respectively). Overall, 14 induction studies^{135,143,209,212,218,219,146,162,163,172,178,182,185,190} and one maintenance study²⁵⁰ reported fistula response and 10 induction^{135,146,155,162,182,185,190,209,212,218} and two maintenance studies^{250,253} reported fistula remission.

Corticosteroid sparing and corticosteroid-free remission were reported in 11^{117,128,187,136,142,144,151,155,174,175,180} and eight^{128,136,142,151,155,175,181,187} medical induction studies and three^{227,248,250} and four^{253,255,260,272} maintenance of medically induced remission studies, respectively. All studies, with one exception, were published prior to 2009. Sustained remission was recorded in four medical induction^{184,202,216,217} and seven maintenance studies of medically

induced remission^{224,229,243,246,267,270,273}. Corticosteroid sparing, corticosteroid-free remission or sustained remission were not reported as outcomes in any surgical induction study or maintenance study of surgically induced remission.

2.3.4.1. Outcome definitions

The Crohn's Disease Activity Index (CDAI) dominated as the primary measurement tool for clinical and clinical-composite primary and secondary outcomes (Table 3) with 77.9% (141 of 181) of studies reporting its use, which was common across both induction (86 of 110)^{114,115,131,132,135-142,117,143-147,149-153,118,154,155,157-162,164,165,120,166-175,121,176,177,179-184,186,187,123,188-192,194-198,125,199-206,210,211,128,212-216,219,129} and maintenance (55 of 71)^{224,225,236,238-241,243-247,227,248-255,257,259,228,260-262,264-268,270,271,229,272,273,275,278-280,282,283,285,286,230,287-289,291,293,231-234} studies. A large number of outcomes were measured with CDAI in the studies including response or remission (in 113 studies), disease relapse or worsening (38 studies), corticosteroid -sparing or -free response or remission (14 studies), sustained remission and response (12 studies) and recurrence (nine studies).

Outcome definitions using the CDAI were heterogeneous with 35 different definitions of response or remission reported in the studies (Appendix table 7). CDAI 100 was the reported response measurement in 38 studies^{120,139,167,169,171,173,176,182,183,188,189,192,142,195,197-199,202-205,213,214,143,215,216,253-255,260,264,268,270,146,149,161,162,164,166}, only one before 2000. CDAI 70 as a primary or secondary response measurement was also reported in 38 studies^{121,129,158,162,164,167,170-172,179,180,182,136,184,188,189,191,194,198,200,201,211,213,140,215,216,245,253,255,264,268,270,142,143,146,151,152,157}, all but three after 2001. Response measures involving changes in the CDAI score mean or median, or mean or median changes in the CDAI score were commonplace across the time-period of the studies. The most common measure involving CDAI was the remission benchmark CDAI <150, which was reported in 81 studies^{115,117,137,139-143,146,147,149,150,118,151-153,157-162,164,120,165-174,121,176,177,179,182-184,186,188,189,191,123,192,195-200,202-204,125,205,206,210,211,213-216,224,230,131,240,246,252-255,257,260,264,268,132,270,136} either as a solo or combination primary or secondary endpoint. However, reporting of CDAI <150

reduced between the two time-periods from 46.4% to 41.4% of studies. Conversely, the reporting of CDAI 70 and CDAI 100 increased between the periods (20.8% to 21.4% and 16.8% to 30.4%, respectively). Fistula studies most commonly reported the change in CDAI score (5, 50%).

Other tools used less frequently to measure clinical response or remission include the Harvey Bradshaw Index (HBI)^{118,127,147,148,186,199,217,230,256,295}, Physician Global Assessments^{118,119,124,147,198,210,279} and the Van Hees Activity Index(VHAI)^{118,140,165,186,230} (Table 3). The Perianal disease Activity Index (PDAI) was used in four (40%) studies of fistula patients and in one non-fistula study^{135,163,190,193,219}.

There were more than 30 definitions of disease worsening or relapse, the majority of which required the CDAI to exceed a benchmark level such as 150, 200 or 250 with, or without an increase from baseline score (Appendix table 7). The need for additional therapy and/or surgery were also commonly used definitions. In maintenance studies, disease recurrence or relapse were frequently defined by benchmark levels of CDAI and the need for additional therapies or surgery. Studies of penetrating disease most commonly used physician assessments of draining fistulas (50% (9, 90.0%) or 100% (6, 60%) reduction from baseline) as trial endpoints. Two (20.0%) studies of fistula patients used imaging techniques, MRI and diagnostic ultrasound, to assess response, one in each time-period^{163,219}.

2.3.5. Endoscopic efficacy outcomes and definitions

The reporting of endoscopic outcomes doubled between the two time-periods, from 14.4% to 30.4% of studies (Figure 8). A summary of outcomes is listed in Table 5 and a full list in Appendix table 8. The reporting of endoscopic outcomes occurred in 31% (22 of 71) of maintenance trials, with reporting more likely in studies of surgically (19 of 19)^{276,277,286–294,278–285} than medically (three of 52)^{225,252,261} induced remission. Endoscopic outcomes were infrequently reported in induction trials (11.8%), with reporting more likely in surgical (three of six)^{219,221,222} than medical (10 of 104)^{139,168,172,175,187,192,201,204,210,211} interventions, and in trials in penetrating disease (1, 10.0%)²¹⁹.

Reporting of endoscopic outcomes is a more recent phenomenon in induction trials, with their first use in a study reported in 2000, as compared with 1984 in maintenance trials.

Table 5: Endoscopic primary and secondary outcomes reported and number of studies reporting, by trial category and sub-category

	Induction of remission				Maintenance of remission			
	Total	Medical	Surgical	Fistula	Total	Medically induced	Surgically induced	Fistula
Number of studies	110	104	6	9	71	52	19	1
Any endoscopic outcome	13 (11.8)	10 (9.6)	3 (50.0)	1 (11.1)	22 (31.0)	3 (5.8)	19 (100)	0
Endoscopic recurrence	2 (1.8)	0	2 (33.3)	0	19 (26.8)	1 (1.9)	18 (94.7)	0
Endoscopic response	10 (9.1)	9 (8.7)	1 (16.7)	1 (11.1)	6 (8.5)	1 (1.9)	4 (21.1)	0
Mucosal healing	2 (1.8)	2 (1.9)	0	0	2 (2.8)	1 (1.9)	1 (5.3)	0
Endoscopic remission	1 (0.9)	1 (1.0)	0	0	0	0	0	0

Note: number of studies (percentage)

Endoscopic recurrence was the most frequently reported endpoint, especially in maintenance trials (19 of 71, 26.8%). Eighteen maintenance studies of surgically achieved remission^{276,277,286,287,289–294,278–285} reported endoscopic recurrence (94.7%) and one of medically achieved remission²²⁵. Only two induction studies^{221,222} reported endoscopic recurrence, both of which were of surgical interventions. Endoscopic response was more commonly reported in induction trials (10 of 110, 9.1%)^{139,168,172,175,187,192,197,201,211,219} than in maintenance trials (6 of 71, 8.5%)^{252,261,276,285,288,291}. Endoscopic mucosal healing was reported in two (of 110, 1.8%) induction^{187,210} and two (of 71, 2.8%) maintenance^{261,288} studies and endoscopic remission in one induction study²⁰¹.

2.3.5.1. Outcome definitions

Endoscopic recurrence was commonly defined with the Rutgeerts endoscopic score, predominantly ≥ 2 ^{278,279,292,294,280,282,284,286,287,289–291}, although a number of benchmarks were used (Appendix table 8). Endoscopic outcomes in induction trials report changes in the Crohn's Disease Endoscopic Index of Severity (CDEIS) score^{139,168,172,175,192,197,201,211,219} or changes in the

Simple Endoscopic Score for Crohn's Disease (SES-CD) score^{187,197,210,219} in place of the Rutgeerts score. The D'Haens²⁶¹ and Marteau²⁹⁰ endoscopic scores were each reported in one trial.

2.3.6. Histologic efficacy outcomes and definitions

Histologic outcomes have been reported with greater frequency since 2009 (Figure 8), but remain uncommonly used (11 of 181, 6.1%) and are unused in studies of fistula patients. Three (of 110, 1.7%) induction studies^{161,201,211} (all medical) reported histologic response, one (of 77, 1.9%) maintenance study of medically induced remission²⁶¹ reported histologic remission and four (of 77, 5.2%) maintenance studies of surgically induced remission^{278,281,287,292} reported histologic recurrence. Three (of 110, 1.7%) induction studies^{139,161,196} and one (of 77, 1.4%) maintenance study²⁹³ reported outcomes related to cytokine expression in mucosal tissues. A number of histology scores are used in the small number of outcomes including D'Haens^{161,211,281,287}, Dieleman²⁰¹ and Reguero²⁹² (Appendix table 9). The reporting of histologic outcomes as additional outcomes increased between the time-periods from 3.2% of studies to 7.1%.

2.3.7. Biomarker outcomes and definitions

Biomarker outcomes were reported in 39 (of 110, 35.5%) induction studies, 38 (of 104, 36.5%) medical interventions^{117,123,148,149,151,155,157,158,162,164,165,168,128,172,176,177,182,186-188,191,192,195,133,199,200,203,205,206,208,211,216,217,136,137,143,145-147} and one (of 6, 16.7%) surgical²¹⁹. Biomarkers were reported in 21 (of 77, 29.6%) maintenance trials, 16 (of 52, 30.8%) of which were maintaining medically induced remission^{228,230,252,258,262,271,272,275,232,234,239,243,244,248-250} and five (of 19, 26.3%) surgically induced^{279,281,287,288,291}. Reporting has increased over time and 35.7% of trials since 2009 have reported a primary or secondary biomarker outcome (Figure 8). Only one (10.0%) study of penetrating disease reported a biomarker outcome²¹⁹.

Serum C-reactive protein measurements^{117,123,177,182,186-188,191,195,199,200,205,145,208,211,216,219,248,250,262,271,272,277,147,279,287,288,291,155,157,162,165,168,176} were the most frequently reported biomarkers (34/181, 18.8%), followed by serum erythrocyte sedimentation

measurements (16 of 181, 8.8%)^{117,145,252,262,271,279,287,291,147,155,158,165,208,211,230,248} (Appendix table 10).

Faecal calprotectin was reported as an outcome in only two studies (1.1%)^{165,200}, one in each time-period. The biomarker was an additional outcome in three (1.7%) further trials^{213–215}, all reported in 2014 and 2015.

2.3.8. PROs and definitions

PROs were reported in 47 (of 110, 42.7%) of induction studies, 45 (of 104, 43.3%) medical induction studies^{118,123,145–147,149,150,157–159,162,165,128,167–172,180–182,185,136,187,188,190,191,193–195,197,199,200,137,205,208,210,211,138–140,142,143} and two (of six, 33.3%) surgical induction studies^{219,220}. In maintenance studies, 28 (of 77, 36.4%) primary or secondary PROs were reported, 24 (of 52, 46.2%) in studies of maintenance of medically-induced remission^{227,232,253,255,256,259–263,267,268,233,269,272,274,275,239,241,242,245,248,250,252}, and four (of 19, 21.1%) in maintenance of surgically-induced remission^{278,288,289,293}. The use of PROs has increased over time, with almost half of RCTs reporting a primary or secondary PRO since 2009 (Figure 8).

Quality of life was the most common outcome, reported in 40.3% (73 of 181) of studies (Appendix table 11). The Inflammatory Bowel Disease Questionnaire (IBDQ) was frequently used to record quality of life, and typically endpoints were specified as the final score or changes in the score (from baseline, mean or median)^{123,128,150,157–159,162,165,167–170,136,171,172,181,182,187,188,190,191,197,199,138,200,208,211,227,232,233,239,241,245,248,139,250,252,253,255,256,260–263,267,140,268,269,274,275,288,289,293,142,143,146,149}. The use of IBDQ to measure PROs increased from 30.4% to 37.5% between 1979–2008 and 2009–2015. The growth in use was in maintenance studies (25.5% to 50.0%), whilst its use in induction studies reduced (33.3% to 28.1%). Reporting of IBDQ in studies of fistula patients was in line with the overall average (three of 10, 30.0%).

Other tools for measuring quality of life included the Short-Form 36^{139,149,205,219,220,252,259,260,268,272} and its components^{149,220,268}, Patient Global Assessments^{147,190,278}, the Gastrointestinal Quality of Life Index^{210,220}, the Hamilton Depression Scale^{180,194} and the Short IBDQ^{145,219}. Patient diaries were

used to measure outcomes related to bowel symptoms¹³⁷, defecation functions^{118,145,185,195} and pain^{118,145,185}, with reports comparatively high (2,20%) in fistula patient studies^{185,219}.

2.3.9. Economic outcomes and definitions

Economic outcomes were reported in three studies^{217,220,263}; two induction and one maintenance study. All three studies reported a measure of the cost of the intervention and one reported the quality adjusted life-years as a measure of utility²¹⁷.

2.3.10. Safety-related outcomes and definitions

Safety-related outcomes were specified as primary or secondary endpoints in 42 (of 110, 38.2%) of induction studies, 38 (of 104, 36.5%) medical induction^{119,120,150–152,155,160–162,164,168,170,123,174–176,181,188,192,195,198,202,204,124,206,207,210–212,215,216,125,131,136,138,139,146} and four (of 6, 66.7%) surgical induction^{218–221} (Appendix table 12). Twenty-two maintenance studies (of 77, 31.0%) also reported primary or secondary safety endpoints; 17 (of were studies of maintenance of medically-induced remission^{225,232,259–262,266,270,272,234,235,239–241,243,252,257} and five were studies of maintenance of surgically-induced remission^{279,281,286,288,290}. Safety outcome reporting has increased steadily over the timeframe with 25% of studies reporting them in the period from 1979 to 1988, rising to 46% between 2009 and 2015 (Figure 8). The most common safety-related were adverse events, which were reported as primary or secondary outcomes in 39 (35.5%) induction studies^{119,120,146,150–152,155,160–162,164,168,123,174–176,181,188,192,195,198,202,204,124,207,210,212,215,216,218–221,125,131,136,138,139,142} and 22 (31%) maintenance studies^{225,232,259–262,266,270,272,279,281,286,234,288,290,235,239–241,243,252,257}. The reporting of adverse events as primary or secondary trial endpoints was most frequently the totality of adverse events but some studies looked for specific treatment related adverse events or reported the stopping of treatment due to adverse events (Appendix table 13).

2.3.10.1. Adverse events

Reporting of any adverse events occurred in 88 (of 110, 80%) induction studies^{114,117,132,134-136,138,139,141-144,118,146-153,155,156,119,157-159,161-164,166-168,121,170-179,123,181,183-191,124,192,193,195-202,125,203-207,209-213,128,214-220,253,129} and 61 (of 77, 85.9%) maintenance studies^{224,225,234,235,237-241,243,245,247,226,248,250-255,257-259,227,260-262,264-268,270,271,228,272,274-276,279-284,229,285-294,230,296,231-233} (Appendix table 13).

Reporting of AEs increased slightly between the two periods from 80.0% to 87.5% (Figure 9).

Serious adverse events were reported in 60 (of 110, 54.5%) induction^{120,124,146,147,149-151,157-161,129,162,164,166-168,170-174,131,175,176,179,182,184,185,187-189,202,135,203,204,206,207,209-214,136,215-218,138,139,142,143} and 31 (of 77, 43.7%) maintenance studies^{225,230,255,257,260,262,264,267,268,270-272,237,278-281,284,288,290,291,293,239,240,245,248,252-254}, and was higher in fistula patient trials (6, 60.0%)^{135,185,209,212,218,245}. The reporting of serious AEs increased from 46.4% of studies before 2009 to 58.9% from 2009 to 2015.

Treatment related adverse events, including those reported as serious, were reported in 69 (of 110, 62.7%) induction^{114,118,136,138,139,142,143,145,146,149-151,119,152,155,157,158,160-164,166,120,167-175,177,123,178,179,182-184,187-191,124,192,195,197-199,201-204,206,128,207,210,211,213,214,217,219,220,222,129,131,135} and 44 (of 77, 62%) maintenance studies^{224,225,243,245,248,253,257,264,266-268,271,232,272,274,275,277-280,282,285,287,233,288,290,292-294,234,237-241}. Six (60.0%) fistula studies reported treatment-related AEs. The reporting of treatment-related adverse events (including serious) grew from 56.8% to 66.1% of trials between the time-periods, respectively.

Gastrointestinal adverse events, including the exacerbation of CD and gastrointestinal signs and symptoms, were the most commonly reported AEs by system organ classification (SOC), reported in 85 (of 110, 77.3%) induction trials and 57 (of 77, 80.3%) maintenance studies (

Appendix table 14).

The ten most commonly reported AEs by higher-level group term (HLGT) are shown in Table 6. Gastrointestinal signs and symptoms, including nausea, vomiting and pain, were reported as AEs in 65.2% (of 181, 118) of studies. Two other HLGTs within the gastrointestinal conditions were in the ten most reported: gastrointestinal inflammatory conditions (71/181, 39.2%), which includes CD as an AE, and gastrointestinal motility and defecation conditions (63/181, 34.8%). Joint disorders, another HLGT, possibly related to CD and the failure of treatment, were reported in 32.6% (59/181) studies.

Figure 9: Proportion of Crohn's Disease RCTs reporting key adverse event and study withdrawal categories, stratified by decade of publication

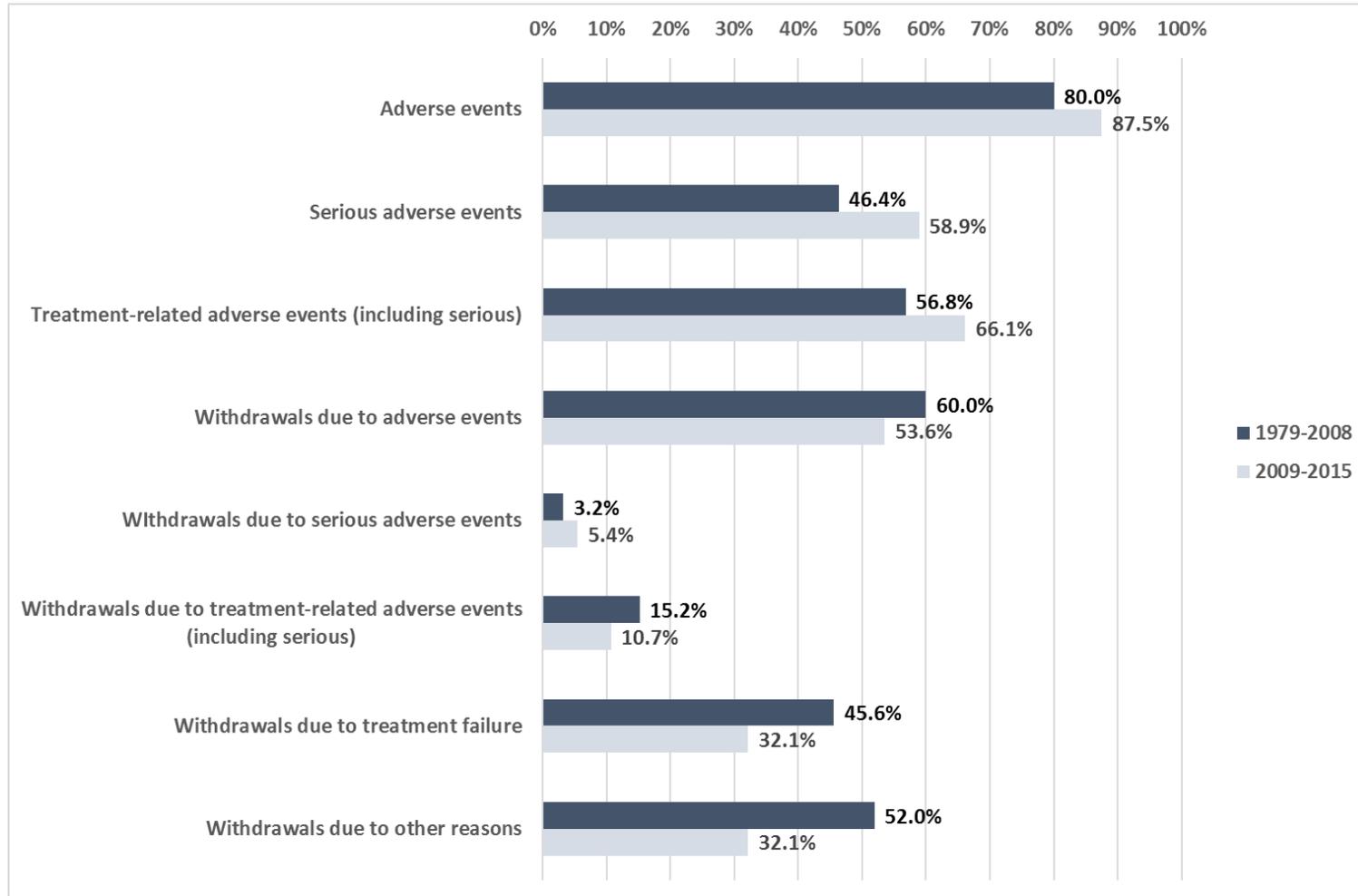


Table 6: Most Commonly Reported Adverse Events by MedDRA Higher Level Group Terms (HLGT) in Randomised Controlled Trials in Crohn's disease

System Organ Classification	Higher Level Group Term	Studies reporting n (%)		Example preferred terms
Gastrointestinal disorders	Gastrointestinal signs and symptoms	118	65.2%	Nausea, vomiting, abdominal pain, flatulence, abdominal distention
Infections and infestations	Infections - pathogen unspecified	95	52.5%	Abscess, infection, opportunistic infection, respiratory tract infection, nasopharyngitis
Nervous system disorders	Headaches	91	50.3%	Headache, migraine
General disorders and administration conditions	General system disorders NEC	73	40.3%	Chest pain, fatigue, oedema
Gastrointestinal disorders	Gastrointestinal inflammatory conditions	71	39.2%	CD, enteritis, colitis
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	63	34.8%	Diarrhoea, constipation, GORD
Musculoskeletal and connective tissue disorders	Joint disorders	59	32.6%	Arthralgia, arthritis, joint swelling, joint stiffness
General disorders and administration conditions	Fatal outcomes	48	26.5%	Death, sudden cardiac death
Nervous system disorders	Neurological disorders NEC	46	25.4%	Dizziness, paraesthesia
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	46	25.4%	Rash, pruritus, dermatitis

Note: NEC not elsewhere classified; GORD – gastro-oesophageal reflux disease

2.3.10.2. Study withdrawals

Withdrawals were most frequently reported due to AEs (102/181, 56.4%) and least frequently for serious AEs (7/181, 3.9%) (Appendix table 13). Withdrawals due to treatment failure were reported in 41.4% (75/181) of studies, and in 45.9% (83/181) of studies for reasons related to non-compliance and loss to follow-up. Withdrawals due to treatment-related AEs (including serious) were reported by 13.8% (25/181) studies, but the proportion fell from 15.2% to 10.7% between the two time-periods (Figure 9). The reduction in the reporting of study withdrawals was common across all categories except serious AEs, which rose slightly from 3.2% to 5.4% of studies.

Study withdrawals were more frequently reported due to adverse events reported in maintenance studies (51/77, 71.8%) than induction studies (68/110, 61.8%). Withdrawals due to treatment failure were more commonly reported in induction trials (50/110, 45.5%) than maintenance trials (25/71, 35.2%). Withdrawals for other reasons (such as protocol non-compliance or loss to follow up) were reported in similar proportions across induction studies (50/110, 45.5%) and maintenance studies (33/71, 46.5%).

2.4. Discussion

2.4.1. Summary of evidence

A comprehensive systematic review of the outcomes and outcome measures reported in RCTs of interventions for Crohn's disease was conducted, summarising data from 181 RCTs. The results demonstrate that trialists have adopted a wide and variable approach to outcomes measurement in the past. Over the decades of clinical trials, more measurement tools have become available and trialists have perhaps opted to measure more outcomes rather than decide which are most important. The results in this chapter provide insights to guide future trial design and support COS development for Crohn's disease by providing a preliminary list of outcomes. Further, the consideration of the measurement instruments used could assist the follow on phase to a COS; deciding how to measure the core outcomes.

The results confirm the predominance of clinical or composite-clinical primary and secondary trial endpoints. Over the history of RCTs for Crohn's disease, the reporting of all types of outcomes has increased with almost half of all studies between 2009 and 2015 now reporting PROs. Biomarkers, endoscopic and histologic outcomes have also increased in reporting, presumably as researchers seek more objective measures of disease activity. Economic outcomes remain rarely reported. Safety-related primary and secondary trial endpoint reporting increased from 25% of studies in the decade from 1979 to 1988 to 41% between 2009 and 2015.

Reporting of adverse events has increased over the same period, whilst the reporting of study withdrawals has generally reduced. It is unclear from the results why the reporting of study withdrawals has reduced. There are likely to be a number of factors and the fact that study withdrawals categories are themselves composite adds complexity. For example, withdrawals from treatment due to adverse events may include a range of different harms that have occurred with the broad category seeking to give an overview of the tolerability of treatment. The reduction in withdrawals may reflect the improvements in follow up that stem from the updated CONSORT statement⁴⁷. In order to ensure the correct approach to ITT analysis, the guidelines now stress that all patients should be followed up. Therefore, patients who withdraw from treatment may not be withdrawn from the study because they continue to be followed up and this could be a factor in the results.

Clinical response was the most commonly reported outcome across all studies. Clinical remission was most commonly reported in studies of induction of remission, and disease relapse or worsening was the most commonly reported outcome in studies of maintenance of remission. Endoscopic endpoints were more commonly reported in maintenance studies, but their use in induction studies is increasing. PROs, biomarkers and safety-related outcomes were all reported in more than a third of studies.

Key disease activity indices and quality of life questionnaires dominate the listings of outcomes. The Crohn's Disease Activity Index (CDAI) was developed over forty years ago as a composite measure incorporating symptoms, signs and simple laboratory parameters²⁹⁷. It was the dominant measurement instrument used in the published trials (primary or secondary endpoint in 77.9%), but with substantial variation including thirty-five definitions of response or remission. Whilst this observation highlights a need for greater standardisation of end-points, the CDAI *per se* is increasingly regarded as sub-optimal as an endpoint for comparative effectiveness research and regulatory approval. The index does not correlate closely with objective signs of inflammation or with mucosal healing at endoscopy^{298,299}. EMA guidance published in 2016 discourages the use of the CDAI as a trial endpoint, and recommends that signs and symptoms of disease activity and inflammation should be measured separately instead of within a combined index⁶⁸. Specifically the primary outcome should be a combination of PROs for signs and symptoms and endoscopy finding of mucosal healing for inflammation. The time trends observed in clinical trials endpoints reporting illustrate how the emphasis is shifting towards inclusion of discrete, objective measures of the inflammatory process (biomarkers, endoscopy and histology). The EMA guidance itself did not affect the studies included in the review as they were all published before the date of the guidance, suggesting that the regulatory decision has been driven to an extent by a research agenda. Given the length of time from trial registration to publication, it is likely to be some time before the impact of the guidance is seen in newer endpoints in trials published in the literature.

C-reactive protein (CRP) is a routinely employed biomarker in clinical practice and was frequently reported among clinical trial outcomes, albeit rarely as a primary endpoint (5 studies). However, CRP lacks sensitivity for active intestinal inflammation in Crohn's disease³⁰⁰, and this limits its value as a primary end-point. There remains active exploration of alternative serum markers of disease activity³⁰¹ but this review suggests no strong candidate has emerged.

Stool biomarkers offer potential to reliably measure gut-related inflammation and in recent years faecal calprotectin (FCP) has become available in routine IBD practice³⁰². Uncertainty remains as to its performance properties particularly for measuring the varied forms of Crohn's disease activity³⁰³ and research continues to explore other stool assays to measure the inflammatory process³⁰⁴. FCP was reported as an endpoint in only two trials included in this review^{165,200}.

An increase in the report of endoscopy and histology-based outcome measures over time was found, albeit they remained at a low level and without emergence of a standardised approach. This heterogeneity likely reflects the current sub-optimal psychometric properties of individual measurement tools, the cost and invasiveness of endoscopy and the inability to quantify the overall extent of intestinal inflammation in Crohn's disease^{305,306}. There is a growing body of research on the potential use of quantitative imaging such as CT and MRI³⁰⁷, but only one trial included in this review included radiological outcomes²¹⁹.

PROs were reported as end-points in almost half of studies since 2009, although commonly as a secondary outcome (60, 33.1%) rather than a primary outcome (10, 5.5%). Questionnaires administered in clinical trials ranged from 'generic' (e.g. EQ-5D) and 'disease specific' (e.g. IBD-Q) health-related QoL instruments to tools focusing on individual domains (e.g. Fatigue Impact Score). Although the IBDQ was the most frequently reported PROM in the trials (85% of studies reporting PROMs), it is currently not deemed valid as it was not developed according to the latest FDA recommendations for product labelling claims³⁰⁸. New disease-specific PROMs tools are under development to meet the stringent guidelines and enable PROMs to support future regulatory approvals of licencing for Crohn's disease.

The review covered data for safety outcomes in clinical trials and found substantial heterogeneity in reporting, which highlights the challenges in categorizing adverse events for a complex, chronic condition with a variable disease course and multisystem manifestations. Lack of treatment efficacy in Crohn's disease may manifest with a diversity of symptoms, which are difficult to

distinguish from genuine treatment side effects. Nevertheless, these data should support renewed attempts to define disease- and intervention-specific adverse events and to standardise safety outcomes as discrete end-points. This is an important consideration for future COS developers.

The results highlight how the reporting of outcomes in trials in fistula patients align with overall reporting. The use of PROs and safety-related endpoints is common across all trials, regardless of disease type. Clinical response was less commonly measured by CDAI, and more frequently measured by fistula closure and the PDAI. These three outcome measures were the most commonly used in fistula trials identified by this review, which supports the findings of a recently developed COS for fistulising disease¹⁰³. Biomarker, histology and endoscopy outcomes were rarely used in fistula trials and are not included in the COS either, contrary to the general shift in outcomes reporting in Crohn's disease trials. However, patient reports (e.g. incontinence and drainage) were more common endpoints in trials of fistula patients than in non-fistula trials, and their importance is borne out in the COS for fistulising disease, which lists several PROMs to be reported in future trials.

The results of this review are independently supported by the key findings of a 2018-published systematic review of outcomes in Crohn's disease¹⁰⁴. It confirms heterogeneity in definitions of response and remission and the need for a core outcome set to standardise endpoint definitions. Both studies unsurprisingly identified the use of CDAI as the most popular outcome measurement tool overall and of IBDQ as the most commonly used PROM. Similarly, CDEIS and SES-CD are highlighted as endoscopic tools most used in induction trials and Rutgeerts in post-surgical trials. Both reviews confirmed the common use of C-reactive protein and increasing use of biomarkers. However, this review had less restrictive inclusion criteria, leading to inclusion of a larger number of RCTs (181 versus 116). This resulted in extra heterogeneity in findings, which are arguably more extensive, particularly in the reporting of safety-related outcomes. Furthermore, whereas this

review focused on primary and secondary endpoints (with supplementary analysis of other outcomes), Ma *et al* considered all outcomes in a singular analysis. This results in differences in the breadth and depth of scope of the reviews and some nuances in key findings between the two reviews. For example, Ma *et al* found that a higher proportion of studies used CDAI, which likely reflects the requirement that trials must have used CDAI (or HBI) at enrolment to be included. Their tighter restrictions on therapies included may also explain the higher proportion reporting adverse events, as the search criteria in this chapter included trials of less traditional therapies. Ma *et al* also found that CDAI 100 was more prevalent as a measure of response than in this chapter's results (although there was an increased use over time), and reported an increased use of faecal calprotectin. These results may reflect some more recent trials included in their review.

2.4.2. Strengths and limitations

One strength of this review was the focus on synthesising data on safety outcomes. The results confirm the variability that exists in reporting of outcomes in published clinical trials of interventions for Crohn's disease. These data provide a comprehensive resource to support current and future efforts¹⁰² to redefine optimal outcomes and measurement tools to be included in future studies of comparative effectiveness. The search strategies employed for this review were broad, ensuring that the systematic review was comprehensive in identifying both the potential range of treatments for Crohn's disease and the outcomes from those treatments. Focusing on RCTs ensures the capture of the best evidence possible.

However, alternative methods are needed to identify the longer terms outcomes and this is one limitation of this work. The systematic review would have been strengthened by the inclusion of systematic reviews, prospective cohorts and retrospective cohorts alongside RCTs and other clinical trials. In particular, this would help to characterise important longer-term harms and may be a useful future piece of research. The limitation of time prevented their inclusion in this review.

This chapter has further limitations. Whilst it includes a comprehensive listing of outcomes from available Crohn's disease trials, it cannot account for publication bias. Further, the validity or reliability of the outcome measures identified in the review were not assessed, although this would form a part of any COS development process and the consideration of outcome measures provides a jump start to the second stage of a COS where developers decide how to measure the chosen outcomes. The screening process would have benefited from an additional reviewer for increased validity. Due to the scale of the project with 9,561 records to be screened, it was not possible to secure the involvement of a second reviewer to the extent that might be involved in a non-PhD piece of research. A more narrowly focused search would have resulted in fewer records to be screened, which might have made it possible to involve a second reviewer, but this could have compromised the strength of the extensiveness of the review.

2.4.3. Conclusions

Our study confirms the variability that exists in reporting of outcomes in published clinical trials of interventions for Crohn's disease. The systematic review of treatments of Crohn's disease in adults identified 181 relevant studies, identifying the key primary and secondary endpoints measured. A median of one primary endpoint and three secondary endpoints are reported per paper in the literature and clinical and composite-clinical outcomes are the most common type of trial endpoints. The reporting of all outcome types has increased over time, with the exception of the reporting of study withdrawals, which has reduced.

The data provide a comprehensive resource to guide the development of new trial endpoints for Crohn's disease and could provide the starting point for a core outcome sets (COS), which would standardise outcomes measured within clinical trials by specifying a minimum set of outcomes that should be measured and reported in trials of a particular condition⁴⁹. COS are usually developed using consensus methods involving patients, health professionals and other stakeholders to decide the most important outcomes for a condition and the first step of that

process is to identify the outcomes currently being measured and reported, which is covered by the work in this chapter.

The results have shown that, over time, there has been the beginning of a shift towards the use of patient reported outcome measures (PROMs) and objective measures of inflammation, rather than the use of composite-clinical measurement tools such as the Crohn's Disease Activity Index (CDAI). This shift, which is supported by regulatory guidance on trial design, requires new outcome measurement tools be developed, which must be transparent and validated. To support this process, there is a need to understand what is being measured within the current composite measurement tools, that is, what individual facets of Crohn's disease are being measured and then aggregated within tools to produce a summary measure of disease status, such as remission or response. The work reported in Chapter 3, tackles this question by disaggregating the endpoints reported in trials to their constituent parts and taking an overview of the lowest level of signs, symptoms and events that are measured in trials.

Chapter 3: Categorisation of outcomes and adverse events in Crohn's disease

3.1. Introduction

A systematic review of the outcomes reported in randomised controlled trials (RCTs) of Crohn's disease in Chapter 2 highlights the measurement of many different types of outcomes as primary and secondary endpoints, and the changing patterns of outcomes measured over time. In particular, the reporting of all types of efficacy and safety outcomes has increased over time, with the exception of study withdrawals reporting, which has reduced. Within efficacy outcomes, there is a reliance on the flawed Crohn's Disease Activity Index (CDAI) (as discussed in Chapter 2) to measure primary and secondary endpoints in trials. The use of such composite measures appears to make the measurement of outcomes across RCTs in Crohn's disease seem homogenous. Guidance from the European Medicines Agency (EMA)⁶⁸ highlights the need for new endpoints in clinical trials that separate out the signs and symptoms of Crohn's disease, measured by patient reported outcomes (PROs), and inflammation, measured by imaging techniques such as endoscopy. The reporting of PROs is in itself complicated and lacks transparency. As an example, a study of PROs reported in cancer trials found that PRO scales with identical names contained different components, which made it difficult to synthesise results³⁰⁹.

Understanding the breakdown of the endpoints measured in RCTs to the level of individual signs, symptoms and events will provide greater transparency on what is measured in the literature. In this chapter such signs, symptoms and events are referred to as "outcomes" where reported in the context of trial endpoints, and "adverse events" where reported in the context of safety sections of trials. Developing such a comprehensive recording of outcomes and adverse events (AEs) may help guide the development of new trial endpoints for Crohn's disease. It could provide the starting point for a core outcome set (COS), which would standardise outcomes measured by specifying a minimum set of outcomes that should be measured and reported in trials of a particular condition⁴⁹.

The complexity of Crohn's disease and the broad scope of treatment suggests there are likely to be numerous and various definitions of outcome measures and a wide reporting of adverse events and this was confirmed in the systematic review in Chapter 2. As such, it is useful to be able to categorise outcomes and AEs and the OMERACT Filter 2.0³¹⁰ provides a conceptual framework to aid such an exercise. OMERACT are a well-established international collaboration aimed at improving outcome measurement in rheumatoid arthritis (RA)⁵¹. Filter 2.0 was developed by the group to assist in COS development and provides a framework within which outcomes can be categorised.

Filter 2.0 was selected as a framework for categorising outcomes and AEs in this chapter for several reasons; firstly, both Crohn's disease and RA are chronic inflammatory diseases with overlapping treatments and sequelae and as such, there is likely to be an overlap in the outcomes and AE categories. A well-established tool with pre-defined categories is useful to assist non-clinical outcomes researchers and methodologists (lacking detailed medical knowledge), providing a useful start to categorisation. Secondly, Filter 2.0 includes AEs alongside efficacy outcomes, categorising them using the same domains, rather than putting them into a single category "adverse events" or "safety-related events". This was important to this research with its focus on identifying the often-overlooked harms of treatment. Thirdly, Filter 2.0 makes use of a range of existing and validated taxonomies and dictionaries to populate its categories, which means it is a robust categorisation framework.

Whilst there is no established COS for Crohn's disease, a disability index for inflammatory bowel disease (IBD) has been proposed using the World Health Organisation's international Classification of Functioning, Disability and Health (ICF)¹⁰⁰. Peyrin-Biroulet et al present two IBD ICF core sets, a comprehensive and a brief core set. The comprehensive set aims to fully characterise what it means to live life with IBD. The authors argue that the brief set captures the essence of the disability faced by patients with IBD and provides a disability index that can be used in both clinical

practice and as a clinical trial endpoint. Within this chapter, the core sets serve as a useful tool to benchmark against the results of the classification. Further, by breaking down the key measurement tools into their composite outcomes, it is possible to check how well they address the proposed core sets.

3.1.1. Aims and objectives

The aim of this chapter is to identify a comprehensive categorisation of outcomes and AEs recorded in RCTs to induce or maintain remission of Crohn's disease at the level of individual symptoms, signs and events, the results of which could support the development of new trial endpoints in RCTs or inform the development of a COS for Crohn's disease. The key objectives are:

- To identify the signs, symptoms and events (outcomes and adverse events) measured in trials of Crohn's disease from the data extracted from a systematic review of outcomes in Chapter 2.
- To categorise the identified outcomes and adverse events into an existing theoretical framework (Filter 2.0) to provide a comprehensive inventory.
- To map the ICF IBD core outcomes onto the theoretical framework to establish how well it reflects the literature.
- To map the most commonly used composite measurement tools onto the theoretical framework to establish how well they reflect the ICF IBD core outcomes and the outcomes reported in the literature.

3.2. Methods

3.2.1. Systematic review

The methods of the systematic review are recorded in Chapter 2.

3.2.2. Outcomes data

To capture the broadest range of outcomes measured, and in contrast to the methods in Chapter 2, all endpoints reported in the trials were disaggregated to their component outcomes and

categorised. These endpoints included those specified as primary and secondary, and those additional endpoints reported in the trials but not pre-specified as primary or secondary endpoints. The point here is to count what is being measured, not how it is being measured. In other words, this was a move away from counting composite-clinical outcome measures and patient reported outcome measures (PROMs), and instead aimed to define the discrete, individual outcomes that they are seeking to measure.

Data on trial endpoints, the measurement tools and definitions used were extracted from the papers as discussed in Chapter 2. Combined endpoints were disaggregated into individual outcome measures, which could then be disaggregated further into a larger number of discrete outcomes.

3.2.2.1. Identifying component outcomes from outcome measurement tools

Disease activity indices (DAIs) and patient reported outcome measures (PROMs) are used to measure disease states that are not directly observable. The decision to categorise all endpoints, rather than just primary and secondary endpoints, in the 181 studies identified in the systematic review in Chapter 2 led to the inclusion of a range of exploratory endpoints. To avoid consideration of tools used on an ad-hoc basis and to focus on those used more reliably in the literature, the decision was taken to break down into components those tools reported three or more times in the trials identified by the systematic review. Those used less frequently were classed as measuring an outcome in their summary form, for example as measuring general quality of life.

If an outcome measure was used for measuring multiple outcomes, e.g., albumin levels were reported as both a measure of nutritional status and inflammation, it was aligned with the most common use to ensure each outcome measure was recorded uniquely within the framework.

The component outcomes within each outcome measurement tool were recorded only once per paper, even if the tool was used for several endpoints. For example, the CDAI might be used to

report remission, response and recurrence endpoints in a study, but the component outcomes at the level of symptoms, signs and events such as the presence of fistula, or diarrhoea, were measured once using that measurement tool.

3.2.3. Adverse events data

AE data were extracted from the papers in the systematic review and standardised using the Medical Dictionary for Regulatory Activities (MedDRA) terminology³¹¹ as described in Chapter 2. The three levels considered most clinically relevant in the MedDRA hierarchy were used for the categorisation process:

1. Preferred terms (PTs): single medical concept for a symptom, sign, disease, diagnosis, therapeutic indication, investigation or medical or surgical procedure.
2. High-level group terms (HLGTs): groups of PTs related by anatomy, pathology, physiology, aetiology or function.
3. System organ class (SOC): the broadest concept, based upon aetiology (e.g. infections and infestations), manifestation site (e.g. gastrointestinal disorders) or purpose (e.g. surgical and medical procedures).

PTs can be linked to more than one SOC but the primary SOC suggested in the MedDRA hierarchy was recorded in the data, even where this disagreed with the SOC reported in the study. This ensured that each AE appeared uniquely in the hierarchy.

The numbers of trials reporting the following categories of AEs was also recorded:

- Adverse events
- Serious adverse events
- Treatment-related adverse events
- Treatment-related serious adverse events
- Treatment withdrawal due to adverse events

- Treatment withdrawal due to serious adverse events
- Treatment withdrawal due to treatment-related adverse events
- Treatment withdrawal due to treatment-related serious adverse events
- Treatment withdrawal due to treatment failure defined as insufficient therapeutic effect, exacerbation of Crohn's, development of complications or Crohn's or need for additional therapy or surgery.
- Treatment withdrawal due to various reasons including protocol non-compliance, lost to follow up, use of prohibited medication and withdrawal of consent.

3.2.4. Data presentation

A frequency count and percentages of studies reporting each outcome and AE was presented. A frequency count and percentages of studies reporting key DAIs and PROMs was presented, with a breakdown of the constituent outcomes measured.

3.2.5. Outcome categorisation

Once a comprehensive list of outcomes and AE was generated, they were categorised into domains within the OMERACT Filter 2.0³¹⁰ framework.

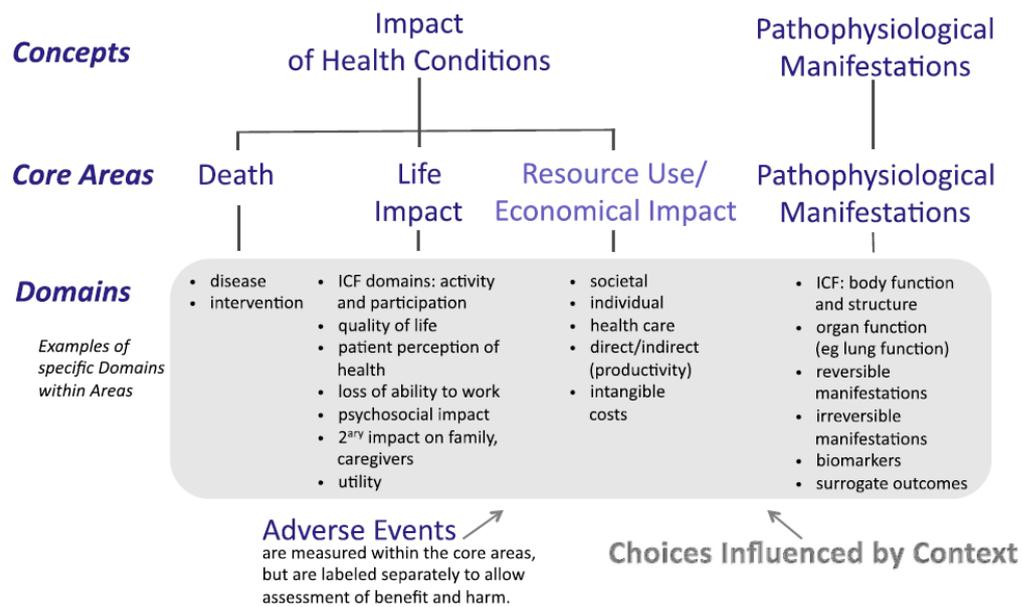
3.2.5.1. OMERACT Filter 2.0

The OMERACT Filter 2.0 framework, shown in Figure 10 below, is designed to support the development of a COS and ensure that it provides a true picture of a disease by covering both the impact of the health condition and its pathophysiological manifestations. Both outcomes and AEs can be situated in the framework.

The framework includes three core areas that cover the impact of the condition (death, life impact and economic impact) and one core area that covers the pathophysiological manifestations of the disease. Below the core areas, the intention is that COS developers should select domains of importance to the condition, ideally at least one within each core area, to form the "core domain set". Within each domain, at least one outcome measure should be selected to form the "core

outcome measurement set". In this chapter, Filter 2.0 was applied in a different way as outcomes measures were extracted from the systematic review, listed as a series of outcomes and then categorised into domains within the framework. AEs were similarly extracted, standardised and categorised within the framework.

Figure 10: OMERACT Filter 2.0 framework for developing Core Outcome Sets (COS)³¹⁰



OMERACT provide guidance on sources of domains: the WHO International Classification of Functioning, Disability and Health (ICF)³¹²; a model of health-related quality of life by Wilson and Cleary (1995)³¹³; and additional domains suggested by OMERACT to ensure a comprehensive representation of the condition.

3.2.5.2. International Classification of Functioning, Disability and Health (ICF)

The ICF is the World Health Organisation (WHO) framework for describing health and health-related states³¹². It was used as the primary source for categorising the outcomes and adverse events into domains due to its hierarchical classification system and the potential for ease of alignment of the resultant framework with the ICF core sets for IBD. The ICF covers four domains:

- b – Body Functions, which focuses on impairments in body function, such as mental function or sensory functions, for example.
- s – Body Structures, which focuses on impairment in body structure, such as the nervous system or respiratory systems, for example.
- d – Activities and Participation, which focuses on performance problems or capacity limitations across the full range of life areas, such as basic learning or composite areas such as social tasks.
- e – Environmental factors, which are contextual factors that might be a facilitator or barrier on the lives of people with health conditions, such as the built environment or the availability of services. This domain was not considered relevant to outcomes and AE reporting.

The online browser³¹⁴ was searched for each verbatim outcome and AE identified through the systematic review. Each outcome and AE was coded to the lowest possible level of the ICF and aggregated to clinically appropriate Filter 2.0 domains with clinical support (KB). An example is shown in Table 7 below of how similar outcomes were grouped into one outcome domain. Five outcomes are coded at ICF level 4 but all related to defecation so are grouped into an outcome domain at an ICF level 3 code of “defecation functions”. For completeness, the ICF level 2 and level 1 codes are shown.

Table 7: Example of coding outcomes into domains using the ICF

Chapter heading (level 1)		Chapter sub-heading (Level 2)		Domain (level 3)		Outcome (level 4)	
Code	Name	Code	Name	Name	Name	Code	Name
b	Body functions	b5	Functions of the digestive, metabolic and endocrine systems	b525	Defecation functions	b5250	Elimination of faeces
						b5251	Faecal consistency
						b5252	Frequency of defecation
						b5253	Faecal continence
						b5254	Flatulence

3.2.5.3. Wilson and Cleary health-related quality of life

Where it was not possible to align outcomes and adverse events with the ICF, the Wilson and Cleary model of health-related quality of life³¹³ was used as second choice. The model includes the following domains:

1. Biological and physical variables, which focus on the functions of components of the body;
2. Symptom status, which focus on the functions of the body as a whole;
3. Functional status, which assess the ability of an individual to perform tasks;
4. General health perceptions, which are a subjective rating of personal health; and
5. Overall quality of life.

Domains one to three align with domains in ICF so these domains were not used. The domains of general health perceptions and overall quality of life are not covered well by the ICF so these domains were considered appropriate for use in categorising outcomes and AEs.

3.2.5.4. Other domains

Finally, Filter 2.0 allows for specification of other domains, dependent upon the specific context in which the core set is being applied, in this case, for treatment of adults with Crohn's disease.

Where it was not possible to align outcomes and AEs to either the ICF or the health-related quality of life model^{313,315}, other domains suggested by OMERACT¹⁰⁰ were used as appropriate. This was a process undertaken with the support of KB to ensure that the domains were of clinical relevance.

The domains resulting from this process were:

- Death due to Crohn's disease;
- Utility of treatment;
- Individual resource use;
- Health care cost;
- Infections;
- Cancers (where not listed by location);
- General system conditions; and
- Biomarkers.

3.2.6. Outcome hierarchy, key indices and questionnaires and the ICF core sets

Filter 2.0 populated with Crohn's disease outcomes was presented in table format with the core areas, domains, outcomes and outcome measures listed. AEs were presented in a separate table with the preferred terms (PTs) and higher-level group terms (HLGTs).

The top level of the resulting Filter 2.0 for Crohn's disease outcomes and AEs in adults, which highlights the outcome domains, was presented in table format and the ICF core set for IBD overlaid to compare the two.

Given the importance of some key disease activity indices and PROMs in Crohn's trials, additional analysis focused on how their composite outcomes map against the populated Filter 2.0 framework.

3.3. Results

Trial endpoint data was extracted from 181 studies identified by the systematic review in Chapter 2.

3.3.1. Outcomes measured by key measurement tools used in Crohn's disease trials

Disease activity indices and patient reported outcome measures were used extensively in Crohn's disease trials and have a significant impact on the frequency reporting of outcomes, and consequently the categorisation process. Table 8 shows the disease activity indices and PROMs identified by the search, the number of studies in which they are used and the number of outcomes they measure. A discussion of how the outcome measurement tools reduce to the outcomes follows and discussion of their impact upon the Filter framework mapping of outcomes is in Section 3.3.5.2. The detail of the items measured in each outcome measure and how they mapped against the Filter 2.0 domains is shown in Appendix table 17 to Appendix table 22.

Table 8: Commonly used indices of disease activity and patient reported outcome measures, the number of outcomes in each and their use in 181 Crohn's disease trials in adults

Measure name	Measure type	Number of outcomes measured	Trials in which it is used (n=181)	
			No.	%
CDAI	Composite-clinical	15	156	86.2
IBDQ	PROM	32	77	42.5
SF-36	PROM	33	15	8.3
HBI	Composite-clinical	12	14	7.7
PDAI	Composite-clinical	5	10	5.5
VHAI	Composite-clinical	8	7	3.9

Important disease activity indices in the articles found by the systematic review were the Crohn's Disease Activity Index (CDAI), the Harvey Bradshaw Index (HBI), the Perianal Disease Activity Index (PDAI) and the Van-Hees Activity Index (VHAI).

Important quality of life questionnaires were the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short-Form 36 questionnaire (SF-36).

3.3.1.1. Crohn's Disease Activity Index (CDAI)

The CDAI is the most commonly used index in the studies in our review, reported by 156/181 studies (86.2%). It is a composite-clinical outcome measure and has seven questions: four on

symptoms and captured by patient diary, two on complications that are assessed by a clinician, one measure of body weight and, finally, a blood test biomarker⁶⁴. The index disaggregates into 15 separate outcomes and is mapped to 15 domains. (Appendix table 17).

3.3.1.2. Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is the second most commonly used outcome measurement tool in the included studies (77/181, 42.5%). It is a validated PROM of health-related quality of life³¹⁶ that is noted in current EMA guidance as a potential secondary endpoint⁶⁸. There are 32 questions in the questionnaire, related to four sub-scales: bowel, emotional, social and systemic. Each sub-scale aims to capture an element of quality of life that is affected in people with IBD. Within the framework, the IBDQ is coded as 32 outcomes, split over 12 domains (Appendix table 18). As with the CDAI, it is possible to report an overall score and this can be measured against cut off values to indicate disease states. It is most commonly used as an average score, but studies also report the separate sub-scales, usually in addition to the overall score. Further detail on its use as a primary or secondary endpoint was discussed in Chapter 2.

3.3.1.3. Short-Form 36 (SF-36)

The SF-36 is also a commonly used health-related quality of life questionnaire, which measures functioning and wellbeing in terms of physical, mental and social dimensions^{317,318}. It lists 36 questions, which group into concepts and provide scores for physical functioning; role limitations due to physical problems; social functioning; bodily pain; general mental health; role limitations due to emotional problems; vitality; and general health perceptions. The scores are also further grouped to provide summary scores: the mental component score and the physical component score. Many studies reported these summary scores along with the overall score. The SF-36 measures 33 outcomes across 10 domains and its use was reported in 15/181 (8.3%) of the included studies (Appendix table 19).

3.3.1.4. Harvey-Bradshaw Index (HBI)

The HBI is a simplified version of the CDAI, designed to make it easier to collect and calculate⁶⁵. Body weight, blood test and the use of anti-diarrhoeal medication are removed to simplify the index. The HBI maps to 11 outcomes and 10 domains in the Filter 2.0 framework (Appendix table 20). It is reported by 14/181 (7.7%) of the included studies.

3.3.1.5. Perianal Disease Activity Index (PDAI)

The PDAI combines scores on the severity of symptoms on five scales: discharge; pain/restriction of activities; restriction of sexual activity; type of perianal disease; and degree of induration⁶⁶. The PDAI maps to five outcomes and five domains in the Filter 2.0 framework and is reported in 10/181 (5.5%) of the included studies (Appendix table 21).

3.3.1.6. Van-Hees Activity Index (VHAI)

The VHAI was designed to overcome some of the perceived disadvantages of the CDAI, mostly the predominance of subjective variables³¹⁹. As such, the VHAI uses a combination of nine measures, proposed as objective measures, to produce an index score. The index maps to eight outcomes and eight domains in Filter 2.0 (sex is not included as an outcome) and is reported by 7/181 (3.9%) of the included papers (Appendix table 22).

3.3.2. Outcomes measured in Crohn's disease trials

Breaking down all endpoint data into individual components results in the identification of 93 outcomes to be categorised into the Filter 2.0 framework. Table 9 lists the outcomes measured in more than 90% of trials in decreasing order of frequency of reporting. The most commonly reported outcomes were abdominal pain, faecal consistency, fistula / fissure / abscess, frequency of defecation, abdominal mass, wellbeing, arthralgia, extra-intestinal lesions and fever. Given that the CDAI is reported in almost 90% of trials, the table is essentially a list of the discrete components of the CDAI. The list of all 93 outcomes in decreasing order of reporting is in Appendix table 15. Thirteen of the 93 outcomes (14.0%) were measured in only one trial.

Table 9: The most common outcomes measured in 90% of Crohn’s disease trials in adults, listed by frequency of reporting

Outcome	Trials measuring outcome	
	No.	% (of 181)
Abdominal pain	169	93.4%
Faecal consistency	169	93.4%
Fistula / fissure / abscess	168	92.8%
Frequency of defecation	168	92.8%
Abdominal mass	164	90.6%
Wellbeing	164	90.6%
Arthralgia	163	90.1%
Extra-intestinal lesions	163	90.1%
Fever	163	90.1%

3.3.3. Adverse events recorded in Crohn’s disease trials

577 AEs were identified in the trials from the systematic review, plus the 10 pre-specified AE categories outlined in the methods chapter, Section 3.2.3. More than half of the AEs (301/577, 52.2%) were reported only once. The most commonly reported AEs, reported in more than 40% of studies were abdominal pain, headache, crohn’s disease (aggravated) and nausea. A number of the pre-specified categories were also reported in more than 40% of studies: total adverse events, discontinuation of treatment due to various reasons, total serious adverse events and discontinuation of treatment due to treatment failure (Table 10). The full list of reported adverse events is shown in Appendix table 16.

Table 10: The most common adverse events reported in Crohn’s disease trials in adults identified by systematic review, listed by frequency of reporting

Outcome	Trials measuring outcome	
	No.	% (of 181)
Discrete adverse events		
Abdominal pain	102	56.4%
Headache	96	53.0%
Crohn's disease (aggravated)	89	49.2%
Nausea	88	48.6%
Pre-specified adverse event categories		
Discontinuation of treatment due to adverse events	102	56.4%
Total adverse events	93	51.4%
Discontinuation of treatment due to various reasons (Protocol non-compliance, lost to follow up, prohibited medication use, withdrawal of consent)	83	45.9%
Total serious adverse events	76	42.0%
Discontinuation of treatment due to treatment failure (insufficient therapeutic effect, exacerbation of Crohn's, development of complications of Crohn's, need for additional therapy or surgery)	75	41.4%

3.3.4. Categorisation into Filter 2.0

The 93 outcomes identified in the systematic review were mapped to 35 outcome domains in the Filter 2.0 framework. The framework is shown in Figure 11 below, showing the outcome domains listed in order of the number of trials measuring the outcomes within their trial endpoints. The domains in bold are those which match, identically or closely, the core outcomes from the brief and comprehensive ICF core sets for IBD¹⁰⁰. A discussion of the alignment between the mapped outcomes in Filter 2.0 and the ICF core sets is presented in a later section (3.3.5). The Filter 2.0 framework with the comprehensive list of domains, outcomes, and outcome measures is shown in Appendix table 23.

The 577 adverse events and 10 pre-specified AE categories have been categorised into the framework across 46 domains, as shown in Figure 12. Again, the domains in bold are those that match the core outcomes from the ICF core sets for IBD and a discussion of fit takes place in a later section (3.3.5). The Filter 2.0 framework of adverse events with the comprehensive list of

domains, the MedDRA preferred terms and the corresponding higher-level group terms (HLGT) is in Appendix table 16.

3.3.4.1. Impact of health conditions concept

A key difference between the outcomes and AEs versions of Filter 2.0 is the split of domains. For outcomes, 15 domains are within the impact of health conditions concept, whilst the same category includes only four domains for the AEs framework (Figure 11, Figure 12).

DEATH CORE AREA

Outcomes in the core area of death were rarely recorded as endpoints in trials (2/181, 1.1%) but were reported in AE sections much more commonly (49/181, 27.1%).

ECONOMIC IMPACT CORE AREA

Two domains were identified for outcomes under the economic impact core area. Outcomes related to individual resource use were reported in 163/181 (90.1%) studies, measured as part of indices in 156/181 (86.1%) and as additional single measures in 83/181 (45.9%) reports. The outcomes included in this domain are the need for additional steroids, therapy or surgery; the need for hospitalisation; steroid dose; withdrawal or tapered steroids; and resection surgery. A number of measures are used for this including indices (CDAI and HBI) but commonly clinician reported outcomes and PROMs (Appendix table 23). A second outcome domain is health care costs, which were measured by three trials (1.7%). Outcomes included costs of interventions, costs per QALYs gained and incremental cost effectiveness ratios, which are the comparison of the differences in costs and QALYs between two treatments.

Only one domain was identified for AEs in the economic impact core areas. Individual resource adverse events were reported in 38/181 (21.0%) trials. These AEs included the need for hospitalisation, surgery and antibiotic therapy (Appendix table 24).

Figure 11: Filter 2.0 showing domains of outcomes measured in endpoints in Crohn's Disease trials (frequency & percentage of studies reporting outcomes in this domain)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/181, 1.1%)	<p>Quality of life (167/181, 92.3%)^{3,4}</p> <p>ICF d810-d839: Education (82/181, 45.3%)^{1,2}</p> <p>ICF d840-d859: Work and employment (82/181, 45.3%)^{1,2}</p> <p>ICF d9: Community, social and civic life (82/181, 45.3%)³</p> <p>Patient perception of health (82/181, 45.3%)</p> <p>ICF d5301: Regulating defecation (77/181, 42.5%)^{1,2}</p> <p>Utility of treatment (71/181, 39.2%)</p> <p>ICF d4: Mobility (14/181, 7.7%)</p> <p>ICF d5: Self-care (14/181, 7.7%)^{3,4}</p> <p>ICF d640: Doing housework (14/181, 7.7%)</p> <p>ICF d240: Handling stress and other psychological demands (3/181, 1.7%)</p> <p>ICF d7: Interpersonal interactions (1/181, 0.6%)^{1,2}</p>	<p>Individual resource use (163/181, 90.1%)</p> <p>Health care cost (3/181, 1.7%)</p>	<p>ICF s540: Structure of intestine (174/181, 96.1%)^{1,2}</p> <p>ICF b525: Defecation functions (172/181, 95.0%)^{1,2}</p> <p>ICF b28012: Pain in stomach or abdomen (169/181, 93.4%)^{1,2}</p> <p>ICF s810: Structures of areas of skin (166/182, 91.7%)³</p> <p>ICF b28016: Pain in joints (163/181, 90.1%)¹</p> <p>ICF b5500: Body temperature (163/181, 90.1%)</p> <p>ICF s220: Structure of eyeball (162/181, 89.5%)</p> <p>ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%)^{1,2}</p> <p>ICF b530: Weight maintenance functions (157/181, 86.7%)¹</p> <p>ICF b430: Haematological system functions (156/181, 86.2%)¹</p> <p>Biomarkers (102/181, 56.4%)</p> <p>ICF b152: Emotional functions (83/181, 45.9%)^{1,2}</p> <p>ICF b640: Sexual functions (83/181, 45.9%)¹</p> <p>ICF b130: Energy and drive functions (82/181, 45.3%)^{1,2}</p> <p>ICF b535: Sensations associated with the digestive system (77/181, 42.5%)¹</p> <p>ICF b134: Sleep functions (77/181, 42.5%)^{1,2}</p> <p>ICF b280: Sensation of pain (25/181, 13.8%)³</p> <p>ICF b515: Digestive functions (14/181, 7.7%)^{1,2}</p> <p>ICF b510: Ingestion functions (6/181, 3.3%)</p> <p>ICF b540: General metabolic function (2/181, 1.1%)</p>
	¹ In IBD ICF comprehensive set	³ Similar item in ICF comprehensive set		
	² In ICF brief set	⁴ Similar item in ICF brief set		

Figure 12: Filter 2.0 showing domains of adverse events reported in Crohn's Disease trials (frequency and percentage of studies reporting outcomes in this domain)

Top level Crohn's Filter framework of adverse events reported in Crohn's Disease trials (number of studies reporting outcomes in this domain)			
Concepts	Impact of health conditions		Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact
Domains	Death (49/181, 27.1%)	Utility of treatment (53/181, 29.3%)* Patient perception of health (5/181, 2.8%)	Individual resource use (38/181, 21.0%)
			<p>Pathophysiological manifestations</p> <p>Infections (106/181, 58.6%)</p> <p>ICF b280: Sensation of pain (105/181, 58.0%)³</p> <p>ICF s540: Structure of intestine (96/181, 53.0%)^{1,2}</p> <p>ICF b28012: Pain in stomach or abdomen (90/181, 49.7%)^{1,2}</p> <p>ICF b535: Sensations associated with the digestive system (90/181, 49.7%)¹</p> <p>ICF b8: Functions of the skin and related structures (76/181, 42.0%)³</p> <p>ICF b435: Immunological system functions (65/181, 35.9%)¹</p> <p>ICF b525: Defecation functions (65/181, 35.9%)^{1,2}</p> <p>ICF b510: Ingestion functions (59/181, 32.6%)</p> <p>ICF b28016: Pain in joints (58/181, 32.0%)¹</p> <p>ICF b540: General metabolic function (50/181, 27.6%)</p> <p>ICF b130: Energy and drive functions (47/181, 26.0%)^{1,2}</p> <p>ICF b5500: Body temperature (47/181, 26.0%)</p> <p>ICF b430: Haematological system functions (39/181, 21.5%)¹</p> <p>ICF b515: Digestive functions (35/181, 19.3%)^{1,2}</p> <p>ICF b7: Neuromusculoskeletal and movement-related functions (33/181, 18.2%)</p> <p>ICF b240: Sensations associated with hearing and vestibular function (31/181, 17.1%)</p> <p>ICF b555: Endocrine gland functions (25/181, 13.8%)</p> <p>ICF b415: Blood vessel functions (24/181, 13.3%)</p> <p>ICF b152: Emotional functions (22/181, 12.2%)^{1,2}</p> <p>ICF b6: Genitourinary and reproductive functions (22/181, 12.2%)³</p> <p>Unspecified: cancer (20/181, 11.0%)</p> <p>ICF b440-b460: Respiratory functions (20/181, 11.0%)</p>

Top level Crohn's Filter framework of adverse events reported in Crohn's Disease trials (number of studies reporting outcomes in this domain)				
Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
				ICF s6: Structures related to the genitourinary and reproductive systems (20/181, 11.0%) ICF b134: Sleep functions (19/181, 10.5%) ^{1,2} ICF b410: Heart functions (18/181, 9.9%) ICF b545: Water, mineral and electrolyte balance functions (18/181, 9.9%) ¹ Unspecified: general system conditions (18/181, 9.9%) ICF b420: Blood pressure functions (16/181, 8.8%) ICF s550-s580: Structures related to the metabolic and endocrine systems (16/181, 8.8%) ICF b530: Weight maintenance functions (13/181, 7.2%) ¹ ICF s3: Structures involved in voice and speech (12/181, 6.6%) ICF b210-b220: Seeing functions and sensations associated with the eye (11/181, 6.1%) ICF b110-b147: Other mental functions (10/181, 5.5%) ICF s8: Skin and related structures (10/181, 5.5%) Biomarkers (9/181, 5.0%) ICF b250: Taste function (8/181, 4.4%) ICF s4: Structures of the cardiovascular, immunological and respiratory systems (8/181, 4.4%) ICF s530: Structure of stomach (5/181, 2.8%) ICF s1: Structures of the nervous system (4/181, 2.2%) ICF s7: Structures related to movement (2/181, 1.1%) ^{3,4} ICF s2: The eye, ear and related structures (1/181, 0.5%)
¹ In IBD ICF comprehensive set ² In IBD ICF brief set ³ Similar item in IBD ICF comprehensive set ⁴ Similar item in IBD ICF brief set * includes reports of 10 pre-specified events: Adverse events, Serious adverse events, Treatment-related adverse events, Treatment-related serious adverse events, Treatment withdrawal due to adverse events, Treatment withdrawal due to serious adverse events, Treatment withdrawal due to treatment-related adverse events, Treatment withdrawal due to treatment-related serious adverse events, Treatment withdrawal due to treatment failure (defined as insufficient therapeutic effect, exacerbation of Crohn's, development of complications or Crohn's or need for additional therapy or surgery), and treatment withdrawal due to various reasons (including protocol non-compliance, lost to follow up, use of prohibited medication and withdrawal of consent).				

LIFE IMPACT CORE AREA

OUTCOMES

Outcomes were categorised into 12 domains in the core area of life impact. Most trials measured outcomes within the quality of life domain (167/181, 92.3% with 163/181, 90.1% as part of a composite index and 16/181, 8.8% reporting single outcome measures). The outcomes in this domain were wellbeing and general quality of life. Measurement of quality of life was through both disease-specific PROMs such as the Gastrointestinal Quality of Life Index³²⁰ and generic quality of life questionnaires, such as the Short-Form 12 health survey³²¹. Wellbeing measures were predominantly PROMs, and included diary card assessments and global assessments of wellbeing (Appendix table 23).

Between 77/181 and 82/181 (42.5% and 45.3%) studies measured outcomes in the following domains: education; work and employment; community, social and civic life; patient perception of health; carrying out daily routine; and regulating defecation. These numbers were primarily accounted for by the use of the IBDQ, which included outcomes such as condition interferes with social life, unable to attend school or work, and needing to rush to the toilet.

39.2% (71/181) of trials measured outcomes within the domain of utility of treatment. This domain includes outcomes related to the efficacy, acceptability and tolerability of treatment. All 71 trials used individual measures to record them such as pill counts, PROMs and clinician reported outcomes.

A minority of studies (14/181, 7.7%) measured outcomes in the domains mobility, self-care, and doing housework. The use of the SF-36 as an outcome measurement tool accounts for these outcomes, which include bending, kneeling or stooping; bathing or dressing; and moderate activities.

The final life impact outcome domains, which were only reported in two or fewer papers, were handling stress or other psychological demands (2/181, 1.1%) and interpersonal interactions and relationships (1/181, 0.6%). The outcomes were measured by questionnaires.

ADVERSE EVENTS

Only two domains in the core area of life impact were relevant for AEs. Utility of treatment was the largest domain with 88.4% of trials reporting AEs within this category. MedDRA preferred terms within this domain included all types of injection or infusion site reactions, post procedural complications, drug intolerance and overdoses (Appendix table 24). In addition, the pre-specified categories of AEs in the methods section 3.2.3 (including all reasons for withdrawal) were counted within this domain. Five trials reported AEs within the patient perspective of health domain and two adverse events were reported: malaise and feeling abnormal.

3.3.4.2. Pathophysiological manifestations concept

Adverse event domains were much more common within the concept of pathophysiological manifestations. Whilst 20 domains were matched to the outcomes measured by Crohn's disease trials, the AEs reported in the same trials matched to 42 domains (Figure 11, Figure 12).

PATHOPHYSIOLOGICAL MANIFESTATIONS CORE AREA

OUTCOMES

The vast majority of trials (174/181, 96.1%) measured outcomes related to the structure of the intestine, including the presence of fistula, abscesses, ulcers or perianal disease. In 85/181 (47.0%) of these studies the presence of changes in the structure of the intestine were not measured as part of a disease activity index (such as the CDAI). Outcome measures included a number of endoscopic scores, such as the Crohn's Disease Endoscopic Index of Severity (CDEIS)³²², the Simple Endoscopic Score for Crohn's Disease (SES-CD)³²², D'Haens endoscopic score³²³, and Rutgeert's score³²⁴, as well as histological scores and other measures such as ultrasound scans and physician assessment (Appendix table 23). Discussion of the endoscopic measures used as primary and secondary endpoints was presented in Chapter 2.

Most trials, 172/181 (95.0%), measured outcomes in the defecation functions domain; 170/181 (93.9%) included endpoints that measured these outcomes as part of an index and 19/181 (10.5%) included endpoints that measured these outcomes as individual measurements. Outcomes within this domain are faecal output, faecal consistency, frequency of defecation, faecal continence, flatulence, diarrhoea, blood with stool and fistula discharge. Measurement of these outcomes was with the CDAI, HBI, VHAI, IBDQ, PDAI, adapted-Vaizey faecal incontinence score, IBS severity scoring system and diary card assessments.

Outcomes in some domains were generally only measured as part of key disease activity indices such as CDAI and HBI and therefore were reported in similar numbers of trials (162/181 - 166/181, 89.5% - 91.7%). These pathophysiological manifestation outcome domains, with examples of outcomes in brackets, were pain in abdomen or stomach; changes in structures of areas of skin (extra intestinal lesions and perianal duration); pain in joints (arthralgia), changes in body temperature (fever or prolonged fever), changes in the structure of the eyeball (uveitis); additional musculoskeletal structures related to movement (arthritis). Similar numbers of trials measured outcomes in two other domains: weight maintenance functions (body mass) was measured by key indices (CDAI, VHAI, 156/181, 86.2%) but also by individual measures (15/181, 8.3%) including BMI and mid-arm muscle circumference. Similarly, haematological system functions (blood abnormalities) were measured through the same key indices (156/181, 86.2%) but also by blood counts and various tests such as haematocrit (23/181, 12.8%).

Outcomes in a second tier of domains were reported by between 77/181 and 83/181 (42.5% and 45.9%) trials, which largely reflects the use of the IBDQ to measure endpoints. These domains were emotional functions, sexual functions, energy and drive functions (including appetite), sensations associated with the digestive system (including nausea and bloating) and sleep functions. There were some individual outcome measures used for each domain too, including outcome specific questionnaires and patient diaries (PROMs).

Biomarkers are reported in 102/181 (56.4%) studies with 102 individual outcome measures, indicating a large amount of variability in measurement, due to exploratory endpoints. The outcomes reported are inflammation and intestinal permeability and a range of measures are used including erythrocyte sedimentation rate, the presence of cytokines and bacteria in mucosal tissues and plasma, and intestinal permeability tests.

Between 2/181 and 25/181 (1.1% and 13.8%) papers measured outcomes in four other domains: sensation of pain (bodily pain and perianal pain), digestive functions (absorption of nutrients), ingestion functions (vomiting, calorie intake, maintenance of full diet, return to full diet and return to liquid diet) and general metabolic functions (liver or kidney function). These outcomes were measured using a range of measurement tools from blood tests through to PROMs.

ADVERSE EVENTS

Out of 42 domains, approximately half of the trials reported AEs in five domains (Figure 12). AEs in the domain of infections were reported in 106 trials (of 181, 58.6%). Infections is not a domain for outcomes. Sensation of pain was reported in 105 trials (of 181, 58.0%) and the most common AEs reported in that domain were headache, back pain, myalgia, pain and proctalgia (adverse events detail is in Appendix table 16). AEs in the structure of the intestine domain were reported in 53.0% (96/181) of trials and the most common AEs were Crohn's disease (aggravated or exacerbated), fistula, rectal haemorrhage and anal fissure. Sensations associated with the digestive system were reported by 49.7% of trials (90/181) and the most common AEs were nausea, dyspepsia and abdominal distention. AEs in the pain in the abdomen domain were reported in 90/181, 49.7% of trials.

Between 58 and 76 (/181, 32.0%-35.9%) of trials report AEs in five domains. AEs in the domain of functions of the skin and related structures were reported in 76/181 trials (42%) with rash, acne, pruritus and alopecia the most common events. Immunological system function domain (65/181, 35.9%) includes the presence of drug-specific antibodies, leukopenia and hypersensitivity as the most common events. Within the defecation function domain (65/181, 35.9%), diarrhoea,

flatulence and constipation are the most common AEs. The domain of Ingestion functions (59/181, 32.6%) is made up of vomiting, dry mouth and retching AEs. The pain in joints domain (58/181, 32.0%) includes arthralgia as its only AE.

A further nine AE domains match those identified in the Filter 2.0 outcomes domains (example outcomes in parentheses): body temperature (pyrexia) (47/181, 26.0%), weight maintenance functions (weight loss) (13/181, 7.2%), haematological system functions (blood abnormalities) (39/181, 21.5%), biomarkers (C-reactive protein) (9/181, 5.0%), emotional functions (e.g. depression) (22/181, 12.2%), energy and drive functions (fatigue, appetite) (47/181, 26%), sleep functions (19/181, 10.5%), digestive functions (intestinal obstructions) (35/181, 19.3%) and general metabolic functions (e.g. laboratory parameters) (50/181, 27.6%).

AEs were reported in a further 23 domains as shown in Figure 12 and Appendix table 16, including cancer (20/181, 11.0%) and general system conditions (swelling, oedema) (18/181, 9.9%) which were not coded from the ICF.

3.3.5. Mapping the ICF core sets for IBD against Filter 2.0

Table 11 shows the Filter 2.0 domains and the key indices and questionnaires mapped against the brief ICF core set for IBD. The brief set, known as the disability index for IBD¹⁰⁰ is the main comparison as this set is designed to be reported in clinical trials. Appendix table 25 shows the same information but mapped against the comprehensive core set for IBD. The outcomes from the environment chapter of the ICF have been omitted as they are contextual and environmental and are not relevant to outcomes and AEs reporting.

Table 11: Filter 2.0 domains and key outcome measurement tools mapped against the ICF brief core set for IBD (disability index for IBD)

Brief set		Filter 2.0?	CDAI?	IBDQ?	SF-36?	HBI?	PDAI?	VHAI?	Adverse events?
ICF code	ICF name								
b130	Energy and drive functions	yes		yes	yes				yes
b134	Sleep functions	yes		yes					yes
b152	Emotional functions	yes		yes	yes				yes
b1801	Body image								
b28012	Pain in stomach or abdomen	yes	yes	yes	b280 - sensation of pain	yes	b280 - sensation of pain		yes
b515	Digestive functions	yes							Yes
b525	Defecation functions	yes	yes	yes		yes	yes	yes	Yes
s540	Structure of intestine	yes	yes			yes	yes	yes	Yes
s770	Additional musculoskeletal structures related to movement	yes	yes			yes			
d5301	Regulating defecation	yes		yes					
d570	Looking after one's health	d5	Quality of life Self-care	yes - quality of life		yes - self care	yes - quality of life		
d7	Interpersonal interactions and relationships	yes		yes					
d810-d839	Education	yes		yes	yes				
d840-d859	Work and employment	yes		yes	yes				

Note: CDAI – Crohn’s Disease Activity Index; IBDQ – Inflammatory Bowel Disease Questionnaire; SF-36 – Short Form 36; HBI – Harvey Bradshaw Index; PDAI – Perianal Disease Activity Index; VHAI – Van Hees Activity Index

3.3.5.1. Filter 2.0 results and the ICF core sets for IBD

There is a good degree of fit between the outcomes measured in Crohn's disease trials and the core sets as shown in Table 11 and Appendix table 25, but there are differences to note. The domains under core areas of death and economic impact / resource use within the impact of health conditions concept, are not covered by the ICF core sets.

The life impact section of Filter 2.0 for Crohn's disease outcomes includes domains for patient perception of health, mobility, doing housework, handling stress and other psychological demands and utility of treatment, none of which is captured by the ICF core sets.

On the pathophysiological manifestations side of the hierarchy, Crohn's disease outcomes are reported in the domains of body temperature, changes in the structure of the eyeball, biomarkers, ingestion functions and general metabolic function, which are not covered the ICF core sets.

There are four outcomes reported in the ICF comprehensive core set for IBD that are not reported in the literature and are not measured by any of the key measures for disease activity and quality of life: body image; immunological system functions; water, mineral and electrolyte balance functions; and procreation functions. Body image is also reported as part of the brief core set, indicating its importance for patients with IBD, according to the consensus process undertaken in developing the IBD ICF core sets. This is the only outcome from the brief core set not captured by the domains in Filter 2.0. Additionally, digestive functions, which involves the breakdown of food and absorption of nutrients, is captured as an AE domain, but not as an outcome domain.

A comparison of the core sets against the AE domains highlights a good level of fit with the body structures and body functions domains of the ICF. Within the brief core set, the only domain not captured is body image. Within the comprehensive set additional missing AE domains are sexual functions and procreation functions. As might be expected, none of the domains related to activities and participation are included as AE domains.

3.3.5.2. Filter 2.0 results, the ICF core sets for IBD and the key measurement tools used in Crohn's disease

CROHN'S DISEASE ACTIVITY INDEX (CDAI)

The CDAI measures mainly outcomes of pathophysiological nature and only one outcome in a domain of the life impact side of the framework (Figure 13): general wellbeing, which sits in the quality of life domain. A number of the comprehensive ICF core outcomes are not represented by the CDAI. More importantly, given its intended use as a clinical trial outcome measure, a number of the brief core set outcomes are not part of the CDAI. The CDAI measures outcomes related to five out of 14 of the brief core set but it does not measure outcomes related to energy and drive, sleep, emotions, body image, digestive functions, regulating defecation and interpersonal interactions and relationships.

INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

The IBDQ covers a broad number of the outcomes of the ICF core sets, which are split reasonably equally across the two Filter 2.0 core areas of life impact and pathophysiological manifestations (Figure 14). Out of the mapped outcome measures, it has the best coverage of the brief core set, as it includes nine of the 14 outcomes. The IBDQ does not include any measure of body image, digestive functions, structure of the intestine, additional musculoskeletal structures related to movement, and looking after one's health. It is interesting to note that if the IBDQ is used in combination with the CDAI, as it frequently is in the literature (71/181, 39.2% of trials) 12 of the brief set outcomes would be measured, leaving only two outcomes unmeasured; body image and digestive functions.

Figure 13: Crohn's Disease Activity Index (CDAI) mapped against Filter 2.0 outcomes in Crohn's trials and the ICF core sets for IBD (measured in 156 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/182, 1.1%)	Quality of life (167/181, 92.3%)^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1,2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1,2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1,2} Utility of treatment (71/181, 39.2%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1,2}	Individual resource use (163/181, 90.1%) Health care cost (3/182, 1.6%)	ICF s540: Structure of intestine (174/181, 96.1%)^{1,2} ICF b525: Defecation functions (172/181, 95.0%)^{1,2} ICF b28012: Pain in stomach or abdomen (169/181, 93.4%)^{1,2} ICF s810: Structures of areas of skin (166/181, 91.7%)³ ICF b28016: Pain in joints (163/181, 90.1%)¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%)^{1,2} ICF b530: Weight maintenance functions (157/181, 86.7%)¹ ICF b430: Haematological system functions (156/181, 86.2%)¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1,2} ICF b640: Sexual functions (83/181, 45.9%) ¹ ICF b130: Energy and drive functions (82/181, 45.3%) ^{1,2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1,2} ICF b280: Sensation of pain (25/181, 13.8%) ³ ICF b515: Digestive functions (14/181, 7.7%) ^{1,2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	¹ In IBD ICF comprehensive set ² In IBD ICF brief set	³ Similar item in IBD ICF comprehensive set ⁴ Similar item in IBD ICF brief set		

Figure 14: Inflammatory Bowel Disease Questionnaire (IBDQ) mapped against Filter 2.0 outcomes in Crohn's trials and the ICF cores sets for IBD (measured in 77 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/182, 1.1%)	Quality of life (167/181, 92.3%) ^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1,2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1,2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1,2} Utility of treatment (71/181, 39.2%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1,2}	Individual resource use (163/181, 90.1%) Health care cost (3/182, 1.6%)	ICF s540: Structure of intestine (174/181, 96.1%) ^{1,2} ICF b525: Defecation functions (172/181, 95.0%) ^{1,2} ICF b28012: Pain in stomach or abdomen (169/181, 93.4%) ^{1,2} ICF s810: Structures of areas of skin (166/181, 91.7%) ³ ICF b28016: Pain in joints (163/181, 90.1%) ¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%) ^{1,2} ICF b530: Weight maintenance functions (157/181, 86.7%) ¹ ICF b430: Haematological system functions (156/181, 86.2%) ¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1,2} ICF b640: Sexual functions (83/181, 45.9%) ¹ ICF b130: Energy and drive functions (82/181, 45.3%) ^{1,2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1,2} ICF b280: Sensation of pain (25/181, 13.8%) ³ ICF b515: Digestive functions (14/181, 7.7%) ^{1,2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	1 In IBD ICF comprehensive set 2 In IBD ICF brief set		3 Similar item in IBD ICF comprehensive set 4 Similar item in IBD ICF brief set	

SHORT-FORM 36 HEALTH SURVEY (SF-36)

The SF-36 survey populates more domains on the life impact side of the Filter 2.0 framework (Figure 15), which is to be expected, as it is a health-related quality of life measure. It also captures emotional and energy and drive functions, as well as a broad definition of bodily pain, all domains of pathophysiological manifestations. It includes several domains not considered in the ICF core sets: patient perception of health, mobility and doing housework. However, it reports only six of the brief set outcomes. If the SF-36 were used in place of the IBDQ alongside the CDAI it provides a much worse fit of the brief set, measuring just nine of the outcomes with the loss of sleep functions, defecation functions, regulating defecation and interpersonal interactions and relationships.

HARVEY-BRADSHAW INDEX (HBI)

The HBI is slightly narrower in scope than the CDAI with the removal of three items (Figure 16). However, in terms of the match with the brief core set, the switch between the CDAI and the HBI would have no impact as they cover (and miss) the same core outcomes. As such, the use of HBI with either the IBDQ or the SF-36 would have the same results as those described above.

Figure 15: Short-Form 36 (SF-36) mapped against Filter 2.0 outcomes in Crohn's trials and the ICF cores sets for IBD (measured in 14 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/182, 1.1%)	Quality of life (167/181, 92.3%) ^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1,2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1,2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1,2} Utility of treatment (71/181, 39.2%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1,2}	Individual resource use (163/181, 90.1%) Health care cost (3/182, 1.6%)	ICF s540: Structure of intestine (174/181, 96.1%) ^{1,2} ICF b525: Defecation functions (172/181, 95.0%) ^{1,2} ICF b28012: Pain in stomach or abdomen (169/181, 93.3%) ^{1,2} ICF s810: Structures of areas of skin (166/181, 91.7%) ³ ICF b28016: Pain in joints (163/181, 90.1%) ¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%) ^{1,2} ICF b530: Weight maintenance functions (157/181, 86.7%) ¹ ICF b430: Haematological system functions (156/181, 86.2%) ¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1,2} ICF b640: Sexual functions (83/181, 45.9%) ¹ ICF b130: Energy and drive functions (82/181, 45.9%) ^{1,2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1,2} ICF b280: Sensation of pain (25/181, 13.8%) ³ ICF b515: Digestive functions (14/181, 7.7%) ^{1,2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	¹ In IBD ICF comprehensive set	³ Similar item in IBD ICF comprehensive set		
	² In IBD ICF brief set	⁴ Similar item in IBD ICF brief set		

Figure 16: Harvey-Bradshaw Index (HBI) mapped against Filter 2.0 outcomes in Crohn's trials and the ICF cores sets for IBD (measured in 14 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/181, 1.1%)	Quality of life (167/181, 92.3%)^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1, 2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1, 2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1, 2} Utility of treatment (71/181, 39.2%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1, 2}	Individual resource use (163/181, 90.1%) Health care cost (3/181, 1.7%)	ICF s540: Structure of intestine (174/181, 96.1%)^{1, 2} ICF b525: Defecation functions (172/181, 95.0%)^{1, 2} ICF b28012: Pain in stomach or abdomen (169/181, 93.4%)^{1, 2} ICF s810: Structure of areas of skin (166/181, 91.7%)³ ICF b28016: Pain in joints (163/181, 90.1%)¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%)^{1, 2} ICF b530: Weight maintenance functions (157/181, 86.7%) ¹ ICF b430: Haematological system functions (156/181, 86.2%) ¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1, 2} ICF b640: Sexual functions (83/181, 45.9%) ¹ ICF b130: Energy and drive functions (82/181, 45.3%) ^{1, 2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1, 2} ICF b280: Sensation of pain (25/181, 13.8%) ³ ICF b515: Digestive functions (14/181, 7.7%) ^{1, 2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	¹ In IBD ICF comprehensive set	³ Similar item in IBD ICF comprehensive set		
	² In IBD ICF brief set	⁴ Similar item in IBD ICF brief set		

PERIANAL DISEASE ACTIVITY INDEX (PDAI)

The PDAI is by its nature much more narrow in scope than either the CDAI or the HBI, which is reflected in its mapping to the domains of the Filter 2.0 framework (Figure 17). All of the outcomes from the PDAI map to the pathophysiological manifestations domains. Only three of the outcomes are included in the brief core set. However, it is the only key index or questionnaire from the literature that is entirely contained in the comprehensive set: all five outcomes measured in the PDAI are part of the comprehensive set. If used alongside the SF-36 it would cover eight of the brief set core outcomes, which is only one less than the combination of the CDAI and the SF-36. The difference is the loss of the outcome measuring additional musculoskeletal structures related to movement (arthralgia). There would also be a switch from the specific reporting of pain in the abdomen or stomach to a broader category of bodily pain.

VAN HEES ACTIVITY INDEX (VHAI)

The VHAI is by nature designed to be complete with objective outcome measures and, as such, it falls entirely within domains of the pathophysiological manifestations core area (Figure 18). It performs weakly against the ICF core sets, with five items within the comprehensive set and only two within the brief set; the latter matched domains are defecation functions and structure of intestine.

Figure 17: Perianal Disease Activity Index mapped against Filter 2.0 outcomes in Crohn’s trials and the ICF cores sets for IBD (measured in 10 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn’s (2/181, 1.1%)	Quality of life (167/181, 92.3%) ^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1,2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1,2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1,2} Utility of treatment (71/181, 32.6%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1,2}	Individual resource use (163/181, 90.1%) Health care cost (3/181, 1.7%)	ICF s540: Structure of intestine (174/181, 96.1%)^{1,2} ICF b525: Defecation functions (172/181, 95.0%)^{1,2} ICF b28012: Pain in stomach or abdomen (169/181, 93.4%) ^{1,2} ICF s810: Structures of areas of skin (166/181, 91.7%)³ ICF b28016: Pain in joints (163/181, 90.1%) ¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%) ^{1,2} ICF b530: Weight maintenance functions (157/181, 86.7%) ¹ ICF b430: Haematological system functions (156/181, 86.2%) ¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1,2} ICF b640: Sexual functions (83/181, 45.9%)¹ ICF b130: Energy and drive functions (82/181, 45.3%) ^{1,2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1,2} ICF b280: Sensation of pain (25/181, 13.8%)³ ICF b515: Digestive functions (14/181, 7.7%) ^{1,2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	¹ In IBD ICF comprehensive set		³ Similar item in IBD ICF comprehensive set	
	² In IBD ICF brief set		⁴ Similar item in IBD ICF brief set	

Figure 18: Van-Hees Activity Index (VHAI) mapped against Filter 2.0 outcomes in Crohn's trials and the ICF cores sets for IBD (measured in 7 studies)

Concepts	Impact of health conditions			Pathophysiological manifestations
Core areas	Death	Life impact	Economic impact	Pathophysiological manifestations
Domains	Death due to Crohn's (2/181, 1.1%)	Quality of life (167/181, 92.3%) ^{3,4} ICF d810-d839: Education (82/181, 45.3%) ^{1, 2} ICF d840-d859: Work and employment (82/181, 45.3%) ^{1, 2} ICF d9: Community, social and civic life (82/181, 45.3%) ³ Patient perception of health (82/181, 45.3%) ICF d5301: Regulating defecation (77/181, 42.5%) ^{1, 2} Utility of treatment (71/181, 39.2%) ICF d4: Mobility (14/181, 7.7%) ICF d5: Self-care (14/181, 7.7%) ^{3,4} ICF d640: Doing housework (14/181, 7.7%) ICF d240: Handling stress and other psychological demands (3/181, 1.7%) ICF d7: Interpersonal interactions (1/181, 0.5%) ^{1, 2}	Individual resource use (163/181, 90.1%) Health care cost (3/181, 1.7%)	ICF s540: Structure of intestine (174/181, 96.1%)^{1, 2} ICF b525: Defecation functions (172/181, 95.0%)^{1, 2} ICF b28012: Pain in stomach or abdomen (169/181, 93.4%) ^{1, 2} ICF s810: Structures of areas of skin (166/181, 91.7%)³ ICF b28016: Pain in joints (163/181, 90.1%) ¹ ICF b5500: Body temperature (163/181, 90.1%) ICF s220: Structure of eyeball (162/181, 89.5%) ICF s770: Additional musculoskeletal structures related to movement (162/181, 89.5%) ^{1, 2} ICF b530: Weight maintenance functions (157/181, 86.7%)¹ ICF b430: Haematological system functions (156/181, 86.2%)¹ Biomarkers (102/181, 56.4%) ICF b152: Emotional functions (83/181, 45.9%) ^{1, 2} ICF b640: Sexual functions (83/181, 45.9%) ¹ ICF b130: Energy and drive functions (82/181, 45.3%) ^{1, 2} ICF b535: Sensations associated with the digestive system (77/181, 42.5%) ¹ ICF b134: Sleep functions (77/181, 42.5%) ^{1, 2} ICF b280: Sensation of pain (25/181, 13.8%) ³ ICF b515: Digestive functions (14/181, 7.7%) ^{1, 2} ICF b510: Ingestion functions (6/181, 3.3%) ICF b540: General metabolic function (2/181, 1.1%)
	¹ In IBD ICF comprehensive set		³ Similar item in IBD ICF comprehensive set	
	² In IBD ICF brief set		⁴ Similar item in IBD ICF brief set	

3.4. Discussion

3.4.1. Summary of evidence

A systematic review of the literature on treatments for adults with Crohn's disease identified 181 studies. Trial endpoints and AE data was extracted from the included studies, which resulted in the identification of 93 unique outcomes and 577 AEs at the level of individual signs, symptoms and events. Key outcome measurement tools (disease activity indices and PROMs) dominate the listings of outcomes, which is not surprising given their prominence in EMA guidance for Crohn's disease.^{68,325} The CDAI is used in 156/181 (86.2%) studies and contributes 15 outcomes to the Crohn's Filter 2.0 framework. IBDQ is used in 77/181 (42.5%) studies and contributes 32 outcomes to the framework. All of the most commonly reported outcome domains are those that include outcomes measured by the CDAI, which is an outdated measurement tool and no longer recommended for use as a trial endpoint, as discussed in Chapter 2.

A large number of discrete AEs are reported (577) but half of these are reported only once across all 181 trials. The most common AEs are abdominal pain, headache, Crohn's disease (aggravated) and nausea. Some of the pre-specified AE categories are also commonly reported: discontinuation due to adverse events; total adverse events; study withdrawal due to various reasons (including loss to follow up and non-compliance); total serious adverse events; and withdrawal due to treatment failure. Treatment-related adverse events were reported in fewer than half of the trials (36.5%, 66/181), highlighting the difficulty in accessing good data on harms caused by the therapies in clinical trials. It is difficult to distinguish whether an adverse event reported without attribution of causality is related to the drug, the underlying disease process, or a drug-disease interaction.

Individual resource use was a well reported domain for outcomes, which certainly reflects the use of CDAI and its question on anti-diarrhoeal medications, but may also reflect the recommendation in EMA guidance that steroid sparing and a reduction in surgical procedures make suitable

secondary endpoints⁶⁸. Individual resource use outcomes were also reported in more than a fifth of studies as AEs, specifically as the need for hospitalisation or surgery. Other economic outcomes were less well measured.

96.1% of trials measured outcomes related to the structure of the intestine, which is the influence of CDAI, but in half of the trials the presence of changes was measured in other ways, often endoscopic and histological scores. Objective assessments of mucosal healing are recommended as co-primary endpoints (with PROMs) of symptomatic remission in the EMA guidance for Crohn's disease⁶⁸. As discussed in Chapter 2 the reporting of such primary and secondary endpoints has increased over the years.

AE domains were predominantly in the pathophysiological core area and infections, pain, the structure of the intestine, sensations associated with the digestive system and pain in the abdomen were all reported in almost half of the trials. All but infections were also outcome domains. Whilst infections are not reported as specific trial endpoints, they are important for many treatments, especially immunosuppressives and biological therapies and often form monitoring requirements in clinical trials and in clinical use^{68,326}.

Biomarkers were measured as outcomes in 102/181(56.4%) of trials. The importance of this domain may be reflective of the inclusion of laboratory measures of inflammation as a potential secondary trial endpoint in EMA guidance⁶⁸. It may also be reflective of the monitoring capabilities and new technologies available to the people running trials. Whilst only 9/181 (5.0%) of trials reported AEs that were classified as biomarkers, many other reported AEs could have been classified in a biomarkers category had it not been possible to categorise them more specifically using the ICF. For example, immunological system functions, haematological system functions and general metabolic functions are all types of biomarkers and AEs in these domains were reported in 35.9%, 21.5% and 27.6% of trials, respectively.

The overlaying of the ICF core sets to the Filter 2.0 domains for outcomes and AEs in Crohn's disease trials, highlighted a good deal of fit, although there are differences. The ICF core sets have been through a rigorous process involving both professionals and patients to identify what is most important for IBD¹⁰⁰ so it might be expected that there should be complete fit. However, it may be too early to expect the core sets to have filtered through to clinical trials in the time from publication (2012) to the dates covered by the systematic review (up to 2015). It is also possible that the important outcomes for Crohn's disease could be different to those that are important for all inflammatory bowel diseases.

The ICF brief core set for IBD, identified as a disability index for IBD by its authors¹⁰⁰, has been designed for reporting in trials and is reasonably well covered; 13 out of 14 outcomes in the brief set are also found in the literature and included in Filter 2.0 domains for Crohn's disease trials. Body image was included as an outcome in both the comprehensive and brief ICF core sets, which indicates a high level of importance was placed in it during the robust development process. However, this domain did not feature in the trial outcomes or AEs. In the IBD ICF comprehensive set, three other domains were included as important – carrying out daily routine, sexual function and procreation function and none of these are reported in the outcomes and AEs (with the exception of sexual function being measured within the PDAI in five trials). This may reflect an unwillingness by patients to report such AEs and a focus by trialists on more focused efficacy outcomes rather than the wider life impacts.

Some domains within Filter 2.0 are excluded from the ICF core sets, as they are not covered within the scope of the ICF, such as death and economic impact domains. Further, on the life impact side of Filter 2.0, the trials measured outcomes in the domains of patient perception of health, mobility, doing housework, handling stress and utility of treatment. Two important domains, reflected in both outcomes and AEs, which are not covered by the IBD ICF sets are patient perception of health and the utility of treatment. This may reflect the fact that these domains are

less about measurable characteristics of function and structure of particular organ systems and more about the perceptions of patients and physicians on the disease course and treatment and therefore again not captured by the design of the ICF.

Some frequently reported pathophysiological outcome domains are not included in the core sets but are within the most reported outcome measurement tool, the CDAI: body temperature and changes in the structure of the eyeball (uveitis). Body temperature was also a well-reported adverse event domain.

None of the outcome measurement tools fit exactly with the ICF core set and only one, the PDAI, was contained entirely within it. This tool is only used in five studies and is used in trials with patients with fistulising disease. The disability index (ICF brief set) has 14 items and the CDAI, HBI, PDAI and VHAI cover only five of the core set items whilst the IBDQ and SF-36 cover nine and six, respectively. No combination of the measurement tools covers the IBD disability index. Interestingly, the use of the CDAI and IBDQ together, which occurs in 40% of the trials, covers only 12 of the 14 outcomes in the brief core set, and the use of a simpler disability index such as the HBI has no impact on the coverage.

3.4.2. Strengths and limitations

One of the key difficulties in capturing the impact of a treatment is understanding the impact on health states that are not directly measurable. Outcome measurement tools are designed to help overcome this problem but it is often not clear exactly what is being measured. Measurement tools can be used for long periods without being updated, as has been the case for the CDAI. A key strength of this research has been to introduce transparency into the outcome measurements by breaking them down into the component signs, symptoms and events that are being measured. Matching the findings of the Filter 2.0 categorisation against the ICF core sets for IBD has provided an external benchmark to a set of outcomes that have been identified through a rigorous and robust process involving reviews, expert surveys, cross-sectional study and a Delphi process. The

method provides a framework for assessing which measurement tools used in the literature address current core outcome sets. Whether the IBD disability index, in the form of the ICF brief core set, is to become an important secondary endpoint as argued for by the authors remains to be seen and there is some doubt as to its relevance^{327,328}. However, it currently stands as the only form of COS that could be applied to Crohn's disease and as such is an appropriate comparison.

The approach taken in this chapter has indirectly developed a method that could be used to assess the uptake of core outcome sets, which also includes the measurement instruments. This is a unique element to the research. The ICF core sets were published in 2012 and the systematic review only included trials published up to 2015, which means that the method applied in this context is unlikely to reflect the uptake of the core sets due to the time it takes for RCTs to be planned, conducted and reported. However, there is the potential for this method to be applied in other contexts where core outcome sets have been recommended and clinical-composite measurement tools and PROMs are frequently used.

The use of existing models for outcome classification in the Filter 2.0³¹⁰, the ICF³¹² and the Wilson and Cleary model of quality of life³¹³ provide a sound basis for the synthesis of the outcomes into a single model. In particular, the ability to categorise both outcomes and AEs within the same domains, rather than by including an "adverse events" domain to catch all is a strength and helps to highlight the need for greater consideration of harms of therapy alongside benefits. The method of sorting the outcomes and AEs into domains and reporting how many trials report those domains gave an understanding of the facets of life being measured in patients with Crohn's disease and was a pragmatic approach to assessing the important events in lieu of other consensus methods.

However, one key weakness of the use of Filter 2.0 stems from the categorisation in domains. The flexibility of the model is also its downfall as it would be possible for another researcher to categorise the outcomes and AEs differently. Decisions were taken on the grouping of ICF coded

outcomes and AEs, with the clinical expertise of KB, but another researcher may have grouped codes to different levels, with a resultant impact on the number of outcomes and AEs captured in that domain and therefore the number of trials reporting those domains. The ICF provides an objective measure of disability to capture a broader range of the impact of a medical condition, but it does not capture how an individual feels about the disability experienced³²⁹. It will therefore always be necessary to include domains from other models, such as quality of life models, to capture how an individual feels about the disabling nature of their condition and their response to it. Within this classification process, it was also necessary to add additional domains and once again, the flexibility in those choices may mean that another researcher would choose differently.

A recently published taxonomy, which suggests a 38 category scale for outcomes classification covering pathophysiological, functioning and resource use elements, identified through a systematic review of outcome classification methodologies, may have resolved this issue, however, by providing a fully specified alternative to Filter 2.0³³⁰. This new taxonomy is more granular than the OMERACT framework and allows for specification on two levels, firstly by classifying into a relevant domain and secondly by identifying entries as adverse events of outcomes. One significant advantage of this taxonomy is the ease of use as it provides a single and comprehensive taxonomy, which avoids the need to compile domains from several different models.

Matching the outcomes from the ICF core sets for IBD against the Crohn's Filter has highlighted what current research might be failing to capture. Perhaps more important has been the approach of mapping the most commonly used disease activity indices and PROMs against both the Filter 2.0 framework for Crohn's disease outcomes and AEs and the ICF core sets for IBD which has highlighted many points. Firstly, it has shown some of the gaps in the measures in terms of the important outcomes that are not included and therefore additional outcomes that researchers may want to measure or additions that should be considered when developing new outcome

measurement tools. Body image is a case in point as it has been ranked as important enough to be included as one of only 14 outcomes in the disability index for IBD, but is not measured at all in the Crohn's trials, and digestive functions is only included as an AE. Secondly, the approach has made clear the choices that researchers currently face when combining disease activity indices and quality of life questionnaires and provides a method for checking how well those tools cover existing core outcome sets. This should support research to develop additional measurement tools to meet existing core outcome sets. It may also help trialists in deciding which measurement tools to use based on their views on the most important aspects of quality of life and on pragmatic decisions of the now explicit trade-off between the ease of measurement of the outcome measurement tools versus the outcomes captured.

The usefulness of frequency reporting of the outcomes within domains was undermined as the disease activity indices and PROMs featured so heavily, i.e. any outcome measured by the CDAI would automatically be at the top of the list due to the reporting of the CDAI in 156/181 (86.2%) papers. This is clearly not necessarily appropriate given that outcomes such as uveitis then appear to be some of the most important but are not in either of the ICF core sets. Perhaps this is reflective of the fact that the ICF sets are for IBD as a whole and uveitis is important only for Crohn's and would therefore be in a core set for Crohn's, but it is impossible to know without some sort of consensus process.

The usefulness of frequency reporting of adverse event categories such as discontinuation due to adverse events; total adverse events; study withdrawal due to various reasons (including loss to follow up and non-compliance); total serious adverse events; and withdrawal due to treatment failure may also be questioned. These outcomes are composites as they are made up of individual adverse event reports, rather than an aggregation of the same events. As such, it can be difficult to understand what to infer from them. A shared criticism with benefit composite measures is that they are not transparent in what they capture. Whilst they can provide a general measure of

how tolerable the treatment is, they are likely to be subject to variation in reporting processes that would make comparisons between trials and drugs difficult. The standardisation of composite outcome measurement tools means that this is not a difficulty for benefit outcomes.

There is a general dilemma in categorisation of adverse events that reflects the challenge of distinguishing between: a. side effects of the drug treatment that are independent of the disease process and could happen to any patient; b. adverse events that are a manifestation of the underlying disease process, reflecting worsening or complications of the disease; and c. adverse events that only happen in people in a particular indication (Crohn's disease in this case) but are specifically caused by the drug. These issues were introduced in Section 1.1.3 and are discussed in detail in Chapter 4.

3.4.3. Conclusions

The systematic review for treatments of Crohn's disease in adults identified 181 relevant studies, yielding 93 outcomes and 577 adverse events. The outcomes and adverse events have been categorised across 35 outcome domains and 46 adverse event domains in the OMERACT Filter 2.0 framework, many of which overlap. The capturing of both outcomes and adverse events within a single model has provided a useful overall assessment, which may support the development of new outcome measurement tools, and a core outcome set.

The comparison with a robustly developed, if somewhat restrictive, core set for IBD and the common disease activity indices and PROMs provides a useful view of the state of outcomes measured in the literature and has highlighted that the currently used measurement tools do not cover all of the outcomes in the IBD disability index. Further research is needed into the gaps, specifically; the omission of body image and digestive functions from trial endpoints and the inclusion of uveitis in the most commonly used disease activity index should be understood.

The results of this chapter and the systematic review of endpoints in Chapter 2 have provided a clear overview of the outcomes and harms recorded in trials of treatments for Crohn's disease

over relatively short periods. However, trial reporting of adverse events is known to be flawed and Crohn's disease is a chronic disease and patients receive therapy over the long term so there is a need to characterise the harms beyond relatively short-term trial periods. Chapter 4 looks at a potential source of additional harms in the summary of product characteristics documents produced for each drug as a condition of regulatory approval.

Chapter 4: Summary of product characteristics as an additional source of adverse events in Crohn's disease

4.1. Introduction

4.1.1. Adverse events monitoring

Randomised controlled trials (RCTs) are the gold standard for monitoring the efficacy of interventions and can identify immediate and common adverse events associated with treatment. Adverse events (AEs) were defined in Chapter 1 as *“any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”*⁵³. As discussed in Chapter 1, capturing all AEs in RCTs is good practice both to protect individuals taking part in studies and to characterise the toxicity profile.

When an AE occurs, the principal investigator assesses whether it is related to the trial intervention and its seriousness⁵³. The outcome of their assessments dictates the speed of reporting and to whom the events are reported, as outlined in the study protocol. For example, international standards require that all serious adverse events (SAEs) that are not previously known to be related to the study drug and documented in the study protocol, must be reported immediately to the sponsor³³¹. Within a UK trial, if the sponsors determine that an SAE is related to the study drug, and is therefore a suspected unexpected serious adverse drug reaction, it will be notified to the Medicines and Healthcare products Regulatory Agency (MHRA) and the trial ethics committee³³². At the end of a trial, all AE data is provided to the sponsor and should be published alongside efficacy results by the trialists in line with the extension of the CONSORT (Consolidated Standards of Reporting Trials) statement³³³.

In comparison to clinical use over time, RCTs test drugs on a small number of carefully selected patients over relatively short periods, which may affect the generalisability of the results³³⁴. As such they are less useful for reporting AEs that are unexpected, rare, associated with long-term

use, have a long latency, or are related to drug-drug interactions, drug-disease interactions, co-morbidities or other susceptibility factors that have not been identified in clinical trials^{335,336}. Difficulties in planning safety analyses in trials include the difficulty in determining which of the event attributes (e.g. dose, duration, severity) should be considered the primary analysis and the inability to pre-specify some events³³⁴.

Further, there is evidence that harms in trials are poorly, and selectively, reported. The omission of adverse events prevents a full assessment of benefit and risk of an intervention, and further compromises the ability to synthesise data in systematic reviews and meta-analyses. Missing safety data may occur simply because adverse events take place in between study visits³³⁴, but more serious forms are also highlighted in the literature. “Distorted reporting” of AEs has been evidenced: 86% of trials included in a sample of Cochrane reviews, and 46% of trials included in systematic reviews synthesising harm outcomes were found to have inadequately reported the primary harm outcome and to have withheld, or downplayed, statistically significant increases in harm^{337,338}. A systematic review by Golder et al (2016) comparing published and unpublished trials found that omitted harms data has an impact on the number of AEs, types of AEs and risk ratios of AEs reported³³⁹. Surveys of trialists find that outcome reporting bias, where pre-specified outcomes are omitted from final publications, occur because of journal space restriction and because of a perceived lack of clinical importance or lack of statistical significance in the outcomes³³⁸.

The CONSORT statement extension should support better reporting of harms. An additional ten items have been added, which include requirements to provide denominators for harms analyses and to “*present the absolute risk per arm and per adverse event type, grade and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, wherever pertinent*”³³³. However, a systematic review of the reporting of harms according to the CONSORT statement demonstrated that adherence to the extended reporting requirements is

inadequate and variable in RCTs³⁴⁰. A study of trials published in high impact journals in 2009 demonstrated that only one in ten (10.8%) trials met all the requirements of the CONSORT statement³⁴¹. It is unclear whether this is due to a lack of knowledge of the statement on the part of trialists or journals.

Compounding these issues of selective reporting is the failure to publish results of trials at all. As many as half of medical and health-related studies are not published, which is primarily because of non-submission due to lack of time or low priority and fear of the research being rejected by journals³⁴². The failure to publish research leads to selective reporting, which may mean that trials with “negative” results are missing from the literature. This may have the greatest impact on rarer and more serious harms, which require systematic review to detect, but which incomplete reporting of RCTs can hamper³⁴³. A systematic review comparing published and unpublished data confirmed that a greater number and a wider range of adverse events were contained in unpublished research³⁴³.

Given these limitations of trial AE reporting in RCTs, other methods of harms reporting are necessary to fully characterise the risk of an intervention. Pharmacovigilance is the practice of monitoring, detecting, understanding and preventing AEs as introduced in Chapter 1. Safety reporting in RCTs is one element of pharmacovigilance, but it continues over the lifecycle of a product, including at marketing authorisation stage and beyond into the post-marketing phase.

4.1.2. Adverse reactions monitoring

Adverse reactions, also known as adverse drug reactions (ADRs) differ from AEs as they are *“any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject”*³⁴⁴.

Pharmacovigilance captures additional information beyond the point of marketing to monitor potential AEs and identify where there are associations between a drug and an AE³⁴⁵. One important element is the summary of product characteristics (SPC), which is the key document

required as part of the regulatory process and provides information to communicate risk, and to advise on the safe and effective use of the drug. Within Europe, the drug manufacturer produces the SPC, which the European Medicines Agency (EMA) approves. It is a living document, initially created mainly from trial data, but regularly updated as more data becomes available in the post-marketing phase.

Spontaneous reports of AEs that occur during the course of treatment are the primary source of update data. Spontaneous reporting systems are an important way to track adverse drug reactions that are rare and drug manufacturers are required to report serious reactions so they should provide comprehensive data³⁴⁶. In the UK, health professionals and members of the public can voluntarily make reports to the Yellow Card scheme when adverse events occur during clinical use of a drug⁵⁴. Disproportionality analysis methods are used to automatically generate signals from pharmacovigilance databases, which identify whether more events occur than would be expected given the background rate of those events³⁴⁷. Signals are investigated to determine if they are causally related to the drug; that is, whether they are adverse reactions or adverse drug reactions (ADRs), rather than adverse events (AEs).

Section 4.8 of the SPC details the undesirable effects, which is a summary of *“all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility”*¹⁵. Unlike in trials, AEs without any suspected causal relationship should not be included. Section 4.4 of the SPC details special warnings and precautions for use, which are messages to healthcare professionals. Messages include, but are not limited to, information on risk management plans, population groups who face greater risk of harm, serious adverse reactions that may occur and the conditions in which they could occur, adverse reactions associated with starting or stopping therapy and any monitoring requirements¹⁵.

4.1.3. Measuring frequency of adverse reactions

Estimating frequency of adverse reactions aids risk assessment, which supports clinical decision-making and health technology assessment. The frequency of adverse reactions is calculated from trials and post-marketing data and is included in section 4.8 of the SPC. The frequency of adverse reactions is currently reported in six categories from very common (affecting more than or equal to one in ten patients exposed to the drug) to very rare (affecting fewer than one in 10,000), as shown in Table 12.

Table 12: Frequency categories for adverse reactions reported in Summary of Product Characteristics (SPCs)

Frequency of adverse event	Numbers affected in frequency category
Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$
Frequency not known	cannot be estimated from the available data

A number of methods are used to estimate the frequency of adverse reactions to be reported in SPCs. If the different sources of adverse reactions data indicate different frequencies, the highest one is included in the SPC¹⁵.

Optimally, data on AEs is pooled across (ideally placebo controlled) trials, where possible without introducing bias, to estimate frequency. Point estimates of the crude incidence rate of an adverse reaction can also be obtained from safety studies designed to detect specific AEs over a defined time-period that can be reasonably attributed to the product. Where adverse reactions are indicated from spontaneous reporting systems, such as the MHRA yellow card scheme⁵⁴, well designed trials can be investigated to choose a frequency category.

In cases where ADRs are suspected, but no AEs have been reported in trials, statistical methods can be used to estimate frequency. The “rule of three” allows the upper limit of a 95% confidence interval to be estimated when an observed event rate is zero. The rule of three states that if a

drug has been tested on patients and none have experienced an event, a reasonable estimate is that the probability of that event occurring is less than $3/n$, where n is the total sample size of patients receiving the drug across all relevant trials and studies¹⁵. Statistically, the rule of three is derived as follows in Equation 4 to Equation 6³⁴⁸. A single event (X) has not been observed in n Bernoulli trials (individual trials asking a yes or no question) and the aim is to identify the probability p for that event. Assuming a binomial distribution with parameters n and p , then:

Equation 4: Probability of event in binomial distribution

$$P(X = 0|n, p) = (1 - p)^n$$

Solving for the upper confidence limit ($1 - p \geq \alpha$) the equation becomes:

Equation 5: Upper limit of probability of event in binomial distribution

$$p_u = 1 - \alpha^{1/n}$$

This approximates to:

Equation 6: Natural logarithm of upper limit of probability of event in binomial distribution

$$1 - \alpha^{1/n} \cong -\ln(\alpha)/n$$

The solution of $-\ln(\alpha) = 2.996$ and therefore the upper confidence limit of a zero-observed event approximates to $3/n$. This can be similarly solved using a Poisson distribution.

4.1.4. Aims and objectives

The aim of this chapter is to investigate potential methods to make use of the SPCs to identify and quantify harms that may be incompletely reported in the literature or those that are less well characterised by trials, such as longer term and rarer harms or those that may be underreported.

The objectives are to:

- Match the trials identified in the systematic review in Chapter 2 to their summary of product characteristics.

- Extract data on adverse reactions from the SPCs, standardise using the Medical Dictionary for Regulatory Activities (MedDRA) and match against the adverse events data extracted from the RCTs in Crohn's disease.
- Examine differences between the datasets of SPC adverse reactions and RCT adverse events to gain an understanding of the best methods to gather data and the usefulness of the data obtained.

4.2. Methods 1

A systematic review of clinical trials was conducted which identified 181 eligible studies from which efficacy outcomes and adverse events data was extracted. The methods used in the systematic review, including how the extracted data were standardised using the Medical Dictionary for Regulatory Activities (MedDRA) terminology, are outlined in Chapter 2.

4.2.1. Inclusion criteria for therapies

SPCs are only available for drugs once they become licensed medicines and therefore all non-drug therapies and experimental and unlicensed drug therapies were excluded from this chapter. Further, given the aim of fully characterising the harms from Crohn's disease treatment, other therapies that would not be considered "standard" treatment were excluded. Conventional therapies were identified from UK clinical guidelines for the treatment of Crohn's disease⁶².

AEs in trials and adverse reactions in the SPCs were compared by therapeutic class rather than at the level of individual drugs. This maximises the availability of adverse event and reactions data and allows for a more detailed view of the harms associated with drugs. The BNF drug classification was used to group therapies.

4.2.2. Selection of summary of product characteristics (SPCs)

SPCs were identified for the maximum possible number of therapies listed in the trials identified through the systematic review in Chapter 2. The electronic Medicines Compendium (eMC)³⁴⁹ was searched for each formulation used in the trials. Where an exact match was found, the SPC was

copied to a word document. Where an exact match was unavailable, the closest match was found. Due to the period of the systematic review results, other pharmaceutical companies now produce generic forms of some drugs in the exact same formulation as the trial. These SPCs were copied to the word document.

Where a SPC was unavailable for an identical formulation, the closest matching SPC was identified. To be considered a close match, the drug must be administered in the same formulation and route of administration as the original paper, although doses could differ as patients could take more than one tablet, for example. As an example, one trial tested Asacol 800mg modified-release tablets. Asacol is one brand of mesalazine and is available in gastro-resistant tablets of 250mg to 800mg, but it is also available as modified-release tablets, modified-release granules, foam, enema and suppositories. In this case, the SPC for gastro-resistant tables of 800mg was used as an exact match.

4.2.3. Data extraction

Data was extracted data from section 4.8 of the SPCs, Undesirable effects and recorded in a Microsoft Excel spreadsheet. The descriptions of selected adverse reactions were read to identify any additional data.

Specific data items were:

- The adverse reaction.
- The MedDRA system organ class (SOC), where reported.
- The frequency of the adverse reaction.

The data was standardised using the same methods as reported in Section 2.2.8 of Chapter 2. In brief, the adverse reactions were mapped against preferred terms (PTs) in the MedDRA hierarchy. The primary system organ classification (SOC) for each preferred term was used, even where it contradicted the SOC reported in the SPC, so that it would be possible to align the extracted data with the RCT data.

The sample sizes for each matched trial were obtained from the results in Chapter 2. The number of patients randomised to the treatment of interest was extracted. The rule of three was used to calculate the upper 95% confidence interval value for the frequency of adverse event that would be expected to be detected in each trial and group of trials using Equation 7.

Equation 7: Rule of three

$$\text{Upper limit of 95\% CI} = 3/n$$

Where n is the trial sample size or aggregated sample size. From this value, it was possible to identify the upper value of adverse reaction risk if a group of trials did not detect an adverse event, which could be matched to a frequency category. In addition, it is possible to draw inference about the frequency category of adverse event that the individual trials will be expected to detect given their size.

4.2.4. Combining data from SPCs within drug classes

Presenting data at the level of drug class required the pooling of data extracted from a number of SPCs. For some therapies in the same drug class, the adverse reaction profile was similar which resulted in the inclusion of multiple entries of the same preferred terms. Each preferred term was included in each frequency category in which it was reported in the SPCs. For example, headache was reported to occur both uncommonly and rarely in one drug class, but this approach was taken to preserve the detail in the data.

4.2.5. Data presentation

Summary tables were produced of preferred terms (PTs) by intervention type that were:

- Recorded as common or very common in the SPCs.
- Recorded as rare or very rare in the SPCs.
- Recorded in SPCs at any frequency, but not in trials.
- Recorded in trials, but not in SPCs.

4.3. Results 1

14 therapies were included in the analysis, which grouped into five therapeutic classes (Table 13): aminosalicylates (5-ASAs), antibiotics, anti-TNFs, corticosteroids and immunosuppressives. Antibiotics were split into sub-classes of macrolides, nitroimidazole derivatives and quinolones. Immunosuppressives were split into two sub-classes of antimetabolites and methotrexate.

The SPCs were found for all medicines recommended for use in NICE guidance (69 of 181 (38.1%) trials identified in Chapter 2). 57 (of 181, 31.5%) trials were excluded as they were not drug therapies. The remaining 55 (of 181, 30.4%) studies were excluded as they involved drugs that are not standard therapy for Crohn's disease. The drug class with most trials for which an SPC could be identified was corticosteroids (19 trials), followed by TNF α inhibitors (17 trials). Budesonide was the active ingredient for most trials for which an SPC could be matched (17), followed by mesalamine (12), azathioprine (11) and infliximab (10).

Three active ingredients were included in the drug class 5-ASAs: mesalamine, which was the focus of 12 trials with three formulations (and therefore three SPCs); Olsalazine, which was the focus of one trial with one formulation and a single SPC; and sulfasalazine, which was the focus of two trials with a single formulation, and therefore one SPC.

Three active ingredients were included in the antibiotics drug class, one in each sub-class, each with a single formulation and therefore a single SPC. Clarithromycin was the macrolides antibiotic and was the active ingredient in three trials. Metronidazole was the nitroimidazole derivative antibiotic and was the active ingredient in three trials. Ciprofloxacin is a quinolone antibiotic and was the active ingredient in seven trials.

Two active ingredients, matching to two formulations and two SPCs, were identified as anti-TNF α biologics. Infliximab was the most common, with ten trials, followed by adalimumab with seven.

Corticosteroids included three different active ingredients. Beclomethasone dipropionate and methylprednisolone were tested in single trials, with one formulation and one SPC in the analysis. There were 14 budesonide trials with three different formulations and therefore three SPCs included.

Three active ingredients were included in the immunosuppressives drug class. Methotrexate was tested in two trials and mercaptopurine (an antimetabolite) had a single trial, and each involved one formulation and one SPC each. There were 11 trials for azathioprine, with two different formulations matched to two SPCs.

Table 13: Table of therapies included in analysis, by drug class, active ingredient, brand name and formulation

Therapeutic Class (n= number of trials)	Active ingredient (n= number of trials)	Brand name, strength and formulation	Trial sample size range	Frequency value (category) determined by rule of 3 upper 95% CI for identifiable AEs
5-ASAs (n=15)	Mesalamine (n=12)	Salofalk 500mg ^{125,198,241,277}	15-153	2 in 100 (common) to 2 in 10 (very common)
		Pentasa slow release 500mg ^{118,233,276,280,284}	44-230	1.3 in 100 (common) to 6.8 in 100 (common)
		Asacol 800mg MR tablets ^{121,228,283}	20-206	1.5 in 100 (common) to 1.5 in 10 (very common)
	Olsalazine (n=1)	Olsalazine Sodium / Dipentium 250mg ²³⁸	167	1.8 in 100 (common)
	Sulfasalazine (n=2)	Salazopyrin tablets ^{224,225}	43-229	1.3 in 100 (common) to 7 in 100 (common)
Antibiotics, Macrolides (n=3)	Clarithromycin (n=3)	Klaricid XL 500mg tablets ^{148,186,252}	19-102	2.9 in 100 (common) to 2 in 10 (very common)
Antibiotics, Nitroimidazole derivatives (n=3)	Metronidazole (n=3)	Metronidazole tablets 500mg ^{150,190,286}	7-81	3.7 in 100 (common) to 4.3 in 10 (very common)
Antibiotics, Quinolones (n=7)	Ciprofloxacin (n=7)	Ciproxin tablets 500mg ^{132,150,153,163,190,209,290}	10-66	4.5 in 100 (common) to 3 in 10 (very common)
Biologics, TNFα inhibitors (n=17)	Adalimumab (n=7)	Humira 40mg/0.8ml pre-filled pen / syringe ^{171,182,209,253,255,268,289}	16-517	6 in 1000 (uncommon) to 1.9 in 10 (very common)
	Infliximab (n=10)	Remicade 100mg powder for concentrate for solution for infusion ^{129,134,135,174,175,187,217,240,245,287}	11-251	1.2 in 100 (common) to 2.7 in 10 (very common)

Therapeutic Class (n= number of trials)	Active ingredient (n= number of trials)	Brand name, strength and formulation	Trial sample size range	Frequency value (category) determined by rule of 3 upper 95% CI for identifiable AEs
Corticosteroids (n=19)	Beclomethasone dipropionate (n=1)	Clipper 5mg sustained release tablets ²⁶⁶	37	8.1 in 100 (very common)
	Budesonide (n=17)	Budenofalk 3mg gastro-resistant capsules ^{131,160,257,278}	43-157	1.9 in 100 (common) to 7 in 100 (common)
		Budenofalk 9mg gastro-resistant granules ²¹⁰	471	6 in 1000 (uncommon)
		Entocort CR 3mg capsules ^{120,123,249,279,149,198,206,232,234,237,239,241}	29-192	1.6 in 100 (common) to 1 in 10 (very common)
	Methylprednisolone (n=1)	Medrone tablets 100mg ²²⁵	225	1.3 in 100 (common)
Immunosuppressive, antimetabolites (n=12)	Azathioprine (n=11)	Azathioprine 50mg tablets ^{117,181,244,247,261,275,286,288,292}	11-58	5.2 in 100 (common) to 2.7 in 10 (very common)
		Imuran injection ^{136,187}	51-67	4.5 in 100 (common) to 5.9 in 100 (common)
	Mercaptopurine (n=1)	Mercaptopurine 50mg ²⁸⁴	47	6.4 per 100 (common)
Immunosuppressive, methotrexate (n=2)	Methotrexate (n=2)	Methotrexate 10mg tablets ^{235,272}	15-63	4.8 per 100 (common) to 2 per 10 (very common)

Note: Numbers in brackets indicate count of trials in drug class and active ingredient. Sum to greater than 69 as some trials test multiple drugs.

4.3.1. Common or very common adverse events recorded in SPCs

Common or very common adverse events are those that occur in more than one in 100 patients, as defined in Table 12. Given the sample sizes of the included trials and based on the rule of three calculations (Table 13), it might be expected that most trials would have the power to detect very common adverse reactions (occurring in one in ten), if not common adverse reactions. Table 14 demonstrates that the trials capture 50% or more of the common or very common adverse reactions identified in the SPCs by drug class. The only exception is anti-TNF α agents, where 75% of the very common or common adverse reactions are not captured in the Crohn's disease trials.

Table 14: Very common and common adverse reactions reported in the Summary of Product Characteristics (SPC) for Crohn's disease treatments, compared with those reported as adverse events in trials, by drug class

Drug class	Very common			Common			Very common and common		
	SPC	In trials		SPC	In trials		SPC	In trials	
		No.	%		No.	%		No.	%
5-ASAs	3	2	66.7%	26	15	57.7%	29	17	58.6%
Antibiotics, Macrolides	0	0	--	11	6	54.5%	11	6	54.5%
Antibiotics, Nitroimidazole derivatives	0	0	--	0	0	--	0	0	--
Antibiotics, Quinolones	0	0	--	2	2	100.0%	2	2	100.0%
Biologics, TNFα inhibitors	16	11	68.8%	94	27	28.7%	110	38	34.5%
Corticosteroids	0	0	--	38	19	50.0%	38	19	50.0%
Immunosuppressive, antimetabolites	5	4	80.0%	14	7	50.0%	19	11	57.9%
Immunosuppressive, methotrexate	7	5	71.4%	13	5	38.5%	20	10	50.0%
Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$;									

4.3.1.1. 5-ASAs

29 adverse reactions were reported as common or very common for 5ASAs in the SPCs identified from the results of the systematic review, as shown in Table 14. Of these 29 adverse reactions, only seven were reported in the 14 relevant trials. One very common adverse drug reaction that is not reported in Crohn's disease trials is interstitial lung disease, which is a progressive and incurable disease causing scarring of the lungs. The full detail of the common and very common adverse drug reactions recorded in SPCs is shown in Table 15.

Table 15: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) - 5-ASAs

SOC	HLGT	PT	Frequency	Not reported in trials	
Blood and lymphatic system disorders	White blood cell disorders	Leukopenia	Common	X	
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Tinnitus	Common		
Eye disorders	Ocular infections, irritations and inflammations	Scleritis	Common	X	
Gastrointestinal disorders	Anal and rectal conditions NEC	Anorectal disorder	Common	X	
	Gastrointestinal motility and defaecation conditions	Diarrhoea	Common		
		Gastrointestinal signs and symptoms	Abdominal pain	Common	
			Dyspepsia	Common	
			Dyspepsia	Very common	
			Flatulence	Common	X
		Nausea	Common		
		Nausea	Very common		
	Vomiting	Common			
	Oral soft tissue conditions	Stomatitis	Common	X	
General disorders and administration site conditions	Body temperature conditions	Pyrexia	Common		
Infections and infestations	Infections - pathogen unspecified	Respiratory tract infection	Common	X	
		Rhinitis	Common	X	
		Sinusitis	Common	X	
	Viral infectious disorders	Influenza	Common		
	Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	Common	
Muscle disorders		Myalgia	Common		

SOC	HLGT	PT	Frequency	Not reported in trials
Nervous system disorders	Headaches	Headache	Common	
	Neurological disorders NEC	Dizziness	Common	
		Dysgeusia	Common	X
	Sleep disturbances (incl subtypes)	Insomnia	Common	
Renal and urinary disorders	Urinary tract signs and symptoms	Proteinuria	Common	X
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease	Very common	X
	Respiratory disorders NEC	Cough	Common	X
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Pruritus	Common	
		Rash	Common	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

4.3.1.2. Antibiotics

11 adverse reactions were reported as common in the SPCs for macrolide antibiotics (Table 14), six of which were reported in the three trials identified through the systematic review (Appendix table 26). The adverse reactions not reported in Crohn's disease trials were minor; dyspepsia, headache, insomnia, rash and hyperhidrosis (excess sweating).

No common or very common adverse reactions were identified in the SPCs for nitroimidazole derivatives.

Only two common adverse reactions were reported in the SPC for quinolone antibiotics, both of which related to gastrointestinal disorders and both of which were reported in trials (Appendix table 27).

4.3.1.3. Anti-TNF α

110 adverse reactions were reported as occurring commonly or very commonly in the anti-TNF α therapies infliximab and adalimumab (Table 14). Five very common adverse reactions, reported to occur in at least one in ten patients, were not recorded in Crohn's disease trials; leukopenia, infusion related reaction, viral infection, lipids increased and musculoskeletal pain. Only one of the very common and seven of the common adverse reactions were reported in the 17 trials for these therapies. Two potentially serious adverse events were not identified in Crohn's disease trials: gastrointestinal haemorrhage and skin cancer (Table 16).

Table 16: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) - anti-TNF α

SOC	HLGT	PT	Frequency	Not reported in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	Common	x
	Platelet disorders	Thrombocytopenia	Common	x
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphadenopathy	Common	x
	White blood cell disorders	Leukocytosis	Common	x
		Leukopenia	Very common	x
		Leukopenia	Common	x
		Neutropenia	Common	x
Cardiac disorders	Cardiac arrhythmias	Tachycardia	Common	x
	Cardiac disorders signs and symptoms	Palpitations	Common	x
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Vertigo	Common	x
Eye disorders	Eye disorders NEC	Eye swelling	Common	x
	Ocular infections, irritations and inflammations	Blepharitis	Common	x
		Conjunctivitis	Common	x
	Vision disorders	Visual impairment	Common	x
Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Gastrointestinal haemorrhage	Common	x
	Gastrointestinal motility and defaecation conditions	Constipation	Common	
		Diarrhoea	Common	
		Gastrooesophageal reflux disease	Common	x
	Gastrointestinal signs and symptoms	Abdominal pain	Very common	
		Dyspepsia	Common	
Nausea		Very common		

SOC	HLGT	PT	Frequency	Not reported in trials
		Vomiting	Very common	
	Salivary gland conditions	Sjogren's syndrome	Common	x
General disorders and administration site conditions	Administration site reactions	Injection site reaction	Very common	
		Injection site reaction	Common	
	Body temperature conditions	Pyrexia	Common	
	General system disorders NEC	Chest pain	Common	x
		Chills	Common	x
		Fatigue	Common	
		Infusion related reaction	Very common	x
		Oedema	Common	x
		Pain	Very common	
	Tissue disorders NEC	Impaired healing	Common	x
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic function abnormal	Common	x
Immune system disorders	Allergic conditions	Allergic respiratory system	Common	x
		Hypersensitivity	Common	
Infections and infestations	Bacterial infectious disorders	Bacterial infection	Common	x
		Cellulitis	Common	x
	Fungal infectious disorders	Candida infection	Common	x
		Fungal infection	Common	x
	Infections - pathogen unspecified	Arthritis infective	Common	x
		Ear infection	Common	
		Impetigo	Common	x
		Lower respiratory tract infection	Common	x
		Necrotising fasciitis	Common	x

SOC	HLGT	PT	Frequency	Not reported in trials
		Oral infection	Common	x
		Paronychia	Common	x
		Respiratory tract infection	Very common	
		Sepsis	Common	
		Sinusitis	Very common	
		Upper respiratory tract infection	Very common	
		Urinary tract infection	Common	
	Viral infectious disorders	Herpes zoster	Common	x
		Influenza	Common	
		Viral infection	Very common	x
Investigations	Enzyme investigations NEC	Blood lactate dehydrogenase increased	Common	x
	Haematology investigations (incl blood groups)	Activated partial thromboplastin time prolonged	Common	x
	Hepatobiliary investigations	Hepatic enzyme increased	Very common	
		Transaminases increased	Common	
	Immunology and allergy investigations	Autoantibody positive	Common	x
	Lipid analyses	Lipids increased	Very common	x
	Metabolic, nutritional and blood gas investigations	Blood uric acid increased	Common	x
	Water, electrolyte and mineral investigations	Blood sodium abnormal	Common	x
Metabolism and nutrition disorders	Bone, calcium, magnesium and phosphorus metabolism disorders	Hypocalcaemia	Common	x
		Hypophosphataemia	Common	x

SOC	HLGT	PT	Frequency	Not reported in trials
	Electrolyte and fluid balance conditions	Dehydration	Common	
		Hypokalaemia	Common	x
	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemia	Common	x
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	Common	
	Muscle disorders	Muscle spasms	Common	
		Myalgia	Common	
	Musculoskeletal and connective tissue disorders NEC	Back pain	Common	
		Musculoskeletal pain	Very common	x
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Miscellaneous and site unspecified neoplasms benign	Benign neoplasm	Common	x
	Skin neoplasms malignant and unspecified	Skin cancer	Common	x
Nervous system disorders	Headaches	Headache	Very common	
		Migraine	Common	x
	Neurological disorders NEC	Dizziness	Common	
		Hypoaesthesia	Common	x
		Paraesthesia	Common	x
	Sleep disturbances (incl subtypes)	Insomnia	Common	
	Spinal cord and nerve root disorders	Nerve root compression	Common	x
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety	Common	x
	Depressed mood disorders and disturbances	Depression	Common	
	Mood disorders and disturbances NEC	Mood altered	Common	x
Renal and urinary disorders	Renal disorders (excl nephropathies)	Renal impairment	Common	x
	Urinary tract signs and symptoms	Haematuria	Common	x

SOC	HLGT	PT	Frequency	Not reported in trials
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	Asthma	Common	x
	Respiratory disorders NEC	Cough	Common	
		Dyspnoea	Common	
	Upper respiratory tract disorders (excl infections)	Epistaxis	Common	x
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Urticaria	Common	
	Epidermal and dermal conditions	Dermatitis	Common	x
		Dry skin	Common	x
		Eczema	Common	
		Pruritus	Common	
		Psoriasis	Common	x
		Rash	Very common	
		Rash	Common	
	Skin and subcutaneous tissue infections and infestations	Fungal skin infection	Common	x
	Skin appendage conditions	Alopecia	Common	
		Hyperhidrosis	Common	x
		Onychoclasia	Common	x
	Skin vascular abnormalities	Ecchymosis	Common	x
Epidermal and dermal conditions	Contusion	Common	x	
Skin vascular abnormalities	Flushing	Common	x	
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Hypotension	Common	x
	Vascular disorders NEC	Hot flush	Common	x
	Vascular haemorrhagic disorders	Haematoma	Common	x

SOC	HLGT	PT	Frequency	Not reported in trials
	Vascular hypertensive disorders	Hypertension	Common	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

4.3.1.4. Corticosteroids

There were 39 adverse reactions reported as occurring commonly in the SPCs for corticosteroids (Table 14). Only nine of these were also identified in the trials of corticosteroid use in Crohn's disease patients, with notable exceptions including osteoporosis, cataracts and arthralgia (Appendix table 28).

4.3.1.5. Immunosuppressives

There were 19 adverse reactions reported as occurring commonly or very commonly in patients taking antimetabolites in the SPCs (Table 14). All but one adverse reaction reported to occur in as many as one in ten patients were reported in the trials in Crohn's disease; decreased appetite. Half of the common adverse reactions were not reported as adverse events in Crohn's disease trials, including several malignancies (Table 17).

20 adverse reactions were listed in the SPC as occurring commonly or very commonly in patients taking methotrexate (Table 14). Stomatitis and decreased appetite are identified as occurring very commonly in the SPCs (at least one in ten patients) but were not reported in trials for Crohn's disease (Appendix table 29). A further eight common adverse reactions were not identified in trials, including skin disorders (e.g. rash) and respiratory disorders (e.g. interstitial lung disease).

Table 17: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) - immunosuppressives - antimetabolites

SOC	HLGT	PT	Frequency	Not in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	Common	
	Platelet disorders	Thrombocytopenia	Very common	
		Thrombocytopenia	Common	
	White blood cell disorders	Leukopenia	Very common	
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis	Common	
	Gastrointestinal signs and symptoms	Nausea	Very common	
		Nausea	Common	
		Vomiting	Very common	
		Vomiting	Common	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis	Common	x
		Hepatotoxicity	Common	
		Liver disorder	Common	x
Infections and infestations	Infections - pathogen unspecified	Infection susceptibility increased	Common	
Metabolism and nutrition disorders	Appetite and general nutrition disorders	Decreased appetite	Very common	x
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphoma	Common	x
	Miscellaneous and site unspecified neoplasms malignant and unspecified	Squamous cell carcinoma	Common	x
	Reproductive neoplasms female malignant and unspecified	Cervix carcinoma	Common	x
		Vulval cancer	Common	x
Soft tissue neoplasms malignant and unspecified	Kaposi's sarcoma	Common	X	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

4.3.2. Rare or very rare adverse events recorded in SPCs

Rare or very rare adverse events occur in fewer than one in 1,000 patients, as defined in Table 12. Given the size of trials and power of three calculations, which place their power to detect adverse reaction at the level of, at most, uncommonly occurring events (Table 13), trials are not powered to identify rare and very rare events. Indeed, this is the purpose of pharmacovigilance, as discussed in Chapter 1 and the introduction to this chapter. A summary of the identified rare and very rare adverse reactions is shown in Table 18 and confirms that a minority of rare and very rare adverse reactions, between 8.5% and 27.6%, were reported as adverse events in drug trials in Crohn's disease.

Table 18: Rare and very rare adverse reactions reported in the Summary of Product Characteristics (SPC) for Crohn's disease treatments, compared with those reported as adverse events in trials, by drug class

Drug class	Rare			Very rare			Rare and very rare		
	SPC	In trials		SPC	In trials		SPC	In trials	
		No.	%		No.	%		No.	%
5-ASAs	41	12	29.3%	35	9	25.7%	76	21	27.6%
Antibiotics, Macrolides	0	0	--	0	0	--	0	0	--
Antibiotics, Nitroimidazole derivatives	1	0	0.0%	24	6	25.0%	25	6	24.0%
Antibiotics, Quinolones	45	5	11.1%	26	1	3.8%	71	6	8.5%
Biologics, TNFα inhibitors	50	5	10.0%	2	0	0.0%	52	5	9.6%
Corticosteroids	13	4	30.8%	17	4	23.5%	30	8	26.7%
Immunosuppressive, antimetabolites	24	5	20.8%	11	3	27.3%	35	8	22.9%
Immunosuppressive, methotrexate	33	3	9.1%	52	6	11.5%	85	9	10.6%
Frequency: RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000									

4.3.2.1. 5-ASAs

The SPCs for 5-ASAs identify 76 adverse reactions that rarely or very rarely occur. 55 of these were not reported in Crohn's disease trials (Table 18). Nine very rare adverse reactions identified in the SPC (occurring in fewer than one in 10,000 patients) were also reported in the trials: anaemia, pancytopenia, pyrexia, death, transaminases increased, arthralgia, myalgia, Stevens-Johnson syndrome and alopecia (Appendix table 30). A number of rare and very rare adverse

events that were not captured in trials were serious disorders of the blood and lymphatic (e.g. aplastic anaemia), respiratory, thoracic and mediastinal (e.g. lung infiltration), hepatobiliary (e.g. hepatotoxicity) and renal and urinary systems (e.g. renal failure).

4.3.2.2. Antibiotics

No rare or very rare adverse reactions were reported in the SPCs for macrolide antibiotics (Table 18).

One rare and 24 very rare adverse reaction entries were present in the SPCs for nitroimidazole derivative antibiotics. Six of the very rare adverse reactions were also reported in trials in Crohn's disease: pancreatitis, arthralgia, myalgia, headache, dizziness and rash (Appendix table 31). Rare and very rare adverse reactions not captured by trials were commonly disorders of the blood and lymphatic and nervous systems (e.g. white blood cell disorders and seizures).

45 rare and 26 very rare adverse reactions were recorded in the SPCs for quinolone antibiotics. Five of the rare were also reported in the trials for Crohn's disease: anaemia, oedema, clostridium difficile colitis, myalgia and photosensitivity reaction (Appendix table 32). One very rare reaction, pancreatitis, was also recorded in the Crohn's disease trials. Rare and very rare adverse reactions not reported by trials were commonly of the blood and lymphatic (e.g. bone marrow failure) and nervous systems (e.g. seizure and migraine), although other serious adverse reactions were reported in other system classes including necrosis (skin) and anaphylactic reactions (immunity).

4.3.2.3. Anti-TNF α

50 rare and two very rare adverse reactions were reported in the SPCs for anti-TNF α therapies (Table 18). Whilst none of the very rare reactions were also reported in the Crohn's disease trials, five rare reactions were (opportunistic infections, lupus-like syndrome, lymphoma, demyelination and multiple sclerosis), leaving 45 rare adverse reactions not detected through Crohn's disease trials. Common categories of disorders were blood and lymphatic (e.g. aplastic anaemia) and

respiratory systems (e.g. interstitial lung disease), disorders of the skin (e.g. Stevens-Johnson syndrome) and neoplasms, including malignancies (Table 19).

Table 19: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - biologics: anti-TNF α

SOC	HLGT	PT	Not reported in trials	Frequency
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Pancytopenia	x	Rare
	Haemolyses and related conditions	Haemolytic anaemia	x	Rare
	Platelet disorders	Immune thrombocytopenic purpura	x	Rare
		Thrombotic thrombocytopenic purpura	x	Rare
	White blood cell disorders	agranulocytosis	x	Rare
		Leukopenia	x	Rare
Cardiac disorders	Cardiac arrhythmias	Cardiac arrest	x	Rare
	Cardiac disorders signs and symptoms	Cyanosis	x	Rare
	Pericardial disorders	Pericardial effusion	x	Rare
Eye disorders	Ocular infections, irritations and inflammations	Endophthalmitis	x	Rare
Gastrointestinal disorders	Gastrointestinal ulceration and perforation	Intestinal perforation	x	Rare
General disorders and administration site conditions	General system disorders NEC	Granuloma	x	Rare
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Autoimmune hepatitis	x	Rare
		Hepatitis	x	Rare
		Hepatitis B	x	Rare
		Jaundice	x	Rare
Immune system disorders	Allergic conditions	Anaphylactic reaction	x	Rare
		Anaphylactic shock	x	Rare

SOC	HLGT	PT	Not reported in trials	Frequency
Infections and infestations	Immune disorders NEC	Sarcoidosis	x	Rare
	Bacterial infectious disorders	Furuncle	x	Rare
	Infections - pathogen unspecified	Infection parasitic	x	Rare
		Meningitis	x	Rare
		Opportunistic infection		Rare
Viral infectious disorders	Hepatitis B	x	Rare	
Investigations	Immunology and allergy investigations	Complement factor abnormal	x	Rare
Musculoskeletal and connective tissue disorders	Connective tissue disorders (excl congenital)	Lupus-like syndrome		Rare
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukaemias	Leukaemia	x	Rare
	Lymphomas Hodgkin's disease	Hodgkin's disease	x	Rare
	Lymphomas NEC	Lymphoma		Rare
	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphoma	x	Rare
	Reproductive neoplasms female malignant and unspecified	Cervix carcinoma	x	Rare
	Skin neoplasms malignant and unspecified	Malignant melanoma	x	Rare
Nervous system disorders	Central nervous system infections and inflammations	Myelitis transverse	x	Rare
	Demyelinating disorders	Demyelination		Rare
		Multiple sclerosis		Rare
Psychiatric disorders	Mood disorders and disturbances NEC	Apathy	x	Rare
	Bronchial disorders (excl neoplasms)	Bronchospasm	x	Rare

SOC	HLGT	PT	Not reported in trials	Frequency
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease	x	Very rare
		Pulmonary fibrosis	x	Rare
		Pulmonary oedema	x	Rare
	Pleural disorders	Pleural effusion	x	Rare
	Pleural disorders	Pleurisy	x	Rare
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema	x	Rare
	Epidermal and dermal conditions	Dermatomyositis	x	Very rare
		Stevens-Johnson syndrome	x	Rare
		Toxic epidermal necrolysis	x	Rare
	Skin vascular abnormalities	Petechiae	x	Rare
	Epidermal and dermal conditions	Erythema multiforme	x	Rare
	Skin vascular abnormalities	Cutaneous vasculitis	x	Rare
	Vascular disorders	Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Vasospasm	x
Decreased and nonspecific blood pressure disorders and shock		Circulatory collapse	x	Rare
Vascular inflammations		Vasculitis	x	Rare

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

4.3.2.4. Corticosteroids

There are 13 rare and 17 very rare adverse reactions reported in the SPCs for corticosteroids (Table 18). Of these, four rare reactions were also reported in the Crohn's disease trials: adrenal suppression, Cushingoid, obesity and rosacea (Appendix table 33). Four of the very rare reactions were also reported in trials in Crohn's disease: Cushing's syndrome, pancreatitis, constipation and dyspepsia. Rare and very rare adverse reactions not reported in Crohn's disease trials included blood and lymphatic system disorders (white blood cell disorders), eye disorders (e.g. cataract), general disorders (e.g. fatigue and malaise) and disorders of the musculoskeletal and connective tissues (e.g. osteoporosis and myalgia)

4.3.2.5. Immunosuppressives

24 rare and 11 very rare adverse reactions are recorded in the SPC for antimetabolites (Table 18). Five of the rare reactions were also reported in the Crohn's disease trials: diarrhoea, death, hypersensitivity, myelodysplastic syndrome and alopecia (Table 20). Three of the adverse reactions were also reported as very rare in the SPCs: death, hypersensitivity and myelodysplastic syndrome. Adverse reactions that were not reported in trials included serious blood and lymphatic system disorders (such as bone marrow failure), malignant neoplasms (including lymphomas and leukaemias) and skin conditions (such as toxic epidermal necrosis).

There were 33 rare and 52 very rare adverse reactions recorded in the SPC for methotrexate and the vast majority were not recorded in trials (76 of 85, 89.4%) (Table 18). Three of the rare reactions were also recorded in the trials for Crohn's disease: vision blurred, hepatitis acute and acne (Appendix table 34). Six very rare adverse reactions recorded in the SPC were also reported in the Crohn's disease trials of methotrexate: neutropenia, pyrexia, pain, pneumonia, cytomegalovirus infection and insomnia.

Table 20: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - immunosuppressives: antimetabolites

SOC	HLGT	PT	frequency	Not reported in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia megaloblastic	Rare	x
		Aplastic anaemia	Rare	x
		Bone marrow failure	Rare	x
		Pancytopenia	Rare	x
	White blood cell disorders	agranulocytosis	Rare	x
		Granulocytopenia	Rare	x
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea	Rare	
	Gastrointestinal ulceration and perforation	Gastrointestinal ulcer	Very rare	x
	Oral soft tissue conditions	Mouth ulceration	Rare	x
General disorders and administration site conditions	Fatal outcomes	Death	Rare	
		Death	Very rare	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic necrosis	Rare	x
		Liver injury	Rare	x
		Venoocclusive liver disease	Rare	x
Immune system disorders	Allergic conditions	Hypersensitivity	Rare	
		Hypersensitivity	Very rare	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukaemias	Acute myeloid leukaemia	Rare	x
		Acute myeloid leukaemia	Very rare	x
		Myelodysplastic syndrome	Rare	
		Myelodysplastic syndrome	Very rare	
	Lymphomas non-Hodgkin's T-cell	Hepatosplenic T-cell lymphoma	Very rare	x

SOC	HLGT	PT	frequency	Not reported in trials
	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphoma	Rare	x
	Metastases	Metastasis	Very rare	x
	Reproductive neoplasms female malignant and unspecified	Cervix carcinoma	Rare	x
	Skin neoplasms malignant and unspecified	Skin cancer	Rare	x
	Soft tissue neoplasms malignant and unspecified	Sarcoma	Rare	x
Reproductive system and breast disorders	Sexual function and fertility disorders	Oligospermia	Very rare	x
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease	Rare	x
		Pneumonitis	Very rare	x
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Photosensitivity reaction	Rare	x
		Stevens-Johnson syndrome	Rare	x
		Stevens-Johnson syndrome	Very rare	x
		Toxic epidermal necrolysis	Rare	x
		Toxic epidermal necrolysis	Very rare	x
	Skin appendage conditions	Alopecia	Rare	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

4.3.3. Adverse reactions reported in SPCs and not in trials

Overall, a large number of adverse reactions recorded in SPCs, and that would be expected to be in clinical trials, were not reported (Table 21). The lowest proportion of these reactions not captured in trials were in the very common and common frequency categories. Given that adverse reactions in these categories occur in more than one in 100 patients, trials would be expected to capture these. Generally, as adverse reactions become rarer, the number of adverse reactions reported in the SPCs, but not in trials increases. Significant proportions of adverse reactions reported in the SPCs are deemed to be related to the drug, but there is not enough information to estimate how many people might be affected with the particular reaction. These are captured in the “frequency not known” category, and account for 40% and more of adverse reactions reported in SPCs, but not in trials, in some drug classes.

4.3.3.1. 5-ASAs

128 adverse reaction entries were recorded in the 5-ASAs SPCs that were not reported in the Crohn’s disease clinical trials (Table 21 and full list in Appendix table 35). The vast majority of the adverse reactions for 5-ASAs were in the rare, very rare or frequency unknown categories (85.2%). The trial sample sizes and rule of three calculations in Table 13 suggest that the upper limit of adverse event detection would be common events.

Table 21: Adverse reactions reported in the Summary of Product Characteristics (SPCs), but not in the clinical trials, of therapies for the treatment of Crohn's disease in adults, numbers and proportions

Drug class	Very common		Common		Uncommon		Rare		Very rare		Frequency not known		Total
	No.	% of total	No.	% of total	No.	% of total	No.	% of total	No.	% of total	No.	% of total	
5-ASAs	1	0.8%	11	8.6%	7	5.5%	29	22.7%	26	20.3%	54	42.2%	128
Antibiotics, macrolides	0	0.0%	5	6.1%	42	51.2%	0	0.0%	0	0.0%	35	42.7%	82
Antibiotics, nitroimidazole derivatives	0	0.0%	0	0.0%	0	0.0%	1	2.9%	18	52.9%	15	44.1%	34
Antibiotics, quinolones	0	0.0%	0	0.0%	18	20.5%	40	45.4%	25	28.4%	5	5.7%	88
Biologics, Anti-TNFα	5	2.6%	67	35.1%	65	34.0%	45	23.6%	2	1.0%	7	3.7%	191
Corticosteroids	0	0.0%	19	10.3%	2	44.8%	9	4.4%	13	6.4%	69	34.0%	112
Immunosuppressives, antimetabolites	1	2.4%	7	17.1%	5	12.2%	19	46.3%	8	19.5%	1	2.4%	41
Immunosuppressives, methotrexate	2	1.5%	8	6.0%	35	26.3%	30	22.6%	46	34.6%	12	9.0%	133

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

4.3.3.2. Antibiotics

There were 82 adverse reactions recorded in the SPCs for macrolide antibiotics that are not recorded in Crohn's disease trials (Table 21 and full list in Appendix table 36). More than half of these (51.2%) are recorded as uncommon, meaning that they occur in between one in 100 and one in 1,000 patients). The rule of three calculations suggested that the trials should have been able to detect common events at the upper limit, given the trial sample sizes (Table 13). The remaining bulk are of unknown frequency, which is where the frequency cannot be estimated from the available data.

The SPCs for nitroimidazole derivatives recorded 34 adverse reactions that are not reported in trials, which are listed in Appendix table 37. The majority of these were very rare (52.9%); occurring in less than one in 10,000 patients (Table 21), which it is unlikely could be detected in the drug trials given the sample sizes (Table 13). The frequency of occurrence could not be estimated for 44.1% of the adverse reactions.

There were 88 adverse reactions recorded in the quinolone SPCs, but not in the corresponding trials for Crohn's disease patients (Appendix table 38). The majority of these (94.0%) were reported to occur uncommonly, rarely or very rarely, which would be beyond the power of the trials to detect based on their sample sizes (Table 13). Only 5.7% could not be assessed for frequency of occurrence.

4.3.3.3. Anti-TNF α

A large number of adverse reactions (191) were recorded in the anti-TNF α SPCs above those recorded in the clinical trials for Crohn's disease (Table 21). The full list is in Appendix table 39. More than two thirds of these adverse events (69.1%) were of common or uncommon occurrence. This pattern is in contrast to the other drug classes where more rarer and unknown harms recorded and is different in terms of the rule of three calculations (Table 13).

4.3.3.4. Corticosteroids

The SPCs for corticosteroids identify 112 adverse reactions that are not reported in the corresponding clinical trials in Crohn's disease (Table 21 and full list in Appendix table 40). 44.8% of these adverse events were reported to occur uncommonly (between one in 100 and one in 1,000 patients), which is more common than the level indicated the trial sample sizes (Table 13). The frequency could not be estimated for a further third of the adverse events (34.0%) (Table 4).

4.3.3.5. Immunosuppressives

41 adverse reactions were reported in the SPCs for antimetabolites, but not in the corresponding clinical trials in Crohn's disease (Table 21 and full list in Appendix table 41). Almost two thirds of these (65.9%) were rarely or very rarely occurring and are unlikely to be identified in trials of those identified for Crohn's disease (Table 13).

For methotrexate, the SPC recorded 133 adverse reactions that were not reported in Crohn's disease trials (Appendix table 42). 83.5% of these were reported to occur uncommonly, rarely or very rarely, above the predicted upper limit for detection, according to the rule of three calculations in (Table 13).

4.3.4. Adverse events reported in trials but not in SPCs

Large numbers of adverse events were recorded in the 69 trials, which were not reported as adverse reactions in the SPCs (Table 22 and detail in Appendix table 43 to Appendix table 50). Overall, three in ten trials did not assess whether the adverse events recorded were possibly related to the study drug. Additionally, whilst some trials indicated the overall numbers of possible treatment-related adverse events, some did not list the adverse events that were possible adverse drug reactions. 41 of 69 (59.4%) trials named adverse events as treatment related, although this varied by drug class from 0% of macrolides trials to 89.5% of corticosteroid trials. 88 of the 488 (18.0%) adverse events that were reported in trials, but not included in the SPCs, were identified as potentially related to treatment in the trials.

Table 22: Adverse events reported in trials but not in the Summary of Product Characteristics (SPCs) of therapies for the treatment of Crohn's disease in adults, numbers and proportions

Drug class	Trials		Trials assessing causation		Trials reporting treatment related AEs		AEs identified as potential ADRs	
	No.	Trial AEs not reported in SPCs	No.	%	No.	%	No.	%
5-ASAs	15	44	9	60.0%	8	53.3%	11	25.0%
Antibiotics, Macrolides	3	6	0	0.0%	0	0.0%	-	0.0%
Antibiotics, Nitroimidazole derivatives	3	39	2	66.7%	1	33.3%	5	12.8%
Antibiotics, Quinolones	7	39	4	57.1%	2	28.6%	5	12.8%
Biologics, TNFα inhibitors	17	120	13	76.5%	12	70.6%	18	15.0%
Corticosteroids	19	76	19	100.0%	17	89.5%	35	46.1%
Immunosuppressive, antimetabolites	12	121	6	50.0%	5	41.7%	13	10.7%
Immunosuppressive, methotrexate	2	43	1	50.0%	1	50.0%	1	2.3%
All trials matched to SPCs	69	488	48	69.6%	41	59.4%	88	18.0%

Note: AE – adverse event; ADR – adverse drug reaction; SPC – summary of product characteristics

4.3.4.1. 5-ASAs

There were 44 adverse events reported in the trials of 5-ASAs in Crohn's disease patients that are not reported as adverse reactions in the relevant SPCs (Table 22). The adverse events were in 16 SOC, with the most reported under the gastrointestinal disorders (12) and general disorders and administration conditions (9) SOC (Appendix table 43). 11 (25.0%) of these were believed to be possible adverse drug reactions in the trials in the seven trials that reported treatment-related adverse events (Table 23).

Table 23: Possible treatment related events in Crohn’s disease trials, not reported in summary of product characteristics (SPCs) – 5-ASAs

SOC	HLGT	PT
Blood and lymphatic system disorders	Platelet disorders	Thrombocytosis
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea haemorrhagic
	Gastrointestinal signs and symptoms	Abnormal faeces
General disorders and administration conditions	General system disorders NEC	Asthenia
		Oedema
	Therapeutic and nontherapeutic effects (excl toxicity)	Drug intolerance
Infections and infestations	Infections - pathogen unspecified	Pyuria
Investigations	Physical examination and organ system status topics	Weight decreased
	Protein and chemistry analyses NEC	C-reactive protein increased
Metabolism and nutrition disorders	Lipid metabolism disorders	Hyperlipidaemia
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	Back pain

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified

4.3.4.2. Antibiotics

There were six adverse events reported in the Crohn's disease trials of macrolide antibiotics that did not also appear in the SPCs (Table 22). None of the included trials assessed causation of the adverse events. Five of the adverse events appear to be features of the disease: Crohn's disease (aggravated), anal abscess, arthralgia, hospitalisation and surgery (Appendix table 44). The final adverse event is vulvovaginal candidiasis.

39 adverse events were reported in trials of nitroimidazole derivatives in patients with Crohn's disease, but not in the drug SPCs. The adverse events were across 13 SOCs, with most under the infection and infestations (9) and gastrointestinal disorders (7) headings (Appendix table 45). Only one trial reported possible adverse drug reactions and identified five that were not included in the SPCs: cushingoid, oedema, insomnia, acne and purpura.

In trials of quinolones in Crohn's disease patients, 37 adverse events were reported that did not feature in the SPCs (Appendix table 46). The adverse events were reported across 10 SOC headings, with the most common reports under infections and infestations (15 adverse events) and gastrointestinal disorders (4) headings. Two trials assessed causation and reported five treatment-related adverse events: cushingoid, infusion related reaction, insomnia, acne and purpura.

4.3.4.3. Anti-TNF α

120 adverse events were reported in the Crohn's disease clinical trials for anti-TNF α therapies that did not feature in the corresponding SPCs (Table 22). Most adverse events were reported under the SOC headings of infections and infestations (44) and gastrointestinal disorders (16). Overall, the excess trial adverse events were reported across 21 SOC headings (Appendix table 47). 18 of the 120 adverse events were assessed as being potential ADRs: cushingoid, six injection site reactions, chest discomfort, chest pain, flushing, type IV hypersensitivity reaction, pharyngitis,

pneumonia, serum sickness, liver function test abnormal, hyperphagia, neoplasm malignant and mood swings (Table 24).

4.3.4.4. Corticosteroids

In trials of corticosteroids, 76 adverse events were reported above those reported in the relevant SPCs (Table 22). Overall, adverse events were reported under 18 SOC headings, with the highest numbers under gastrointestinal disorders (14) and investigations (12) (Appendix table 48). Almost half of these were assessed as being related to the study drug in the 17 (of 19, 89.5%) trials reporting treatment-related adverse events (Table 25).

Table 24: Possible treatment related events in Crohn’s disease trials, not reported in summary of product characteristics (SPCs) – biologics: anti-TNF α

SOC	HLGT	PT
Endocrine disorders	Adrenal gland disorders	Cushingoid
General disorders and administration conditions	Administration site reactions	Injection site bruising
		Injection site erythema
		Injection site haemorrhage
		Injection site irritation
		Injection site pain
		Injection site pruritus
	General system disorders NEC	Chest discomfort
		Chest pain
		Flushing
Immune system disorders	Allergic conditions	Type IV hypersensitivity reaction
		Pharyngitis
		Pneumonia
		Liver function test abnormal
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Hyperphagia
		Neoplasm malignant
Psychiatric disorders	Mood disorders and disturbances NEC	Mood swings
		Surgery
Vascular disorders	Embolism and thrombosis	Venous thrombosis
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified		

Table 25: Possible treatment related events in Crohn’s disease trials, not reported in summary of product characteristics (SPCs) – corticosteroids

SOC	HLGT	PT
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia
	Coagulopathies and bleeding diatheses (excl thrombocytopenic)	Increased tendency to bruise
Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Melaena
	Gastrointestinal signs and symptoms	Vomiting
	Salivary gland conditions	Dry mouth
General disorders and administration site conditions	General system disorders NEC	Flushing
		Oedema
		Oedema peripheral
Infections and infestations	Fungal infectious disorders	Vulvovaginal candidiasis
	Infections - pathogen unspecified	Anal abscess
		Conjunctivitis
Injury, poisoning and procedural complications	Bone and joint injuries	Hand fracture
Investigations	Endocrine investigations (incl sex hormones)	Blood cortisol decreased
	Haematology investigations (incl blood groups)	White blood cell count increased
	Hepatobiliary investigations	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Protein and chemistry analyses NEC	Blood albumin decreased
		Protein total decreased
	Renal and urinary tract investigations and urinalyses	Blood creatinine increased
	Water, electrolyte and mineral investigations	Blood calcium decreased
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite
	Bone, calcium, magnesium and phosphorus metabolism disorders	Hypocalcaemia
	Lipid metabolism disorders	Lipohypertrophy

SOC	HLGT	PT
Musculoskeletal and connective tissue disorders	Joint disorders	Joint swelling
	Musculoskeletal and connective tissue disorders NEC	Back pain
Psychiatric disorders	Mood disorders and disturbances NEC	Affect lability
		Mood altered
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract disorders (excl infections)	Nasal mucosal ulcer
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions Skin appendage conditions	Eczema
		Alopecia
		Hair growth abnormal
		Hypertrichosis
		Hot flush
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified		

4.3.4.5. *Immunosuppressives*

121 excess adverse events were reported in Crohn's disease trials for antimetabolites above those reported in the relevant SPCs (Table 22). The highest numbers of adverse events were reported under the SOC headings infections and infestations (22) and investigations (16), with reports under 24 headings overall (Appendix table 49). Only five of 12 trials (41.7%) reported possible treatment-related adverse events and 35 (28.9% of 121) of these were not included in the SPCs (Table 26).

Adverse events that were reported in Crohn's disease trials of methotrexate, but not the SPC, were across 13 SOC headings, and numbered 43 in total (Table 22). Trial excess adverse events were most commonly reported under the investigations (9), infections and infestations (5) and gastrointestinal disorders (5) headings (Appendix table 50). Only one trial assessed causation of adverse events and identified one potential treatment-related adverse event; infusion related reaction.

Table 26: Possible treatment related events in Crohn’s disease trials, not reported in summary of product characteristics (SPCs) – immunosuppressives: antimetabolites

SOC	HLGT	PT
Endocrine disorders	Adrenal gland disorders	Cushingoid
Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract
General disorders and administration conditions	Administration site reactions	Injection site reaction
Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Post procedural complication
Investigations	Haematology investigations (incl blood groups)	White blood cell count decreased
	Hepatobiliary investigations	Transaminases increased
	Musculoskeletal and soft tissue investigations (excl enzyme tests)	Bone density decreased
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Hyperphagia
Nervous system disorders	Neurological disorders NEC	Paraesthesia
Psychiatric disorders	Mood disorders and disturbances NEC	Mood swings
Skin and subcutaneous tissue disorders	Skin appendage conditions	Acne
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Surgery
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified		

4.4 Discussion 1

Identifying common, very common, rare and very rare adverse reactions that are identified in the SPCs but not in the trials was a potentially sound way to identify additional harms from Crohn's disease treatments that are not captured in RCTs. We might expect a trial testing an active substance in 100 patients to identify very common and common adverse reactions provided the risk of those events was distributed equally across all patient factors, such as age, sex, disease severity, co-morbidities, additional therapies, etc. 23 of the 69 (33.3%) trials included in the work in this chapter had a sample size of at least 100 patients, with the majority (46 of 69, 66.7%) therefore having a lower power to detect adverse events.

Even for the larger trials, it is unlikely that adverse reactions are distributed evenly across a population, and it is well understood that certain adverse reactions may occur commonly but only after a lengthy exposure, which would be beyond the follow up period of trials. The classic example of this phenomenon is osteoporosis with long-term corticosteroid use³⁵⁰, and this adverse reaction is picked up in the results of common and very common adverse reactions that are not reported in trials, but are captured in the SPC. However, it is one of 39 common or very common adverse reactions, 30 of which were not identified in trials, and osteoporosis and its frequency in corticosteroid use is identified as important because of the prior knowledge of the causal relationship. It is difficult to pick out which are the important ones without in depth knowledge of the condition and the therapy.

Looking at the rare and very rare adverse reactions confirmed that the majority are not reported in trials, as expected, given that they occur in fewer than 1 in 1,000 patients. However, this then leads to questions about the ones that are identified in trials. They cover a broad range; for example, in 5 ASAs, the rare and very rare adverse reactions reported in both SPCs and trials ranged from alopecia and pyrexia to Steven-Johnsons syndrome (a rare and serious disorder that affects the skin, mucous membrane, genitals and eyes, causing skin erosion, blindness and

death)³⁵¹. In addition, some of the rare and very rare adverse reactions are classic signs of CD, such as arthralgia, fistula, constipation and dyspepsia, which are reported in the SPCs and trials for macrolide antibiotics and corticosteroids. It could be argued these adverse events represent the obvious things that cannot be missed and may suggest selective reporting. There is also a risk that the SPCs are identifying false positives, if the exploratory methods used to generate signals fail to account for the increased risk of falsely identifying a signal when conducting multiple statistical tests, a phenomenon known as ‘multiplicity’³⁵².

Examination of the adverse reactions captured in SPCs but not recorded in trials leads to some queries, particularly in the case where rule of three calculations suggest they should have been identified in trials. Anti-TNF α agents have a different pattern to the other drug classes, with many more common and very common adverse reactions that are not identified in trials. This may reflect the fact that these drugs are newer to market and are being monitored more actively and therefore more adverse reactions are being detected. New biologics are marketed under the black triangle scheme, which alerts prescribers to the need for intensive monitoring and reporting of all adverse reactions. This requirement would not have been in place for older treatment like azathioprine and 5-ASAs and represents a source of bias in what is reported to the regulators. It could also reflect the greater disease severity in the population receiving this drug class, who may have a higher tolerance for drugs with more side effects, as discussed in Chapter 1.

The additional adverse reactions in the SPCs may also reflect the fact that in a trial setting, a patient might stop their treatment upon experiencing an ADR, and so would not have the opportunity to experience other ADRs. In other words, there are competing risks that remove patients from the pool and mean that trials cannot fully characterise the safety profile. The potential for this to impact upon the adverse events identified in trials may be compounded if the events are not independent. Multiplicity remains a concern for signal generating statistical methods³⁵².

Making sense of the adverse events reported in trials, but not in SPCs, is also complex. Within our results for 5-ASAs, gastrointestinal disorders such as Crohn's disease, enteritis, intestinal obstruction were reported in the trials, but not in the SPCs for the drugs. Such adverse events are features of Crohn's disease and may indicate failure of therapy rather than an adverse reaction. An adverse event of surgery reported in the trials but not in the corresponding SPC may be a surgery related to Crohn's disease or something unrelated. There are clearly irrelevant adverse events reported in the trials, such as arthropod sting, fracture and pregnancy, which is a result of good practice procedures of reporting everything to allow for complete capture and signal detection methods. Further, 18 adverse events were assessed as potential adverse drug reactions in the trials, but were not included in the SPCs. This may be because the initial assessment was deemed incorrect or that post-marketing surveillance determined that the link was not causal after all once data was aggregated for all

An issue that is common to all the strands of analysis in the preceding sections is related to the coding of adverse events. As an example, lower respiratory tract infection is reported as an adverse reaction in the SPCs for anti-TNF α therapies but not in the trials. However, upper respiratory tract infection and respiratory tract infection are reported in the trials and the SPCs. In any system where data is coded, there will be inter-observer variability due to the potential to code one data item in different ways. For example, the MedDRA hierarchy places hepatic function abnormal in the hepatobiliary disorders SOC, whilst liver function test abnormal belongs under the investigations SOC. These are potentially the same event. MedDRA is constantly updated and specific training is needed to be able to code adverse events: a systematic review found that this leads to variability in coding and even inaccurate coding³⁵³. Additional coding might lead to greater accuracy and specificity, but it may also dilute signals.

Complicating the issue is that the SPC includes data for all patient populations. Therefore, the data may relate to a number of different disease groups, all of which might have distinct co-

morbidities or co-therapies. Some therapies for Crohn's disease are also prescribed for rheumatoid arthritis (RA), potentially in different doses and with dissimilar drug combinations. As the RA population is almost quadruple the size of the CD population, adverse reactions signals may be lost in a broad review if they differ, a phenomenon known as "masking" or "cloaking"³⁵⁴.

Differences in the safety profiles of different drug classes may also reflect the age of the drugs. SPCs developed over different time-periods may have reported the occurrence of adverse reactions differently, specifically with the use of fewer frequency groups. As such, SPCs for older groups may not report any adverse events as occurring in some groups, as was seen in the results section.

The multitude of difficulties in the results suggest the need for an alternative method, which provides a greater focus and helps to reduce the uncertainty. Whilst combining different therapies into drug classes offered a way to maximise data use, it may be further complicating the approach. It was decided to simplify the analysis by focusing on one drug as a case study. An alternative method to investigating long term and rare harms was developed which identified key harms from the literature and the use of data tools, which allow for the grouping of different terms used to describe the same harm. This new method is discussed in the next section, 4.5.

4.5. Methods 2

Infliximab was selected as a single drug case study. The adverse events for the infliximab trials were used from the work reported in the previous section alongside the SPC for Remicade (Merck, Sharp & Dohme Limited, Hertfordshire, UK)³⁵⁵. This drug was chosen due to its prominence in the literature at the time of the research, the need to balance risks against the benefits for patients, the occurrence of both common and rare adverse reactions, the comprehensive monitoring of adverse reactions through the black triangle scheme, and because of the authorisation of biosimilars (see Chapter 5). In an attempt to counter the issues related to the broad range of preferred terms captured in the preceding results, the focus was reduced to those harms that

were known to occur and be causally related, or were theoretically possible based upon factors such as the mechanism of action. Further, the decision was taken to focus on serious harms, as those would be the ones of most concern to those interested in assessing risk.

4.5.1 Identifying and categorising key serious harms

The primary sources for harms are the list of conditions identified in the SPC section 4.4 Special warnings and precaution for use³⁵⁵, the British National Formulary monitoring requirements³²⁶ and the EMA guideline on the development of new medicines for Crohn's disease⁶⁸. Additionally, a drug class review on targeted immune mediators was consulted which located evidence on adverse events³⁵⁶. A single list of adverse events and reactions was created from the sources, which were grouped into harm categories.

4.5.3. Standardised MedDRA queries (SMQs)

Where possible, the harm categories were matched to standardised MedDRA queries (SMQs). This matching was done using the definition and inclusion criteria of the SMQs from MedDRA³⁵⁷. SMQs were developed by MedDRA in response to the recognition of the need for tools to support the identification and retrieval of safety data, which may be complicated due to the potential for multiple ways of coding the same event³⁵⁷. They aim to group all preferred terms that are relevant to a defined condition and may include signs, symptoms, diagnoses, and physical and laboratory findings. SMQs are designed to support the identification of individual safety case reports, but are being used in this chapter to investigate whether additional safety data can be identified from the SPCs to support the characterisation of harms beyond the trials. The use of SMQs offers the potential to group initial symptoms of adverse events that might be detected in trials with longer-term adverse reactions that are identified in the post-marketing period.

A working group determines the list of conditions for which a SMQ will be defined; at March 2018 there were 103 SMQs available for use and a further seven in development or testing³⁵⁸. All SMQs offer a "narrow" scope and a "broad" scope. The "narrow" scope is the grouping of preferred

terms that are highly likely to represent the condition, designed to maximise the specificity of the search. The “broad” scope maximises sensitivity by including preferred terms that might relate to the condition of interest, but need further investigation of the case to be certain. Additionally, some SMQs use an algorithmic approach to identify likely cases, such that a combination of preferred terms in a single patient might indicate the particular condition. An example might be the identification of acute hepatitis for an individual case, which might be through the recording of the preferred term for acute hepatitis, or instead via a combination of preferred terms involving a laboratory result alongside signs and symptoms. The multiple adverse events recorded for that individual case would then highlight acute hepatitis. As the analysis in this chapter does not incorporate case data, both the broad scope terms and the algorithmic approach are irrelevant.

4.5.3. Data presentation and analysis

Once each harm category was matched against an SMQ (or SMQs), the preferred terms were listed in tables per SMQ. Included in the tables is the following data:

- either the system organ classification (SOC) or higher-level group term (HLGT);
- the preferred term (PT);
- a marker of whether they were reported in infliximab trials;
- a marker of whether they were reported in the SPC; and
- the frequency of reporting in the SPC.

Only those preferred terms in the SMQ and reported in either the trials or the SPC were included in the analysis, but a summary of the total number of preferred terms in each SMQ is reported.

4.6 Results 2

The focus on infliximab resulted in the inclusion of adverse events from ten trials (referenced in Table 13). The median sample size of these trials was 112 participants (IQR: 42-222).

4.6.1. Identifying harm categories

The SPC for Remicade highlights potential serious adverse reaction relating to infusion reactions and hypersensitivity, hepatobiliary events, neurological events, heart failure and haematologic reactions³⁵⁵.

The BNF requires that patients receiving infliximab be monitored for delayed hypersensitivity, hypersensitivity reactions, infection and non-melanoma skin cancer³²⁶.

In addition, the EMA suggests that for drugs acting as immunomodulators (such as biologics), particular attention should be paid to serious infections, autoimmune diseases and tumours and that the long term nature of treatment of biologics requires that attention be paid to the development of antibodies⁶⁸.

A drug class review on targeted immune mediators located evidence on serious infection, malignancy, autoimmunity, demyelination, serious hepatic incidents, cardiovascular harms and specific events such as injection site reactions³⁵⁶.

As a result, eight adverse reaction categories were identified, as shown in Table 27: autoimmunity; blood disorders; cardiac events; hepatic events; hypersensitivity; immunogenicity; infection; malignancies; and neurological events.

Table 27: Harm categories identified through review of key literature, and matched standardised MedDRA queries (SMQs)

Harm category	Matched SMQ	Adverse event / reaction	Source	Listed in source as
Autoimmunity	No relevant SMQ. Autoimmune diseases / immune mediated conditions SMQ in development.	Autoimmune diseases	CHMP ⁶⁸	Special attention
		Autoimmunity	Thaler et al ³⁵⁶	Groups of interest
		Autoimmune processes	SPC ³⁵⁵	Special warnings / precautions for use
		Antibodies	CHMP ⁶⁸	Must investigate
Blood disorders	No relevant SMQ.	Haematologic reactions	SPC ³⁵⁵	Special warnings / precautions for use
Cardiac events	Cardiac failure.	Cardiovascular events & congestive heart failure	Thaler et al ³⁵⁶	Groups of interest
		Heart failure	SPC ³⁵⁵	Special warnings / precautions for use
Hepatic events	Drug-related hepatic disorders.	Hepatic events	Thaler et al ³⁵⁶	Groups of interest
		Hepatobiliary events	SPC ³⁵⁵	Special warnings / precautions for use
Hypersensitivity	Hypersensitivity. Infusion-related reaction SMQ in development.	Delayed hypersensitivity	BNF ³²⁶	Monitoring requirement
		Hypersensitivity reaction	BNF ³²⁶	Monitoring requirement
		Injection site or infusion reactions	Thaler et al ³⁵⁶	Groups of interest
		Infusion reactions and hypersensitivity	SPC ³⁵⁵	Special warnings / precautions for use
Infection	No relevant SMQ. Opportunistic infection SMQ in development.	Infection	BNF ³²⁶	Monitoring requirement
		Serious infections	CHMP ⁶⁸	Special attention
		Serious infections	Thaler et al ³⁵⁶	Groups of interest
		Infections	SPC ³⁵⁵	Special warnings / precautions for use
		Hepatitis B reactivation	SPC ³⁵⁵	Special warnings / precautions for use
Malignancies	Malignancies	Non-melanoma skin cancer	BNF ³²⁶	Monitoring requirement
		Tumours	CHMP ⁶⁸	Special attention
		Lymphoma and other malignancies	Thaler et al ³⁵⁶	Groups of interest
		Malignancies and lymphoproliferative disorders	SPC ³⁵⁵	Special warnings / precautions for use
Neurological events	Demyelination Peripheral neuropathy	Demyelination	Thaler et al ³⁵⁶	Groups of interest
		Neurological events	SPC ³⁵⁵	Special warnings / precautions for use

Note: CHMP – Committee for Medicinal Products for Human Use; SPC – summary of product characteristics; SOC – system organ classification; SMQ – standardised MedDRA query

4.6.2. Matched SMQs and AE and ADR results by harm category

4.6.2.1. Autoimmunity

Autoimmunity, autoimmune diseases or autoimmune processes are listed as adverse reactions of concern in three of the sources consulted (Table 27). There is no SMQ for autoimmunity, although a SMQ for autoimmune diseases / immune mediated conditions is under development by the MedDRA working group³⁵⁸. As such, this category was excluded.

4.6.2.2. Blood disorders

The SPC for infliximab highlights that haematologic reactions have been reported with the use of anti-TNF α agents and that these should be monitored for³⁵⁵. Whilst there are plenty of SMQs related to specific haematological disorders, there was no SMQ closely matching the description in the SPC and therefore this category was excluded from the analysis (Table 27).

4.6.2.3. Cardiac events

Heart failure is listed as a special warning and precaution for use in the SPC for infliximab³⁵⁵ (Table 27). Cardiovascular events and congestive heart failure are listed as adverse events of interest for anti-TNF α therapy patients in Thaler et al³⁵⁶. The cardiac failure SMQ is defined as “a condition in which the heart is unable to pump an adequate amount of blood to meet metabolic and physiological needs of body”³⁵⁷. The narrow scope query includes terms that describe existing cardiac failure as well as a small number of terms for signs, symptoms, investigation findings and procedures that indicates or specify cardiac failure. 30 preferred terms are included in the narrow scope. Two of these terms were also reported in the SPC, but none was reported in the trials (Table 28). Cardiac failure and pulmonary oedema were reported as uncommon in the SPC. The preferred terms are linked to Cardiac disorders SOC and respiratory, thoracic and mediastinal disorders SOC, respectively. Uncommon events are unlikely to occur in trials with median 112 participants.

4.6.2.4. Hepatic events

Hepatic events and hepatobiliary events are identified as adverse events of interest and special warnings and precautions for use (Table 27)^{355,356}. Jaundice, non-infectious hepatitis and liver failure are reported to have occurred with use of Remicade in the SPC. The drug-related hepatic disorders SMQ was the closest match, which is a sub-SMQ of the much broader hepatic disorders SMQ. It includes terms for potentially drug-related liver disorders and there are 233 preferred terms in the narrow definition. Seven of these terms are recorded in the SPCs, three are reported in the trials and one is reported in both SPC and trials (

Table 29).

Hepatic function abnormal is under the SOC of hepatobiliary events and is reported to occur commonly in the SPC (between one in 100 and one in 10 patients). It is not reported in trials though. However, three related preferred terms that fall under the investigations SOC are reported: alanine aminotransferase abnormal, hepatic enzyme increased and transaminase increased. The latter was reported as a possible treatment-related adverse event in trials and is reported in the SPC as commonly occurring.

Hepatitis and hepatocellular injury are reported to occur uncommonly (between one in 1,000 and one in 100), autoimmune hepatitis and jaundice are reported to occur rarely (between one in 10,000 and one in 1,000) and hepatic failure is reported to occur but with unknown frequency in the SPC. Hepatocellular injury and hepatic failure are also included in the SMQ of drug related hepatitis – severe events only, which includes 79 preferred terms.

Table 28: Cardiac events standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Frequency of reporting in SPC					
				Very common	Common	Uncommon	Rare	Very rare	Not known
Cardiac disorders	Cardiac failure		x			x			
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema		x			x			

Note: SOC – System Organ Classification; PT – preferred term. Frequency: VERY COMMON, ≥ 1/10; COMMON, ≥ 1/100 to < 1/10; UNCOMMON ≥ 1/1,000 to < 1/100; RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000; and frequency not known, cannot be estimated from the available data.

Table 29: Drug related hepatic disorders standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Frequency of reporting in SPC					
				Very common	Common	Uncommon	Rare	Very rare	Not known
Hepatobiliary disorders	Autoimmune hepatitis		x				x		
	Hepatic failure		x						x
	Hepatic function abnormal		x		x				
	Hepatitis		x			x			
	Hepatocellular injury		x			x			
	Jaundice		x					x	
Investigations	Alanine aminotransferase abnormal	x							
	Hepatic enzyme increased	x							
	Transaminases increased	X TRAE	x		x				

Note: SOC – System Organ Classification; PT – preferred term. Frequency: VERY COMMON, ≥ 1/10; COMMON, ≥ 1/100 to < 1/10; UNCOMMON ≥ 1/1,000 to < 1/100; RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000; and frequency not known, cannot be estimated from the available data.

4.6.2.5. Hypersensitivity

As shown in Table 27, the SPC for Remicade identifies infusion reactions and hypersensitivity, including anaphylactic shock and delayed hypersensitivity, as special warnings and precautions for use³⁵⁵. The BNF lists delayed hypersensitivity and hypersensitivity reactions as monitoring requirements³²⁶. Injection site or infusion reactions were adverse events of interest in a drug class review of anti-TNF agents³⁵⁶.

There is a SMQ for hypersensitivity and a further SMQ is in development for infusion-related reactions³⁵⁸. The hypersensitivity SMQ is designed to identify “all cases possibly related to hypersensitivity / allergic reactions”³⁵⁷. The narrow definition, with greatest specificity, includes 270 preferred terms for which allergy is one of the main (and most likely) causes. This is distinguished from the broad definition, where hypersensitivity is only one of many possible causes of the included events.

18 preferred terms from the hypersensitivity SMQ are also featured in the SPC and trials for Remicade (Table 30). One preferred term is recorded in the SPC, but not the trials, in each of the following system organ classification (SOC) headings: blood and lymphatic system disorders; eye disorders; respiratory, thoracic and mediastinal disorders; and vascular disorders. Each of these adverse reactions are recorded to occur uncommonly or rare and therefore might not be expected to be found in the trials.

Six preferred terms under the immune system disorders SOC heading are recorded in either SPC or trials. One preferred term, serum sickness, is reported in both trials and the SPC, where it is reported to occur uncommonly. Two events are reported solely in trials and both are reported as potentially treatment related: hypersensitivity and type IV hypersensitivity reaction (delayed hypersensitivity). Three preferred terms were recorded solely in the SPCs: anaphylactic shock as a rare reaction; anaphylactic reaction as an uncommon event; and allergic respiratory symptom

as a common reaction. A commonly occurring reaction would be expected to occur in trials, but this may reflect the variable coding.

Eight preferred terms under the skin and subcutaneous skin disorders SOC were recorded in either SPC or trials. Three preferred terms were reported in both trials and the SPC, all as common adverse reactions in the SPC. Two of these terms were reported as potentially treatment related in the trials: rash and urticarial. One other event, hypersensitivity vasculitis, appeared solely in trials. A further four terms appeared solely in the SPCs, all either as uncommon or rare reactions. Two of these, Stevens-Johnson syndrome and toxic epidermal necrolysis, are rare and very serious reactions.

Table 30: Hypersensitivity standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Frequency of reporting					
				Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	Immune thrombocytopenic purpura		x					x	
Eye disorders	Periorbital oedema		x			x			
Immune system disorders	Allergic respiratory symptom		x		x				
	Anaphylactic reaction		x			x			
	Anaphylactic shock		x					x	
	Hypersensitivity	X TRAE							
	Serum sickness	x	x			x			
	Type IV hypersensitivity reaction	X TRAE							
Respiratory, thoracic and mediastinal disorders	Bronchospasm		x					x	
Skin and subcutaneous tissue disorders	Dermatitis bullous		x			x			
	Eczema	x	x		x				
	Erythema multiforme		x					x	
	Hypersensitivity vasculitis	x							
	Rash	X TRAE	x		x				
	Stevens-Johnson syndrome		x					x	
	Toxic epidermal necrolysis		x					x	
	Urticaria	X TRAE	x		x				
Vascular disorders	Circulatory collapse		x					x	

Note: SOC – System Organ Classification; PT – preferred term.

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

4.6.2.6. *Malignancies*

A number of malignancy terms, including tumours, malignancies, non-melanoma skin cancer, lymphoma, and lymphoproliferative disorders, were identified as important adverse reactions for infliximab in the literature (Table 27)^{68,326,355,356}. The SMQ for malignancies was identified, which is a combination of four sub-SMQs for malignancy-related tumours, malignancy related therapeutic and diagnostic procedures, malignant or unspecified tumours and tumour markers. The SMQ includes 2,205 unique preferred terms in the narrow definition.

19 of these terms were recorded in either the SPC or trials, none was reported in both (Table 31). All but one, intestinal resection (reported in trials), are under the SOC heading neoplasms, benign, malignant and unspecified. Ten further preferred terms appeared only in trials: basal cell carcinoma, bladder cancer, breast cancer, carcinoma in situ, natural killer-cell lymphoblastic lymphoma, neoplasm malignant (as a potentially treatment related event), neoplasm skin, rectal adenocarcinoma, rectal cancer and renal cell carcinoma. Eight preferred terms are recorded in the SPC, 6 as rare reactions (cervix carcinoma, Hodgkin's disease, leukaemia, lymphoma, malignant melanoma and non-Hodgkin's lymphoma) and 2 with unknown frequency (hepatosplenic T-cell lymphoma and neuroendocrine carcinoma of the skin).

Table 31: Malignancies standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Very common	Common	Uncommon	Rare	Very rare	Not known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	x							
	Bladder cancer	x							
	Breast cancer	x							
	Carcinoma in situ	x							
	Cervix carcinoma			x			x		
	Hepatosplenic T-cell lymphoma			x					x
	Hodgkin's disease			x			x		
	Leukaemia			x			x		
	Lymphoma			x			x		
	Malignant melanoma			x			x		
	Natural killer-cell lymphoblastic lymphoma	x							
	Neoplasm malignant	X TRAE							
	Neoplasm skin	x							
	Neuroendocrine carcinoma of the skin			x					x
	Non-Hodgkin's lymphoma			x			x		
	Rectal adenocarcinoma	x							
	Rectal cancer	x							
Renal cell carcinoma	x								
Surgical and medical procedures	Intestinal resection	x							

Note: SOC – System Organ Classification; PT – preferred term. Frequency: VERY COMMON, ≥ 1/10; COMMON, ≥ 1/100 to < 1/10; UNCOMMON ≥ 1/1,000 to < 1/100; RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000; and frequency not known, cannot be estimated from the available data.

4.6.2.7. Neurological events

Neurological events, namely demyelinating disorders and peripheral neuropathy, were identified as important adverse events associated with the use of Remicade (Table 27)^{355,356}. There is no SMQ available for neurological events, but there are SMQs for both demyelination and peripheral neuropathy. An SMQ is also available for Guillain-Barre syndrome, and the SMQ introductory document recommends all three are included in any case search to identify all demyelination disorders. However, none of the narrow search terms in the Guillain-Barre syndrome SMQ matched any preferred terms in the trials or SPC, so it is not reported.

Demyelination is defined in the SMQ as the “loss of myelin with preservation of the axons or fibre tracts”, and identifies central demyelination as occurring within the central nervous system and peripheral as affecting the peripheral nervous system.³⁵⁷ Included in the SMQ are terms for central and peripheral demyelination, but also terms containing the root “demyel” and other terms for conditions specifically related to demyelination. 40 preferred terms are included in the narrow definition SMQ and three matched terms in trials and the SPC (Table 32). Demyelination was listed in both trials and the SPC. Multiple sclerosis was listed in the trials and myelitis transverse, which is often an early symptom of MS, was listed as a rarely occurring adverse reaction in the SPC for Remicade.

Within the SMQ for peripheral neuropathy, the condition is defined as an “impairment of the peripheral motor, sensory and autonomic nervous system”³⁵⁷. It includes all terms for peripheral neuropathy and related concepts, as well as signs, symptoms and laboratory findings. There are 36 preferred terms in the narrow definition SMQ, two of which are reported in either trials or SPC (Table 33). Neuropathy peripheral was identified as an uncommon reaction in the SPC for Remicade and sensory loss, which can be an early symptom of peripheral neuropathy, was identified as an adverse event in the trials.

Table 32: Demyelination standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders	Demyelination	x	x				x		
	Multiple sclerosis	x							
	Myelitis transverse		x				x		

Note: SOC – System Organ Classification; PT – preferred term.

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Table 33: Peripheral neuropathy standardised MedDRA query (SMQ) matched against the summary of product characteristics (SPC) and trial adverse events data

SOC	PT	Reported in trials	Reported in SPC	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders	Neuropathy peripheral		x			x			
	Sensory loss	x							

Note: SOC – System Organ Classification; PT – preferred term.

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

4.6.2.8. Infection

Infections and serious infections were listed in all four sources of literature on important harms for Remicade (Table 27)^{68,326,355,356}. An SMQ for infection is unavailable, although one for opportunistic infections is under development³⁵⁸. The SOC heading of infections and infestations offers an opportunity to consider the differences and similarities in reporting between trials and the SPC for Remicade. 27 preferred terms for infections and infestations were reported in the trials, three of which were reported as potentially treatment related – infection, pharyngitis and pneumonia (Table 34). Only one preferred term, tuberculosis, was also reported in the SPC and was listed as occurring uncommonly. However, the SPC lists a number of types of infections and gives examples, and some of the examples do match the adverse events reported in trials. For example, the SPC lists bacterial infections as occurring commonly and specifies abscess as one type. Five preferred terms for abscess were reported as in the trials adverse events: abdominal abscess, abdominal wall abscess, abscess, anal abscess and pelvic abscess. Sepsis was also an example and is reported in the trials.

Viral infections are reported to occur very commonly and two of the examples given in the SPC, herpes virus infection and influenza, were reported in the trials. The SPC reports that opportunistic infections occur rarely and a number of examples are given with one clearly corresponding to a preferred term reported in trials: cytomegalovirus infection. Five further preferred terms are listed in the SPC but not the trials: fungal infection reported to occur uncommonly; infection parasitic, meningitis and hepatitis B reactivation reported to occur rarely; and vaccine breakthrough infection reported with unknown frequency.

Table 34: Infections under the SOC Infections and infestations matched against summary of product characteristics (SPCs) and Crohn's disease trials adverse events data

HLGT	PT	In trials	In SPC	Very common	Common	Uncommon	Rare	Very rare	Not known	Comment
Bacterial infectious disorders	Bacterial infection		x		x					SPC: (e.g. sepsis, cellulitis, abscess)
	Legionella infection	x								
	Nocardiosis	x								
Fungal infectious disorders	Fungal infection		x			x				SPC: (e.g. candidiasis)
Infections - pathogen unspecified	Abdominal abscess	x								
	Abdominal wall abscess	x								
	Abscess	x								SPC: listed as example of bacterial infection
	Anal abscess	x								
	Appendicitis	x								
	Bronchitis	x								Listed as an example of LRTI in SPC
	Ear infection	x								
	Eye infection	x								
	Gastroenteritis	x								
	Gastrointestinal infection	x								
	Infection	X TRAE								
	Infection parasitic			x				x		
	Infectious colitis	X								
	Meningitis			x				x		

HLGT	PT	In trials	In SPC	Very common	Common	Uncommon	Rare	Very rare	Not known	Comment
	Nasopharyngitis	x								
	Opportunistic infection		x				x			SPC: (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus])
	Pelvic abscess	x								
	Pharyngitis	X TRAE								
	Pneumonia	X TRAE								Listed as example of LRTI in SPC
	Respiratory tract infection	X								
	Rhinitis	X								
	Sepsis	x								SPC: listed as example of bacterial infection
	Skin infection	x								

HLGT	PT	In trials	In SPC	Very common	Common	Uncommon	Rare	Very rare	Not known	Comment
	Vaccine breakthrough infection		x						x	SPC: (after in utero exposure to infliximab)
Mycobacterial infectious disorders	Tuberculosis	x	x			x				
Viral infectious disorders	Cytomegalovirus infection	x								Listed as example of opportunistic infection in SPC
	Hepatitis B		x				x			SPC: listed as hepatitis B reactivation
	Hepatitis C	x								
	Herpes virus infection	x								SPC: listed as example of viral infection
	Influenza	x								SPC: listed as example of viral infection
	Viral infection		x	x						SPC: (e.g. influenza, herpes virus infection)

Note: SOC – System Organ Classification; PT – preferred term; HLGT – higher-level group term; LRTI – lower respiratory tract infection
Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

4.7. Discussion 2

4.7.1. Summary of evidence

The work in this chapter builds upon both the systematic review in Chapter 2 and the outcomes classification hierarchy in Chapter 3. The aim was to examine potential methods of fully characterising the harms that are incompletely described in RCTs due to the factors discussed in Section 4.1, including the limited population involved, length of trials and evidence of reporting bias. The data source used was the summary of product characteristics (SPC). The initial methodology involved organising the drugs into classes and comparing RCT adverse events against adverse reactions from the SPCs. 14 therapies were included in the analysis, which grouped into five drug classes. The SPCs were found for 69 studies identified in the systematic review, 38.1% of the total. Corticosteroids were the drug class with most trials for which an SPC could be matched, followed by anti-TNF α inhibitors, and budesonide was the active ingredient with the most trials for which an SPC could be matched.

Based upon the known issue that RCTs fail to characterise rare events and the selective reporting which may introduce bias and prevent the identification of all risks, the intention was to identify common and very common and rare and very rare adverse reactions that were not reported in trials. However, difficulties arose from this method due to a number of reasons. The grouping of drugs into classes, some of which were much older and had been developed under different reporting protocols for adverse reactions, meant there was potential bias in the data in both trials and SPCs. Identifying important harms was potentially compromised due to the use of therapies for other more common conditions that may have a different risk profile, such as rheumatoid arthritis, and the ability to code events in different way using MedDRA.

A new approach sought to refine the analysis and reduce the noise by focusing on one treatment, infliximab (Remicade[®]), using the evidence base to identify the key harms from that treatment. Standardised MedDRA queries (SMQs) grouped preferred terms to overcome the difficulties

caused by multiple ways to code the same reaction in MedDRA and the potential for trials to identify earlier symptoms of longer-term adverse reactions. The narrow definition SMQs were deemed most relevant to the aims of the chapter as summary data is being used, and the narrow terms maximise specificity rather than sensitivity. Ten trials were included for infliximab, with a median treatment sample size of 65 (interquartile range: 31-125 participants). It might therefore be expected that trials would identify very common (affecting at least one in ten) and perhaps common events (affecting at least one in 100). The capture of uncommon harms (affecting more than or equal to one in 1,000, but fewer than one in 100 patients), rare or very rare harms (affecting fewer than one in 1,000 patients) would not be expected. Analysing trials in aggregate gives improved power for detecting rarer adverse events and, as described in Section 4.1.3, is the approach taken by spontaneous reporting systems to establish the frequency of occurrence of adverse reactions. Indeed, a rule of three calculation³⁵⁹ for the 10 trials combined (total 937 participants receiving infliximab) suggests that any adverse reactions not identified in trials have a 95% confidence interval upper limit of occurrence of three in 1,000 patients, which is within the rare category. This is a much-improved potential for detection of adverse reactions than based on any single trials alone.

The use of harm categories and SMQs greatly reduced the number of preferred terms identified. Only six adverse reactions in the SPC matched directly to adverse events recorded in the RCTs. Using the SMQs, 29 adverse reactions were identified from the SPC that were not reported in the RCTs (four preferred terms under the infections and infestations SOC for which there was no SMQ). 17 of these were rarely occurring adverse reactions, and offer the strongest potential as additional data on the harms of Remicade therapy in Crohn's disease. This is a significant improvement on 52 rare and very rare adverse reactions that were identified for anti-TNF α therapies using the initial methodology.

This leaves 12 non-rare adverse reactions that deserve further consideration. Three of these were reported as frequency not known (hepatic failure, hepatosplenic T-cell lymphoma and neuroendocrine carcinoma of the skin) which are likely to be signals that have been identified through spontaneous reporting. However, two are common or very common in occurrence according to the SPC, which should appear in the trials unless they are adverse events that occur through extended use. Hepatic function abnormal was a commonly occurring adverse reaction in the hepatic events harms category that was unreported in RCTs. However, three preferred terms within the drug-related hepatic disorders SMQ that indicate abnormal liver function were reported in trials: alanine aminotransferase abnormal, hepatic enzyme increased and transaminases increased. It is conceivable that these are similar but coded differently and the SMQ has succeeded in pulling them together. Similarly, allergic respiratory symptom is reported as a common adverse reaction but is not reported in trials. However, hypersensitivity was reported as an adverse reaction in trials and is grouped within the hypersensitivity SMQ, which may again signal a success in the grouping of different codes for similar events.

Uncommon adverse reactions could not be expected to occur in trials given their size as the rule of three (as derived in Equation 4 to Equation 7) would put the estimates of missing adverse events outside of this frequency grouping (Table 13). There are seven preferred terms that fall into this category of uncommon events not reported in RCTs, and whilst six of these offer no immediate explanation, but would be of interest because of their potential seriousness (cardiac failure, hepatitis, hepatocellular injury, periorbital oedema, dermatitis bullous and anaphylactic reaction), the remaining one potentially highlights another SMQ linking. Neuropathy peripheral is an uncommon adverse reaction recorded in the SPC, but is not recorded in trials. However, sensory loss is recorded in trials and is within the peripheral neuropathy SMQ. Given that sensory loss is an initial symptom of peripheral neuropathy, this might reflect a coding variation or it could reflect the time course differences in adverse events identified in RCTs versus post-marketing surveillance. Sensory loss is likely to be a short-term observation of peripheral neuropathy, the

former of which could be identified in RCTs, whilst the latter would almost certainly not be. The use of SMQs allows for the initial symptoms and final outcomes to be identified together.

4.7.2. Strengths and limitations

A key strength of this approach is the ability to make use of existing data to characterise more completely the harms from a specific therapy in Crohn's disease. Harms reporting is complex and there is a high volume of data to incorporate from both trials and SPCs. This method enabled the vast amounts of data to be summarised and interpreted. The results in Section 4.3.2 show that up to 91.5% of rare and very rare adverse events reported in the SPCs are not reported in trials, which gives an indication of the potential value of this approach.

A search of the literature to identify important harms for Crohn's disease and then matching the SMQ and trials data allowed for 17 rare harms to be identified, some of which are very serious. Narrow SMQ searches were used to ensure specificity of the preferred terms, but research suggests the choice of narrow or broad makes little difference probably because medical coders are trained to code the most important events, which are in the narrow search³⁶⁰. Knowing the very serious adverse events, even if they are very rare, is an important consideration for those involved in health technology assessment and can have a significant impact upon the benefit-risk balance of a drug. This method has the potential to add value to such processes.

The ability to understand the risk associated with this smaller number of most relevant harms could help to systematically and comprehensively characterise harms and support clinical decision-making. Assessing harms requires a different paradigm to assessing efficacy, where the hierarchy of evidence is not relevant but instead there is a need to consider all available evidence on harms and explore different methods in order to reach a conclusion on risk^{334,347,361}. The approach taken in this chapter attempts to work within the altered paradigm in an efficient way to maximise the value of existing data. This approach is in line with research into other sources of harms data, which included observational studies, unpublished work and, more recently, social

media^{334,336,343,346,362}. It may be useful in contributing important harms to a core outcome set development process by identifying a list of harms that can be included in the outcomes to be prioritised as part of consensus methods.

The CONSORT statement makes clear how trials should report harm and a joint response by industry and journal editors emphasises a key problem is in identifying those harms that are most clinically significant as this is what supports decision-making³⁶³. The authors argue for clinical trials to filter reported harms to help identify key harms. This could be based upon the mechanism of action, or consideration of previous agents in the class, but they suggest it could also come from clinical experience or a systematic review to identify other harms. In essence, the methods described here have applied a clinical filter using a literature review and SMQs, but to the pharmacovigilance information from the SPCs, rather than RCT adverse events. This is a novel approach.

However, the method is not without limitations. Many of the difficulties relate to the general processes involved in generating data in SPCs (and trials), and are not specific to this method alone. One issue of vital importance is the limited consideration of seriousness or causation of adverse events in clinical trials. Results in Chapter 2 highlight that few trials record serious adverse events and serious treatment-related adverse events are even less likely to be reported. Of the 69 trials included in this chapter, only 69.1% assessed causation of adverse events and even fewer (59%) reported individual adverse events that were assessed as possibly treatment related. The CONSORT statement extension identifies poor reporting as the summation of adverse events without reference to seriousness and made suggestions that have improved reporting, but it remains a current issue^{333,363}. In addition, competing risks and the independence of adverse reactions need to be assessed and their impact understood.

The guidance for SPCs states that within each frequency grouping in the table of undesirable events, adverse reactions should be presented in the order of decreasing seriousness¹⁵. However,

this does little to quantify the seriousness of each event, especially if attempting to compare between different system organ classifications, and the preferred terms do not indicate it either. As an example, cardiac failure sounds very serious, but is actually graded from Class I where it causes no limitations at all, to Class IV where patients are unable to carry on any physical activity and have symptoms at rest, although there is risk of progression³⁶⁴. Therefore even where a list of preferred terms is identified using this method, it would need further investigation to understand seriousness.

Whilst spontaneous reporting systems represent a cost-effective method of monitoring drug safety, there are issues with under-reporting of adverse reactions, poor quality reporting and the absence of a clear denominator to quantify risk^{334,365,366}. Significant under-reporting of adverse reactions is a well-understood limitation of spontaneous reporting systems. Estimates of underreporting from one systematic review range from 82% to 96%, with little improvement in the reporting of serious adverse reactions, and this can delay the identification of signals and create difficulties in quantifying risk^{365,367}. Reasons for under-reporting by health professionals are multiple. They include a lack of knowledge about the reporting system (including mistaken beliefs that the system is only for monitoring severe reactions or conversely that all adverse reactions are known about when the drug comes to market), worry about correctly identifying adverse reactions and attributing causation, and administration reasons such as a lack of time or inability to locate forms³⁶⁵⁻³⁶⁷.

Further limitations exist at the point of identifying signals from the spontaneous reports. Disproportionality methods are quick, inexpensive, and able to identify previously unknown harms, which is especially useful in the case of rare events³⁴⁷. However, when a drug is used for a variety of conditions there is the chance for signals in one condition to be diluted, or for the opposite and one to be identified that doesn't hold for all conditions. This could be a factor in our case study of Remicade, as Crohn's disease is much less common than rheumatoid arthritis, and

the drug is used in both. However, an analysis of two spontaneous databases found that significant masking was in fact rare in large databases³⁶⁸. In addition, there is a risk of false positive signals of adverse reactions due to multiplicity, if appropriate statistical techniques are not used^{334,352}.

SMQs are designed to reduce the problem of signal dilution and there is evidence that both applicants and the FDA increasingly use them in the applications for market review, and that the results impact the decisions made³⁶⁹. This is a significant change from a survey of MedDRA users in 2007 which suggested that they were not well used³⁷⁰, and indicates a growing acceptance of the tools. Caution should be paid though, as an analysis of one year of data from the French spontaneous reporting database indicated variable performance across different SMQs in terms of their ability to correctly detect cases with fairly low positive predictive value³⁶⁰. Although the use of SMQ here is on data that should already have been through this process and have been validated against other data, in the case of FDA market approvals, 26% of SMQ searches used at the point of labelling did not mention validation³⁶⁹. If the same finding applied in the EU, this would still have implications for the accuracy of the data in our results.

When signals are detected, reference will be made to the clinical trial data. Underreporting may not be as great a concern in clinical trials as in spontaneous reporting systems (although selective reporting is still a concern as discussed in Chapter 3), but quality and completeness are an issue, even for serious adverse events. One study found that adverse events were reported incorrectly in 15.1% of investigator reports and clinical or laboratory findings were not included in 30% of reports³⁷¹. Even where cases are reported correctly, a study estimates that 12% of reports were coded differently by 2 different coders in clinical trials and that 8% of investigator reports were coded incorrectly³⁵³. This reduces the usefulness of pharmacovigilance at each stage of the lifecycle of a drug.

Frequency reporting within the SPC is flawed, as it does not report on the duration of treatment, which can often increase the risk of adverse reactions³³⁴. Further, it does not consider the different indications, unless there is a great deal of evidence in support of an adverse reaction that is particular to one indication. Alternative systems of adverse event classification have been proposed to overcome these flaws. One such system, discussed in Chapter 1 is the DoTs system, which classifies adverse reactions according to dose, time and susceptibility factors⁵⁶.

In addition, the use of the rule of three can lead to estimates of adverse reaction frequency in SPCs higher than adverse events that were actually reported in trials³⁷². This is best illustrated by example, such as where adverse reactions that did not appear in the trials would be recorded as rare in the SPC, but some adverse events that did occur within trials were reported as very rare. Greater clarity in reporting is proposed by Crowe et al³⁷² who recommend that incidence rates should be included (as well as comparator incidence rates for alternative treatments) and that frequencies estimated using the rule of 3 should be recorded separately. Additionally, evidence points to under-reporting in SPCs of drug interaction information, with only 33% of SPCs reporting drug interaction information equivalent to that published in the literature³⁷³. Accounting for such measures within SPCs would help to identify the data with most uncertainty.

The faults of the two data sources, RCTs and SPCs, are on opposite sides of the denominator and population sides of a risk calculation, which may result in differences in absolute risk values (or even the ability to calculate absolute risk values). However, research by Zink et al (2018) demonstrated similarities in the ranking of adverse reactions taken from the two sources³³⁴. This supports the use of both sources to improve the safety profile of medicines, despite the biases involved in both.

A final, limitation specific to the methods in this chapter, is the failure to include harms data from observational studies, which arguably would include the longer-term harms. The work on this chapter built upon the systematic review in Chapter 2, which was of both harm and efficacy

outcomes. Work by Golder et al³³⁹ has demonstrated that more comprehensive information on harms can be obtained by a review focused on adverse events and with consideration of both published and unpublished work. The differences between the harms identified in the SPCs and the trials might have been less had this approach been taken, although it would be a very complex undertaking for the grouping of trials in the first methods section, 4.2. The approach taken was pragmatic in light of the restricted time of a PhD project, and the ability to build upon the work from an earlier chapter, but does bear consideration regardless.

4.7.3. Conclusions

This chapter presents a novel method for triangulating the literature on key harms, the adverse events reported in randomised controlled trials and the adverse reactions recorded in SPCs. The use of SMQs provides the opportunity to group initial symptoms, which are more likely to be identified in RCTs, with the longer-term outcomes identified through post-marketing surveillance. Whilst spontaneous reporting systems are undoubtedly flawed, the design of trials to estimate benefit and their short-term nature, particularly for chronic conditions like Crohn's disease, means that pharmacovigilance relies upon such reports. Methods to bring together a variety of harms data must be considered efficient research, especially where they allow for the identification and quantification (albeit in broad frequency groups) of harms. Methods that help to identify the most rare and serious harms from drugs add value by supporting a better understanding of the benefit-risk balance of a therapy, which is useful for a range of decision-makers from clinical to health-care payer and could also potentially support the inclusion of harms in core outcome set development. Other methods would be needed for non-drug therapies, such as polymeric diet and surgery, and for widely used drug therapies such as mercaptopurine and prednisolone for which no randomised clinical trial evidence was found in the systematic review in Chapter 2.

Further research would be valuable to validate the findings in this chapter and could involve an analysis of the performance of standardised MedDRA queries on a sample of Yellow Card

spontaneous reports. Additionally, the research could be repeated as new SMQs are developed, particularly those for opportunistic infections, infusion-related reactions and autoimmune diseases and immune mediated conditions, which were all identified as important harm categories for infliximab.

The work in Chapter 5 continues the focus on infliximab as a case study and seeks to estimate the benefit-risk balance of a biosimilar where there is no direct evidence of harm and efficacy in Crohn's disease patients.

Chapter 5: Value assessment and quantitative benefit-risk modelling: a case study of infliximab in Crohn's disease

5.1. Introduction

Biosimilars offer the opportunity for less expensive treatment of chronic conditions, while achieving comparable health outcomes to reference medical products (RMP), enabling reduced expenditure on the therapies or the extension of treatment to allow more patients to benefit within the same budget. Medicine regulators seek assurance that there are no clinically meaningful differences in efficacy and safety to the RMP^{81,374} using processes described in detail in Section 1.3.2. This normally requires a clinical trial in a population sensitive to potential differences in efficacy, safety, or immunogenicity between the biosimilar and originator. Evidence of similarity in one clinical indication is assumed to extrapolate to other indications for which the medicine is approved based on a qualitative assessment of the totality of the evidence, including the structural, physicochemical, functional, and non-clinical data in addition to clinical studies^{81,374}.

Biosimilars are not intended to be superior to the originator (these would be biobetters³⁷⁵), although advances in technology and improved manufacturing processes over time may in fact mean that biosimilars could become more efficacious and less harmful than their originator products. However, they may be less efficacious and there is also a risk that they carry an inferior safety profile (if only marginally). Uncertainties regarding the safety of biosimilars at the point of marketing authorisation are inherently related to the use of non-inferiority trials to justify near-equivalence of efficacy, the absence of trial evidence for all indications due to the process of extrapolation and the lack of long-term experience and data. These uncertainties were discussed further in Section 1.3.3.2. The primary reason for adopting biosimilars and acceptance of the potential risks with no improved health benefits is the opportunity for cost savings. With each new biosimilar, health care payers therefore face the question of whether the cost savings can justify the increased uncertainty in their clinical performance.

At the point of launch, and for a long period after, the biosimilar will have less safety data than the originator and therefore there will always be uncertainty about the net health benefit (NHB). As explained in Section 1.1.2.2, the NHB is the net benefit of investing resources in a given intervention, rather than in investing the same resources in another marginally cost-effective intervention³⁷. In other words, in the presence of budget constraints, spending on this biosimilar means forgoing the health benefits of investing in another drug.

Biological therapies have improved the quality of life of patients with Crohn's disease, but they are expensive and are linked to serious adverse events³⁷⁶. The first Crohn's disease (CD) biological treatment patent to expire was for originator infliximab (IFX) (Remicade, Merck Sharp & Dohme Limited, Hertfordshire, UK). As discussed in Section 1.3.3, the pattern of regulatory approvals, with some countries initially rejecting the drugs or limiting their approved indications, highlights the difficulties arising from the subjective nature of benefit-risk balance assessment and extrapolation from evidence in rheumatoid arthritis (RA)^{68,86,377}. A key concern was that CD patients are more likely than other patients to develop antibodies to infliximab (ATI), which trials in other indications are unable to rule out^{94,378}. The consequences of developing ATI, known as immunogenicity, include reduced efficacy and increased likelihood of adverse events, particularly infusion reactions, which are rare but can be severe. Even minor differences between the biosimilar and originator have the potential to cause significant harm for patients³⁷⁹.

With each new biosimilar, health care payers therefore face the question of whether the cost savings can justify the increased uncertainty in their clinical performance. A range of quantitative methods for benefit-risk assessment are available, but to date, there has been no quantitative benefit-risk analysis of biosimilars, which may reflect the further challenge of assumed equivalence in benefits with the RMP. Health economic modelling can be used as part of the health technology assessment to evaluate the benefit-risk balance by pooling the available evidence and reflecting uncertainty in inputs, to estimate the likelihood of a biosimilar providing

a net health gain³⁹. The INHB between the biosimilar and originator represents the added value of the biosimilar considering both the reduced costs and the increased uncertainty surrounding its clinical performance given societal resource constraints³⁷ and, in effect, represents a quantitative approach to the benefit-risk assessment of biosimilars.

The work presented in this chapter aimed to quantitatively assess the benefit-risk balance of biosimilar versus originator, using IFX as an exemplar, to determine whether the cost savings justify the increased uncertainties in efficacy and safety and to assess the value of conducting further trials in CD to reduce uncertainty in key parameters. The results of the model were discussed in the context of emerging evidence from clinical use and ongoing trials in CD.

5.2. Methods

5.2.1. Literature review

The model was developed as a proof-of-concept rather than to inform clinical decision-making and therefore a pragmatic approach was taken to literature review. A search of MEDLINE was used to identify economic models used to evaluate infliximab. Where possible, parameter values were guided by previous economic models and included parameters from clinical trials, observational studies, meta-analyses and data generated by authors of previous economic models. However, the focus on the development and consequences of ATI necessitated additional targeted searches of MEDLINE to obtain parameter values. Given the assumption of biosimilarity, and the lack of clinical trial data for Inflectra in CD, the parameter values were obtained for the originator drug, and assumed equivalent in the base case.

The following section discusses the evidence from the clinical trials of originator IFX and the implications of their use in modelling.

5.2.1.1. Pivotal infliximab monotherapy trials

The pivotal IFX trials were identified by the systematic review reported in Chapter 2. Two trials were used to evidence the efficacy of originator infliximab in patients with moderate to severe

Crohn's disease, in order to obtain regulatory approval from the EMA³⁸⁰. The pivotal induction therapy trial was a double-blinded randomised controlled trial (RCT) of 108 patients by Targan et al (1997)¹²⁹. This RCT included 108 patients with moderate to severe CD, defined as $220 \leq$ Crohn's disease activity index (CDAI) score ≤ 400 . Patients were randomised to receive a single infusion of IFX at a dose of 5, 10 or 20 mg / kg body weight, or placebo. The primary endpoint was response at week 4, which was defined as a 70-point reduction in CDAI score. The response rate at 4 weeks was 81% (22/27) in the 5mg/kg infusion group, 50% (14/28) in the 10mg/kg group, and 64% (18/28) in the 20mg/kg group, compared to 16% (4/24) in the placebo arm. The authors concluded that a single infusion of IFX was effective for short-term treatment in patients with moderate-to-severe CD.

Hanauer et al (2002)²⁴⁰ conducted the pivotal IFX maintenance therapy RCT in 523 patients with a CDAI score ≥ 220 . The ACCENT I trial aimed to assess the efficacy and safety of repeated infusions of IFX over 1 year, in patients who responded to an initial infusion. All patients received an initial 5mg/kg dose infusion of IFX at week 0. Response was defined as a reduction in CDAI by $\geq 25\%$ and ≥ 70 points, and was checked at week 2. Responders were randomised to placebo (group I), IFX 5mg/kg (group II) and IFX 10mg/kg (group III). Maintenance infusions were received at weeks 2 and 6, and every 8 weeks afterwards. The co-primary endpoint was remission (CDAI < 150) at week 30 and time to loss of response up to week 54. Remission at week 30 was achieved by 20.9% (23/110) of patients in group I (placebo), 38.9% (44/113) of patients in group II (5mg/kg) and 45.5% (51/112) of patients in group III (10mg/kg). The median time to loss of response was 19 weeks in group I, 38 weeks in group II and more than 54 weeks in group III.

The ACCENT I trial informed the EMA approved dosing strategy for Crohn's disease, but does not provide the appropriate data for modelling efficacy and harm as it does not contain an assessment of induction therapy. As with Targan et al, the initial response is tested after a single dose. IFX was initially developed as a single dose drug, with retreatment to be given once the condition

flared. However, over time it became clear that episodic treatment resulted in a greater risk of ATI (45.8%, 95% CI: 41.7-50.0%) compared to maintenance schedules (12.4%, 95% CI: 10.8-14.1%), demonstrated by systematic review and meta-analysis³⁸¹. Consequently, the current recommended treatment pathway for IFX does not reflect the early clinical trials and necessitates the use of other data sources in modelling.

5.2.2. Model structure

A decision analytic model was constructed, to compare the benefits and risks of IFX biosimilar and originator. The model was adapted from a published one-year cost-effectiveness analysis of IFX dose escalation versus initiation of adalimumab by Kaplan et al (2007)³⁸² by the inclusion of adverse events.

A hypothetical cohort of 100,000 biologic-naïve 35-year-old 70-kg patients with moderate-to-severe CD was simulated through the model (Figure 19), which was structured over 4-weekly intervals to capture costs and outcomes. The perspective of the analysis was that of the National Health Service (NHS) in the UK following marketing authorisation for Inflectra in 2013. For the purposes of the economic analysis, which requires a single payer perspective, costs were restricted to those of the NHS in the UK. Although CD is a chronic condition, a one-year time-horizon was justified, as this was a proof-of-concept model with a focus on short-term outcomes.

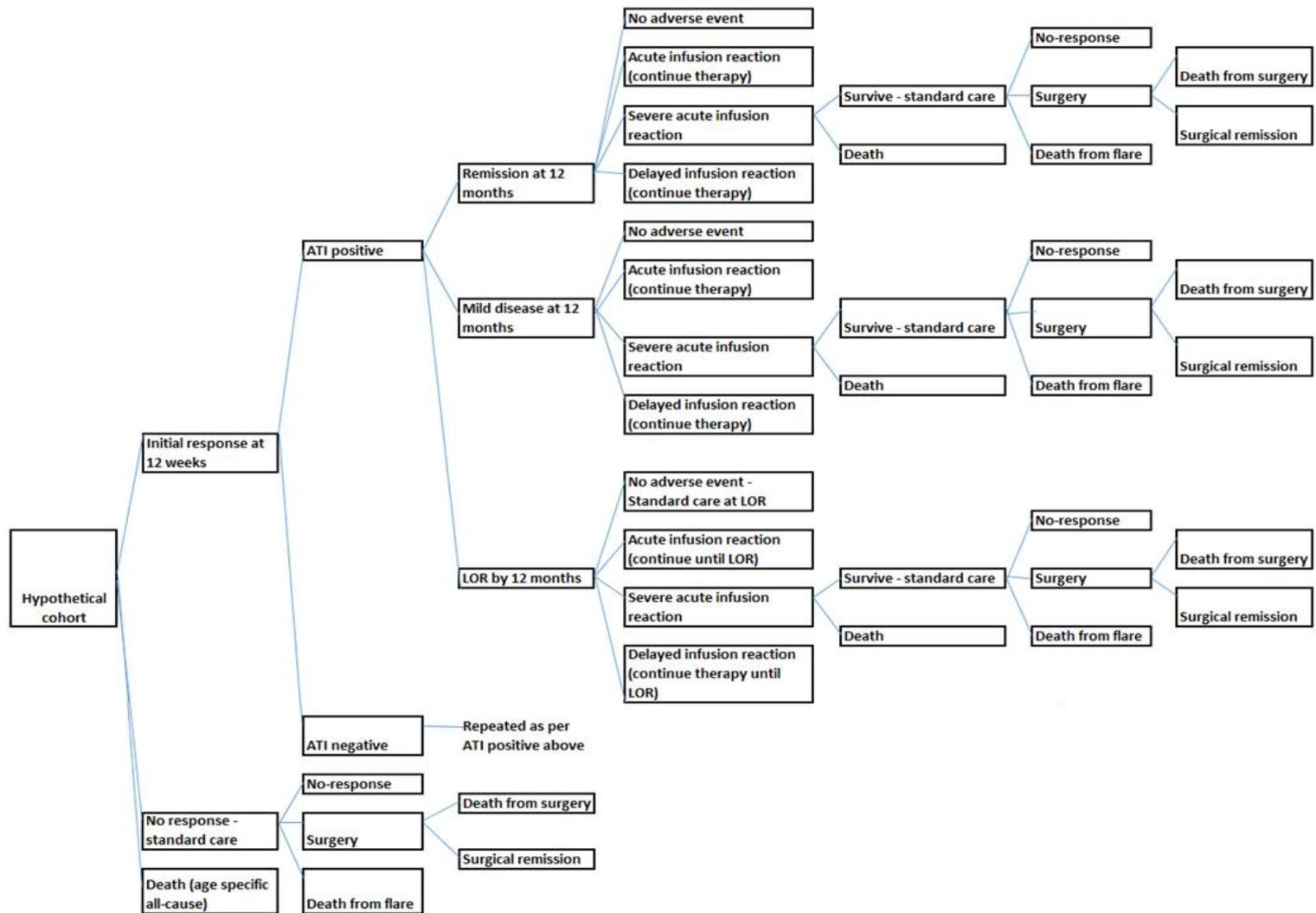


Figure 19: Partial schematic representation of the decision-analysis model comparing Inflectra and Remicade. (Abbreviations: ATI – antibodies to infliximab; LOR – loss of response)

Due to the concern regarding immunogenicity of the biosimilar, the development of ATI is an important modifier in the model, influencing the rate of primary and secondary non-response³⁸³, and the likelihood of infusion reaction. Acute or severe infusion reactions take place within 24 hours of infusion and delayed infusion reactions take place between 24 hours to 14 days after infusion³⁸⁴. In line with common practice⁵⁹, the disease states were defined by the CDAI: moderate-to-severe disease equates to a CDAI score ≥ 220 , remission to a score < 150 and response to a reduction in CDAI score ≥ 70 points, resulting in mild disease (≥ 150 CDAI score < 220).

All patients enter the model in period 1 in moderate-to-severe disease state and received IFX therapy of 5mg/kg at weeks 0, 2 (period 1) and 6 (period 2), in accordance with the summary of product characteristics (SPC)^{380,385}. Initial response and the development of ATI are measured at week 12 (period 4). Those with no initial response ceased treatment with IFX, moved to standard care therapy in period 4, initially remaining in moderate-to-severe disease state. Standard care includes all other possible therapies and surgeries, as outlined in NICE clinical management guidance⁶².

Patients with primary response were in a mild disease state during periods 2 and 3 and entered ATI status-dependent remission or mild disease states in period 4. IFX maintenance therapy continued every 8 weeks unless they experienced secondary non-response (loss of response), or a severe infusion reaction, upon which they moved to standard care (or died). Patients who experience secondary non-response do so from a mild disease state. Acute and delayed infusion reactions were managed in the same period and IFX was not withdrawn. Patients could only experience one infusion reaction over the year and all were assumed to be in period 4, following the 4th infusion, consistent with the findings of the pivotal trial of IFX maintenance therapy in Crohn's disease, ACCENT I²⁴⁰.

At the end of one year, patients who remained on IFX could be in remission or experiencing mild disease or had moved to standard care or died. Patients receiving standard care could end the

year in a moderate-to-severe disease state or post-surgical remission as it seems clinically unrealistic that patients who have failed standard care, then failed anti-TNF α therapy, could return to standard care and achieve remission or mild disease. Death in the model could result from age-specific, all-cause mortality, severe infusion reaction, surgery or disease flare. Age-specific, all-cause mortality³⁸⁶ was applied during week 12, meaning none had experienced maintenance therapy.

Moves to alternative treatment or surgery take place at the end of each period to allow for benefits, harms and costs to be allocated in whole periods. Benefits and harms took the form of utility values, health state preferences measured as quality adjusted life years (QALYs). The effects of IFX treatment occur within the period of treatment. SC is assumed to take two periods to have effect³⁸². Secondary non-response is assumed to take place at 38 weeks in line with the median in patients receiving the standard therapy of 5mg/kg of infliximab from ACCENT I (group II)²⁴⁰. The effect of IFX is assumed to wash out 19 weeks after stopping IFX due to a severe infusion reaction, in line with the median time to offset of response during placebo maintenance in ACCENT I²⁴⁰.

The model was constructed in Microsoft Excel using visual basic language for probabilistic sensitivity analysis (PSA).

5.2.3. Model parameters

Parameter estimates for ATI development, efficacy, adverse events, health utilities and costs were obtained from targeted MEDLINE literature reviews of infliximab cost-effectiveness models and meta-analyses of infliximab immunogenicity and its impacts as discussed in Section 5.2.1. Parameters were selected purposively for methodological convenience, rather than through systematic review and evidence grading as the model intended to act as a proof of concept, rather than produce answers for clinical decision-making. Model inputs are shown in Table 35.

Table 35: Clinical event rates, health state utility values assigned to clinical events, and costs included in the model

Parameter estimate	Base	Range for univariate sensitivity analysis		Distribution for probabilistic sensitivity analysis	Ref.	Type of source data
		low	high			
Antibodies to infliximab (ATI) probability						
ATI development during maintenance use ⁺	0.124	0.108	0.141	Beta_R(95,19) Beta_I(6,1)	381	Meta-analysis
Efficacy transition probabilities						
Initial response to infliximab at 12 weeks**	0.833	0.667	1	Beta_R(195,1383) Beta_I(84,594)	387	Observational
ATI+ responders in remission at 12 months	0.21	N/A	N/A	Dir(30)	388,389	Meta-analysis and cost-effectiveness study
ATI+ responders in response at 12 months	0.121	N/A	N/A	Dir(18)	388,389	Meta-analysis and cost-effectiveness study
ATI+ responders lost response at 12 months**	0.669	0.535	0.803	Dir(97)	389	Meta-analysis
ATI- responders in remission at 12 months	0.482	N/A	N/A	Dir(187)	388,389	Meta-analysis and cost-effectiveness study
ATI- responders in response at 12 months	0.278	N/A	N/A	Dir(108)	388,389	Meta-analysis and cost-effectiveness study
ATI- responders lost response at 12 months**	0.24	0.192	0.288	Dir(93)	389	Meta-analysis
Adverse event transition probabilities						
ATI+ responders experience acute IR**	0.315	0.252	0.378	Beta(78,170)	390	Systematic review and meta-analysis
ATI+ responders experience delayed IR**	0.054	0.043	0.065	Beta(7,122)	390	Systematic review and meta-analysis
ATI+ responders experience severe IR**	0.094	0.075	0.113	Beta(10,96)	390	Systematic review and meta-analysis
ATI- responders experience acute IR**	0.142	0.114	0.17	Beta(133,804)	390	Systematic review and meta-analysis
ATI- responders experience delayed IR**	0.021	0.017	0.025	Beta(12,569)	390	Systematic review and meta-analysis
ATI- responders experience severe IR**	0.061	0.049	0.073	Beta(3,46)	390	Systematic review and meta-analysis
Death from severe IR~	0.004	0	0.01	Beta(2,609)	391	Systematic review and meta-analysis
Age-specific all-cause mortality~	0.001	0	0.005	Beta(1,630)	386	UK life tables

Parameter estimate	Base	Range for univariate sensitivity analysis		Distribution for probabilistic sensitivity analysis	Ref.	Type of source data
		low	high			
Adalimumab therapy						
12 week remission rate	0.29	N/A	N/A	N/A	392	Open label trial
12 week response rate	0.39	N/A	N/A	N/A	392	Open label trial
12 week no response rate	0.41	N/A	N/A	N/A	392	Open label trial
Ustekinumab therapy						
Initial response at week 16	0.474	N/A	N/A	N/A	393	Post-hoc analysis
Responders in remission at week 44	0.386	N/A	N/A	N/A	394	Randomised controlled trial
Responders in response at week 44	0.312	N/A	N/A	N/A	394	Randomised controlled trial
Responders lost response at week 44	0.302	N/A	N/A	N/A	394	Randomised controlled trial
Vedolizumab therapy						
Initial response at week 10	0.478	N/A	N/A	N/A	395	Randomised controlled trial
Responders in remission at week 52	0.280	N/A	N/A	N/A	395,396	Randomised controlled trials
Responders in response at week 52	0.213	N/A	N/A	N/A	395,396	Randomised controlled trials
Responders lost response at week 52	0.507	N/A	N/A	N/A	395,396	Randomised controlled trials
Standard care therapy^{&}						
Remain moderate-to-severe disease	0.680	0.544	0.816	Dir(30)	382	Cost-effectiveness study
Require surgery**	0.312	0.250	0.375	Dir(14)	382	Cost-effectiveness study
Death from surgery	0.002	N/A	N/A	Beta(96,63831)	382	Cost-effectiveness study
Death from Crohn's disease flare	0.008	N/A	N/A	Dir(0.3)	382	Cost-effectiveness study
Quality of life utilities						
Medical remission#	0.89	0.67	1	Beta(11,1)	397	Cost-effectiveness study
Mild disease#	0.81	0.61	1	Beta(12,3)	397	Cost-effectiveness study
Moderate-to-severe disease#	0.74	0.56	0.93	Beta(15,5)	397	Cost-effectiveness study
Surgery#	0.4	0.3	0.5	Beta(36,55)	398	Cost-effectiveness study

Parameter estimate	Base	Range for univariate sensitivity analysis		Distribution for probabilistic sensitivity analysis	Ref.	Type of source data
		low	high			
Surgical remission#	0.8	0.6	1	Beta(11,3)	397	Cost-effectiveness study
Severe infusion reaction#	0.4	0.3	0.5	Beta(36,55)	398	Cost-effectiveness study
Utility decrement per acute or delayed IR~	0.01	0	0.1	Beta(0.1,14)	399	Cost-effectiveness study
Death	0	N/A	N/A			
Costs (GBP)						
Inflectra vial cost*	378	189	420	N/A		
Remicade vial cost	420	N/A	N/A	N/A	400	NICE technology appraisal
Adalimumab subcutaneous injection cost	358	N/A	N/A	N/A	400	NICE technology appraisal
Ustekinumab vial & subcutaneous injection cost	2,147	N/A	N/A	N/A	75	NICE technology appraisal
Vedolizumab vial cost	2,050	N/A	N/A	N/A	76	NICE technology appraisal
Infusion (day case hospital attendance)	697	N/A	N/A	N/A	401	UK NHS data
Remission therapy (4 weeks)#	58	43	72	Lognormal(4.1,0.1)	401,402	Cost effectiveness study and NHS data
Mild disease therapy (4 weeks)#	165	123	206	Gamma(61.5,2.7)	401,402	Cost effectiveness study and NHS data
Moderate-to-severe disease therapy (4 weeks)#	257	193	321	Gamma(61.5,4.2)	401,402	Cost effectiveness study and NHS data
Post-surgery therapy (4 weeks)##	257	129	386	Gamma(15.4,16.7)	401,402	Cost effectiveness study and NHS data
Surgery#	11,116	8,337	13,894	Gamma(61.5,180.9)	401,402	Cost effectiveness study and NHS data
Delayed IR (outpatient hospital attendance)	135	N/A	N/A	N/A	401	UK NHS data
Severe IR (non-elective long stay admission)	2,581	N/A	N/A	N/A	401,403	Clinical review and UK NHS data
<p>Note: Parameter values are identical in the base case for both treatments due to the assumption of biosimilarity. _R indicates distribution for Remicade parameter and _I for Inflectra parameter. Abbreviations: IR - infusion reaction; ATI+ patients who developed antibodies to infliximab; ATI- patients who did not develop antibodies to infliximab; NHS – National Health Service; N/A – not applicable. Key: + reported confidence interval used as range; ** reported mean +/-20% used as range; ~ range determined by authors; & Silverstein standard care outcomes with remission and response parameters shared proportionately between moderate to severe disease and surgery outcomes to reflect more severe disease pathway; # reported mean +/- 25% used as range; * BNF reported prices, range of 50% to 100% of Remicade price; ## reported mean +/- 50% used as range, to account for uncertainty in costs</p>						

An explanation of the sources of the parameter values follows in Section 5.2.3.1 to Section 5.2.3.6. Section 5.2.5 discusses how the ranges and distributions were identified.

5.2.3.1. ATI development

The rate of ATI development for Remicade (ATI_R) during maintenance use were taken from a meta-analysis³⁸¹ as ACCENT I had 46% inconclusive samples and were considered potentially biased²⁴⁰. In the base case, this is also the ATI development rate for Inflectra (ATI_I).

5.2.3.2. Efficacy

Early clinical trials focused on single infusions, and the pivotal maintenance trial, ACCENT I, contained only patients who had responded to the initial infusion, as discussed in Section 5.2.1.1. To provide an estimate of the induction phase response, the probability of response at 12 weeks was taken from an observational study³⁸⁷ identified from a previous economic model³⁸⁸.

The limited availability of data by ATI status for maintenance therapy necessitated that we derive some parameter values. The rates of secondary non-response (LOR) by ATI status were derived from a meta-analysis of the impact of ATIs on clinical outcomes³⁸⁹. Rates of remission and response by ATI status at 1 year were calculated by adjusting the rates for IFX monotherapy calculated by Saito et al³⁸⁸ proportionately by our calculated LOR probabilities.

Standard care probabilities were based upon the results of a Markov analysis of the natural history of Crohn's disease before the introduction of biologics by Silverstein et al (1999), who reported two-month transition probabilities across 8 states⁴⁰⁴. We used the figures derived by Kaplan et al, who reported probabilities of six states from non-anti-TNF management (referred to as standard care in this model)³⁸². Remission and mild disease states were not considered clinically realistic and were not included as pathways from standard care as explained in Section 5.2.2 (Figure 19). Therefore, all patients who moved to standard care were split between the surgery and moderate-to-severe disease states in proportion to the ratio between the probabilities in Kaplan et al³⁸².

5.2.3.3. Adverse events

The probabilities of acute and delayed infusion reactions by ATI status were calculated from a meta-analysis of the impact of antibodies on the risk of infusion reactions, with supplementary data on severe infusion reactions provided by the corresponding author³⁹⁰. Data on mortality from serious adverse events was taken from Siegel et al (2006)³⁹¹ and was used for the risk of death from severe infusion reaction. The risk of death from age-specific, all-cause mortality was taken from UK life tables for the period of 2012-14³⁸⁶.

5.2.3.4. Utilities

Utility values for disease states and surgery were taken from two published cost-effectiveness models where they had been derived for the appropriate disease states^{397,398}. They adapted utility estimates reported in an evaluation of methods used to measure utility in Crohn's disease by Gregor et al (1997)⁴⁰⁵. The utility value for non-responding active disease in Lindsay et al (2008) was assumed for the surgery state. Acute and delayed infusion reactions do not affect disease activity but a 0.01 utility decrement was applied per event³⁹⁹. In the absence of other utility estimates, the following assumptions were made: utility for a severe infusion reaction is the same as that for surgery due to the need for hospitalisation in both; and post-surgical utility equalled moderate-to-severe disease for one period, then surgical remission for the remainder of the year.

5.2.3.5. Resource use

Patients receiving IFX (and other biologics) also receive standard care. Vial sharing was not assumed so each infusion required four vials and an NHS day case hospital attendance. Acute infusion reactions were managed at the time of infusion within the day case hospital attendance⁴⁰¹. Delayed infusion reactions required an additional outpatient clinical visit. Severe infusion reactions were assumed to require a 4 night hospital stay, based upon a study of another biologic agent⁴⁰⁶, which aligns with a long stay non-elective NHS hospital admission. Post-surgical

therapy was assumed to be in line with standard care resource use for moderate-to-severe disease.

5.2.3.6. Costs

Standard care costs were taken from a previous Markov model by Bodger, Kikuchi and Hughes (2009), inflated using the retail price index^{401,402}. IFX vial prices were from the British National Formulary (BNF), as reported in NICE technical appraisals^{75,76,400}. Costs of day case hospital attendances, outpatient clinic visits and long stay non-elective admissions were from contemporary NHS reference costs⁴⁰¹.

5.2.4. Outcomes

Estimates of efficacy, ATI risk and adverse events for Inflectra were assumed equivalent to Remicade in the base case analysis, in line with the assumption of biosimilarity. The outcomes of the analyses were one-year costs and QALYs for treatment, and the proportion of patients who experienced: sustained remission for 12 months, sustained response for 12 months, remission, response, no adverse events following IFX treatment for 12 months, moved to standard care, developed ATIs, non-response (primary and secondary), infusion reactions (acute, delayed and serious), surgeries and death.

Assuming biosimilarity implies equal outcomes. Given the effect that this has on the outcomes (equal expected QALY), comparative value was determined from the Incremental Net Health Benefit (INHB) rather than the incremental cost-effectiveness ratio (ICER) as the ICER is a ratio of the difference in expected costs against the difference in expected benefit and this presents mathematical difficulties. INHB is the difference in Net Health Benefit (NHB) between each intervention³⁷. INHB was calculated as the incremental benefit (in QALYs) of the biosimilar compared with the originator, minus the incremental cost divided by the threshold for cost-effectiveness:

Equation 8: Incremental net health benefit (INHB)

$$INHB = (E_I - E_R) - (C_I - C_R)/\lambda$$

Where E and C are the expected benefit (QALY) and costs for Inflectra (I) and Remicade (R), respectively, and λ is the cost-effectiveness threshold for a QALY (assumed £30,000)²⁷.

A positive INHB means that the intervention of interest provides a health gain and is cost effective at the given threshold³⁷. It is a clearer statistic than the ICER, where the same value can have two different interpretations. It also has analytical strength in terms of sensitivity analysis where it can add in understanding the point at which Inflectra is no longer the preferred option, i.e. when INHB is equal to 0.

5.2.5. Sensitivity analyses

One-way deterministic analyses were performed for all variables to determine the thresholds over which the risks associated with biosimilar therapy outweigh the benefits, indicated by a negative INHB. Where available, ranges were based on confidence intervals provided in the literature, otherwise plausible ranges were assumed (for example, +/- 20%) around the mean. The results were presented in a tornado plot to examine the impact on INHB. Extreme value analysis was also conducted to identify the impact of each variable in the model. Percentages and utilities were varied from 0-1 and costs from £1 to twice the deterministic value.

A two-way sensitivity analysis was conducted to assess the interaction between the development of ATI_I and the price differential between the two drugs. This identifies the discount in vial price required to compensate for a higher rate of antibodies to Inflectra.

A probabilistic sensitivity analysis (PSA) with 10,000 Monte Carlo draws from distributions was conducted. All parameters were included in the PSA except fixed costs: Inflectra and Remicade vial costs and NHS costs for short-stays, long-stays and day cases, which affected the costs of infusions, serious infusion reactions and delayed infusion reactions. Efficacy, adverse event and utility parameters were drawn from beta distributions as a beta distribution is constrained to lie

between zero and one, which fits for our probability and utility parameters. A beta distribution can be estimated from two parameters (α , β), which are the observed number of events in a known population size.

Dirichlet distributions were used for related probability parameters (i.e. disease state and outcomes of standard care) as these allow for the sampling of multiple parameters, which must all sum to one to represent the total population. To fit a Dirichlet distribution, a series of Gamma distributions are used to estimate the individual outcome events, based upon two parameters (α , β). The first parameter, α , is the observed number of events and the second parameter, β , is set to unity. The Dirichlet draw for each parameter is obtained by dividing the draw for the outcome of interest by the sum of the draws for all the parameters in the distribution.

Costs were drawn from gamma or lognormal distributions as these distributions are strictly positive and allow for extreme outliers (Table 35). Lognormal was used for the smaller costs associated with standard care remission therapy, as the Lognormal distribution tends to cluster more around the mode, than the gamma distribution. The necessary parameters for the draws were obtained through the mean and ranges of each cost variable.

The ranges used for deterministic sensitivity analysis (described earlier in this section) were used for the PSA. It was assumed that the unknown biosimilar standard deviations for the rate of initial response and development of ATI were 50% higher than the originator drug to reflect the uncertainty in efficacy and immunogenicity.

5.2.6. Scenario analyses

To consider the robustness of the assumptions in the base case, seven scenarios with alternative structural assumptions were tested:

Scenario (i) tested the impact of a 25% reduction in the price of Remicade® in response to the biosimilar entrance to the market.

Scenario (ii) tested the clinical likelihood that patients with secondary non-response may be reluctant to stop therapy with IFX in the hope that they regain response. Patients with secondary non-response who experienced no adverse events continued with IFX, remaining in the moderate-to-severe disease state.

Scenario (iii) tested a shorter washout period (8 weeks, based upon clinical opinion of KB) in those who experienced a severe infusion reaction and stopped IFX therapy.

Scenario (iv) tested a shorter time to LOR in patients who developed ATIs (15 weeks, in line with the lower quartile of the interquartile range from ACCENT I)²⁴⁰ to reflect the potential for increased clearance of the drug due to antibodies.

Scenario (v) assumed patients switch to adalimumab (ADA) upon IFX failure. Therapy begins with an 80mg subcutaneous injection in week 0, followed by 40mg in week 2 and every other week as per the product label⁴⁰⁷. Initial response is checked at week 12 and patients transition to standard care if no response.

Scenario (vi) assumed patients switch to ustekinumab (UST) upon IFX failure. UST is infused at an initial dose of 6mg/kg, with further therapy (90mg) administered subcutaneously at week 8 and every subsequent 12 weeks⁴⁰⁸. Initial response is checked at week 16 and patients transition to standard care if no response.

Scenario (vii) assumed patients switch to vedolizumab (VED) upon IFX failure. VED is administered as 300mg infusions at weeks 0, 2 and 6, followed by maintenance infusions at week 14 and every 8 weeks after⁴⁰⁹. Initial response is checked at week 14 and patients transition to standard care if no response.

Patients in scenarios (v) to (vii) all have a washout period of six weeks prior to starting a second biologic whereupon they receive standard care. Standard care continued when starting the new therapy, under the same assumptions as the base case. Patients who switch following a severe

infusion reaction continue their response to IFX until it is lost at week 33. However, an improvement in disease course prompted by the second biologic will override the IFX response. Patients who change biologic following primary or secondary non-response experience moderate-to-severe disease during the washout period and until the new therapy takes effect. LOR for UST and VED was assumed to take place in line with IFX for model simplicity and an absence of other evidence. Adverse events were not modelled for the second-line biologics.

Initial response to ADA at week 12 in the IFX failure population was taken from an open label trial as the best match for the dose and timing of outcomes³⁹². No LOR was assumed over the year, based upon the results of a systematic review of adalimumab use after IFX failure⁴¹⁰.

The initial response for UST at 16 weeks was taken from a follow-on analysis of a key trial for UST in the IFX failure population (UNITI-1)³⁹³. Sustained remission at 44 weeks in the UNITI-1 population was taken from the long term safety follow up study, and response was calculated by applying the ratio of response to remission at 8 weeks in the same study³⁹⁴.

The initial response for VED was taken from GEMINI-3, a pivotal study of induction therapy in anti-TNF α failure patients³⁹⁵. The week 10 response rate was used, as a week 14 rate was unavailable in the literature. Sustained remission in anti-TNF α failure patients at week 52 was from a RCT of maintenance therapy in line with the dosing pattern from the SPC³⁹⁶. The GEMINI-3 ratio of week 10 response to remission was applied to the long-term remission to calculate long-term response.

UST and VED infusions use single vials and require a day case hospital attendance. ADA and UST subcutaneous injections are patient-administered and are assumed to require no additional resource.

ADA, UST and VED vial and subcutaneous injection prices were from the British National Formulary (BNF), as reported in NICE technical appraisals^{75,76,400}.

5.2.7. Value of information analysis

As discussed in Chapter 1, value of information (VOI) methods expose the costs of uncertainty by quantifying the probability that the decision is wrong and the (cost) consequences if it is wrong⁵⁷. The VOI method calculates the net benefit that is lost over all the PSA simulations as a result of choosing the intervention based on expected net benefit over all simulations, rather than being able to choose the optimal intervention in each simulation⁵⁸. This value, known as the Expected Value of Perfect Information (EVPI) is the difference between the maximum possible expected net health benefit (NHB) that would be attained if the optimal intervention was chosen in each individual simulation, minus the expected NHB from the PSA, and is shown in Equation 9.

Equation 9: Expected value of perfect information (EVPI)

$$EVPI = E_{\theta} \max_i NHB(i, \theta) - \max_i E_{\theta} NHB(i, \theta)$$

Where the first part expresses the expected NHB from treatment i given current information θ , and the second part expresses the expected NHB from the same treatment given perfect information⁴¹¹.

Given that there is more uncertainty in some parameters than others, especially those related to the biosimilar, it is useful to calculate the EVPI for individual parameters in the model, the expected value of perfect parameter information (EVPPI). This is achieved by running the simulation for each possible value of the parameter of interest and averaging the maximum NHB for each run to obtain the expected NHB with certainty for the parameter of interest. The difference between this and the expected NHB is the EVPPI.

A VOI analysis was conducted by inputting the results of the PSA into the Sheffield Accelerated Value of Information (SAVI)⁴¹² tool to identify the value of conducting further research to reduce uncertainty. This was used to assess the value of conducting further clinical research. The annual Expected Value of Perfect Information (EVPI) per patient was calculated, and the annual and 10-year population EVPI estimated based on the number of patients affected by Crohn's disease and likely to benefit from the treatment each year in England. The population number was taken from

the costing template made available by NICE to support NHS organisations to plan for the financial implications of implementing the infliximab technical appraisal guidance⁴¹³. To examine the effect of vial price differentials, a second base case scenario was explored where the price of Remicade falls to match Inflectra. A partial EVPI (EVPPI) analysis was conducted to examine the value in reducing the uncertainty around individual model parameters.

5.2.8. Discounting

The model did not extend beyond a year so the results were not discounted. A discount rate of 3.5% per annum was applied to the population EVPI.

5.2.9. Reporting

The analysis is reported in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines⁴¹.

5.3. Results

5.3.1. Base case

The decision analytic model base case results in expected one-year quality-adjusted life-years (QALYs) of 0.803 for both Inflectra and Remicade, with expected one-year costs of £18,087 and £19,176, respectively (Table 36). The additional benefit of Inflectra to society, based solely on the reduced cost of Inflectra, is represented in the 0.04 (95% Central Range 0.00-0.09) incremental net health benefit (INHB) versus Remicade.

For both treatments, 48.9% of patients are in remission at the end of the year in the base case, 35% of whom have sustained remission since IFX induction therapy. The model predicts that 44.8% of patients treated with IFX would experience a full year without adverse events, and an equal percentage would move to standard care at some point during the year. 10.3% of the cohort developed ATI. 16.6% experienced primary non-response to IFX, and 24.4% experienced secondary non-response. 13.6%, 2.1% and 5.4% of the cohort had acute, delayed or severe infusion reactions, respectively, and 14.0% of the cohort had surgery (Table 37).

Table 36: Model results for base case and scenarios – expected costs and QALYS and net health benefit

		Base case	(i) Remicade price drop	(ii) LOR and no AEs continue IFX	(iii) 8 week wash-out after SIR ends IFX	(iv) quicker LOR in patients with ATI	(v) switch to ADA upon IFX failure	(vi) switch to UST upon IFX failure	(vii) switch to VED upon IFX failure
Vial cost	Inflectra	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378
	Remicade	£ 420	£ 315	£ 420	£ 420	£ 420	£ 420	£ 420	£ 420
Expected QALY	Inflectra	0.803	0.803	0.803	0.802	0.801	0.816	0.811	0.813
	Remicade	0.803	0.803	0.803	0.802	0.801	0.816	0.811	0.813
Expected cost	Inflectra	£ 18,087	£ 18,087	£ 18,729	£ 18,097	£ 17,821	£ 18,166	£ 19,421	£ 21,366
	Remicade	£ 19,176	£ 16,453	£ 19,867	£ 19,187	£ 18,890	£ 19,255	£ 20,511	£ 22,455
Net health benefit	Inflectra	0.200	0.200	0.179	0.199	0.207	0.211	0.164	0.101
	Remicade	0.164	0.254	0.141	0.162	0.172	0.174	0.128	0.064
Incremental	QALY	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Cost	-£ 1,089	£ 1,634	-£ 1,138	-£ 1,089	-£ 1,069	-£ 1,089	-£ 1,089	-£ 1,089
	NHB	0.036	-0.054	0.038	0.036	0.036	0.036	0.036	0.036
	Vial cost	-£ 42	£ 63	-£ 42	-£ 42	-£ 42	-£ 42	-£ 42	-£ 42
	ICER	Dominant	Dominated	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

Note: Scenarios: (i), 25% reduction in Remicade price; (ii), patients with LOR but no AEs continue IFX; (iii), 8 week IFX wash out; (iv), LOR at 15 weeks with ATIs; (v), switch to adalimumab; (vi), switch to ustekinumab; (vii), switch to vedolizumab.

Abbreviations: QALY - quality adjusted life year, NHB - net health benefit, ICER - incremental cost effectiveness ratio, IFX - infliximab, AEs - adverse events, ATI - antibodies to infliximab; SIR – severe infusion reaction

Table 37: Model results for base case and scenarios - clinical outcomes

	Base case	(i) Remicade price drop	(ii) LOR and no AEs continue IFX	(iii) 8 week wash-out after SIR ends IFX	(iv) quicker LOR in patients with ATI	(v) switch to ADA upon IFX failure	(vi) switch to UST upon IFX failure	(vii) switch to VED upon IFX failure	
Clinical outcomes	Sustained remission	35.0%	35.0%	35.0%	35.0%	35.0%	35.7%	35.4%	35.7%
	Remission	48.9%	48.9%	48.9%	48.9%	48.9%	50.1%	43.2%	51.3%
	IFX for 12 months with no AEs	44.8%	44.8%	62.2%	44.8%	44.8%	44.8%	44.8%	44.8%
	Standard care	44.8%	44.8%	27.5%	44.8%	44.8%	18.4%	29.9%	27.7%
	Developed ATIs	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%
	Primary non-response	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%
	Secondary non-response	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%
	Deaths	0.5%	0.5%	0.5%	0.5%	0.5%	0.2%	0.2%	0.2%
	Acute infusion reactions	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%
	Severe infusion reactions	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%
	Delayed infusion reactions	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%
	Surgeries	14.0%	14.0%	14.0%	14.0%	14.0%	2.8%	3.6%	3.6%

Note: Scenarios: (i), 25% reduction in Remicade price; (ii), patients with LOR but no AEs continue IFX; (iii), 8 week IFX wash out; (iv), LOR at 15 weeks with ATIs; (v), switch to adalimumab; (vi), switch to ustekinumab; (vii), switch to vedolizumab.

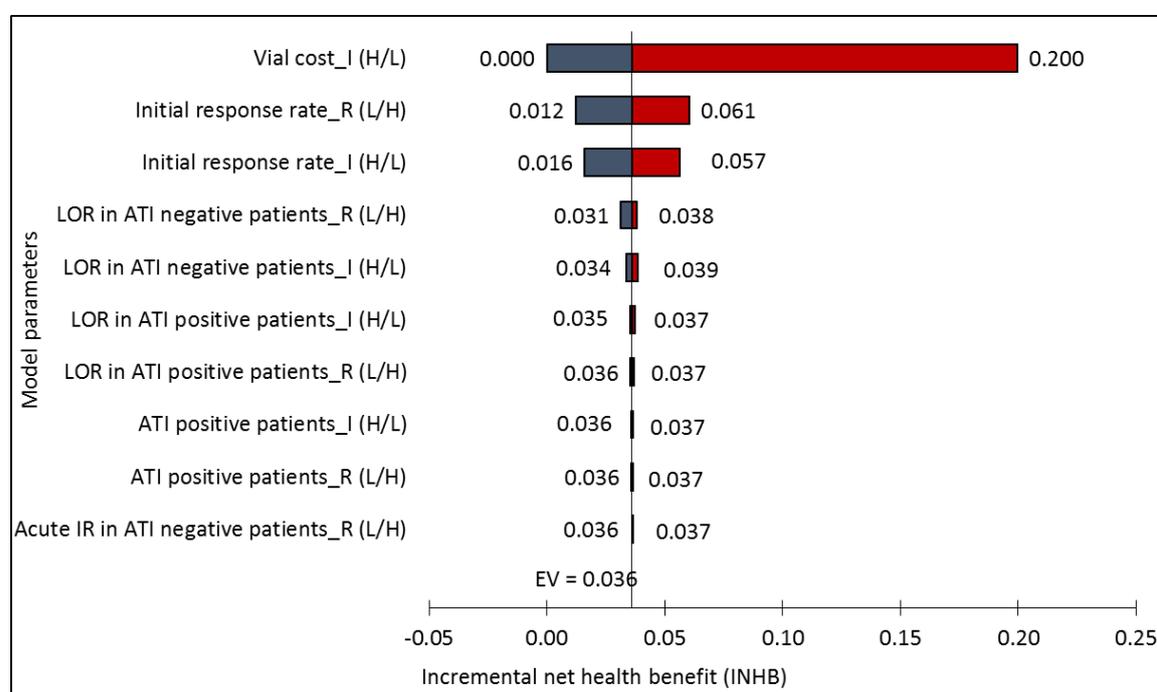
Abbreviations: QALY - quality adjusted life year, NHB - net health benefit, ICER - incremental cost effectiveness ratio, IFX - infliximab, AEs - adverse events, ATI - antibodies to infliximab; SIR – severe infusion reaction

5.3.2. Base case sensitivity analyses

5.3.2.1. One-way sensitivity analysis

One-way sensitivity analyses demonstrated that the model was most sensitive to the Inflectra vial price and initial response rates of Inflectra and Remicade (Figure 20). The INHB was stable for most model parameters, which were able to take extreme values without altering the result that Inflectra has a positive benefit-risk profile. The INHB advantage of Inflectra was outweighed in the model only when the vial price exceeded that of Remicade.

Figure 20: Tornado plot of the univariate analysis.



NOTE: PANEL PRESENTS THE TEN PARAMETERS THAT LED TO THE GREATEST CHANGE IN OVERALL INCREMENTAL NET HEALTH BENEFITS (INMB). INFLECTRA PARAMETERS (SUFFIXED **_I**), REMICADE PARAMETERS (SUFFIXED **_R**). L/H REFER TO LOWER AND HIGHER LIMITS OF PARAMETER ESTIMATES.

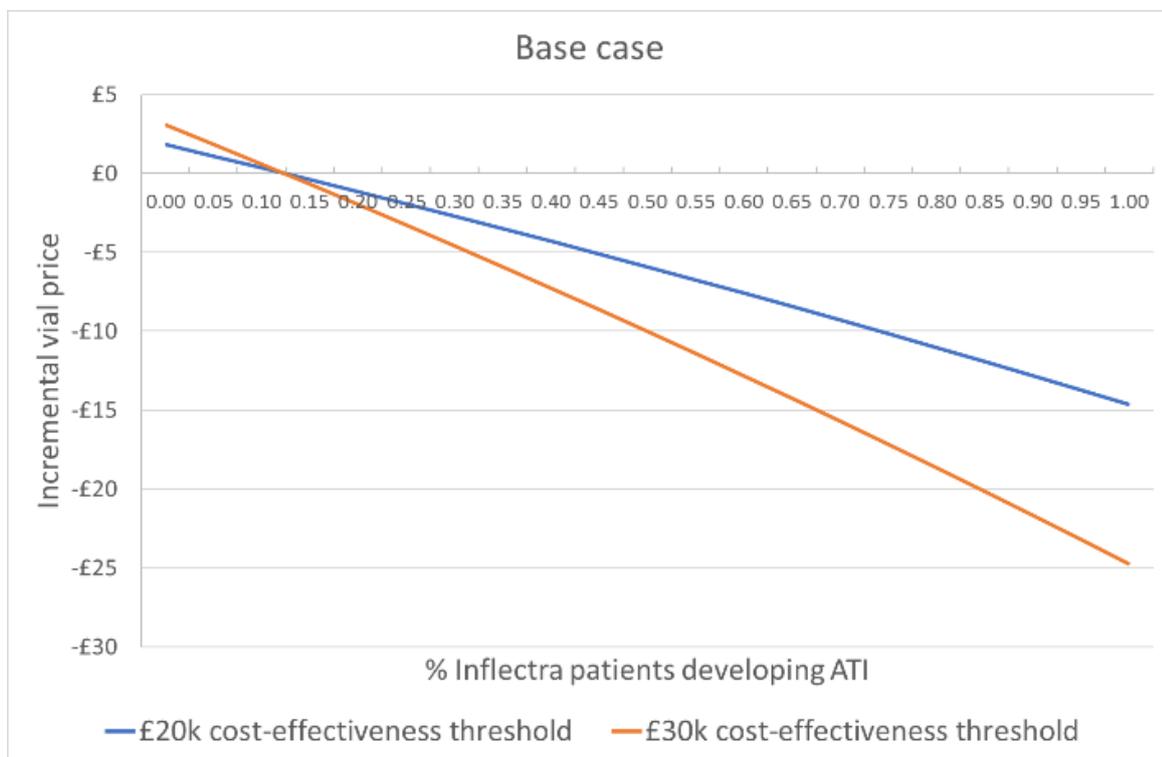
ABBREVIATIONS: ATI – ANTIBODIES TO INFLIXIMAB, LOR – LOSS OF RESPONSE, IR – INFUSION REACTION

5.3.2.2. Two-way sensitivity analysis of vial price versus ATI development

A two-way sensitivity analysis shows how the Inflectra vial price would need to adjust in response to increasing rates of developing ATI in order to remain the preferred choice. Based on a cost-effectiveness threshold of £30,000 per QALY²⁷, and assuming 50% of patients develop ATI for Inflectra (ATI_I), compared with 12.4% who develop ATI from Remicade (ATI_R), then 57.7% of

patients would switch to standard care after experiencing a serious infusion reaction or secondary non-response and, within that, 18% of patients would have a surgery. Inflectra remained the preferred option provided it is priced below £410 per vial (compared with £420 for Remicade). Even in a worst case scenario where all Inflectra patients develop ATI, resulting in 75% of patients moving to standard care and 23% having surgeries, a vial of Inflectra could be priced up to £395 and it would remain the treatment of choice with a positive INHB (Figure 21).

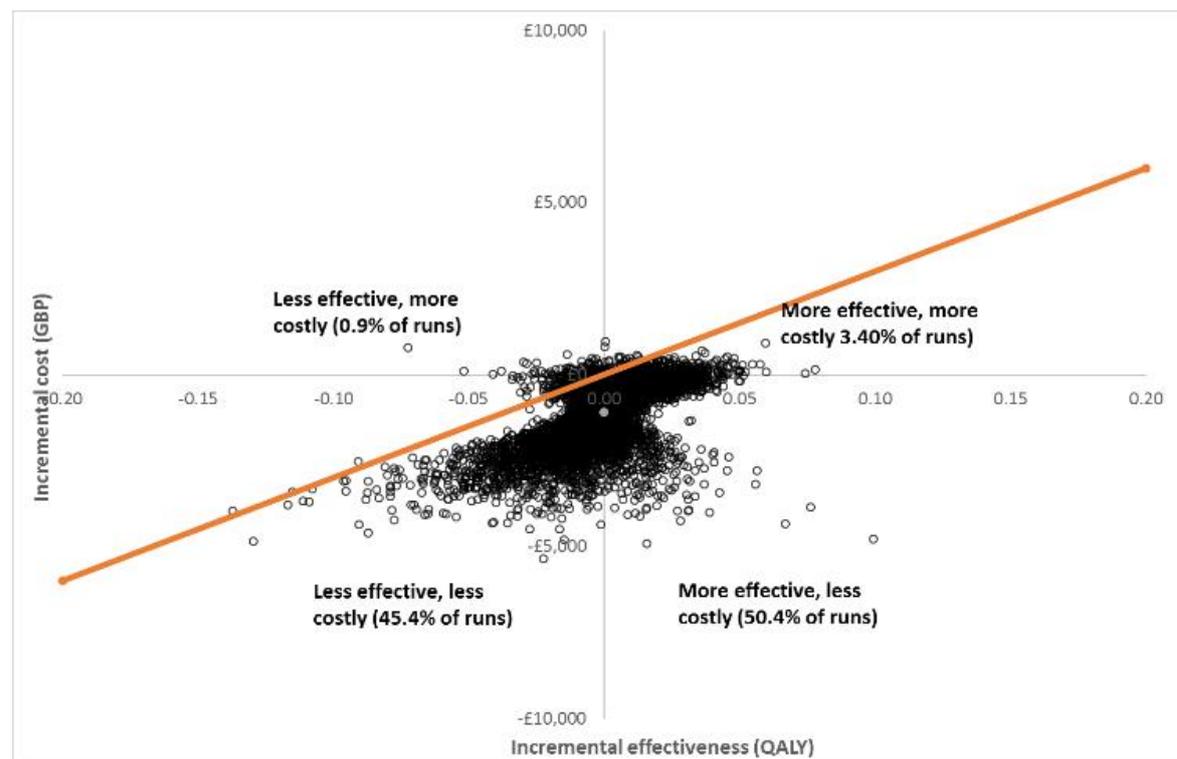
Figure 21: Results of the base case two-way analysis of risk of Inflectra antibodies (ATI) against incremental vial price.



5.3.2.3. Probabilistic sensitivity analysis

The net-benefit plane⁴¹⁴ illustrating the joint distribution of incremental costs and QALYs (Figure 22) shows the clustering of simulations on the vertical axis due to the minimal differences in QALYs between the two interventions. Inflectra had the better benefit-risk balance, illustrated by a positive INHB, in 97.6% of simulations.

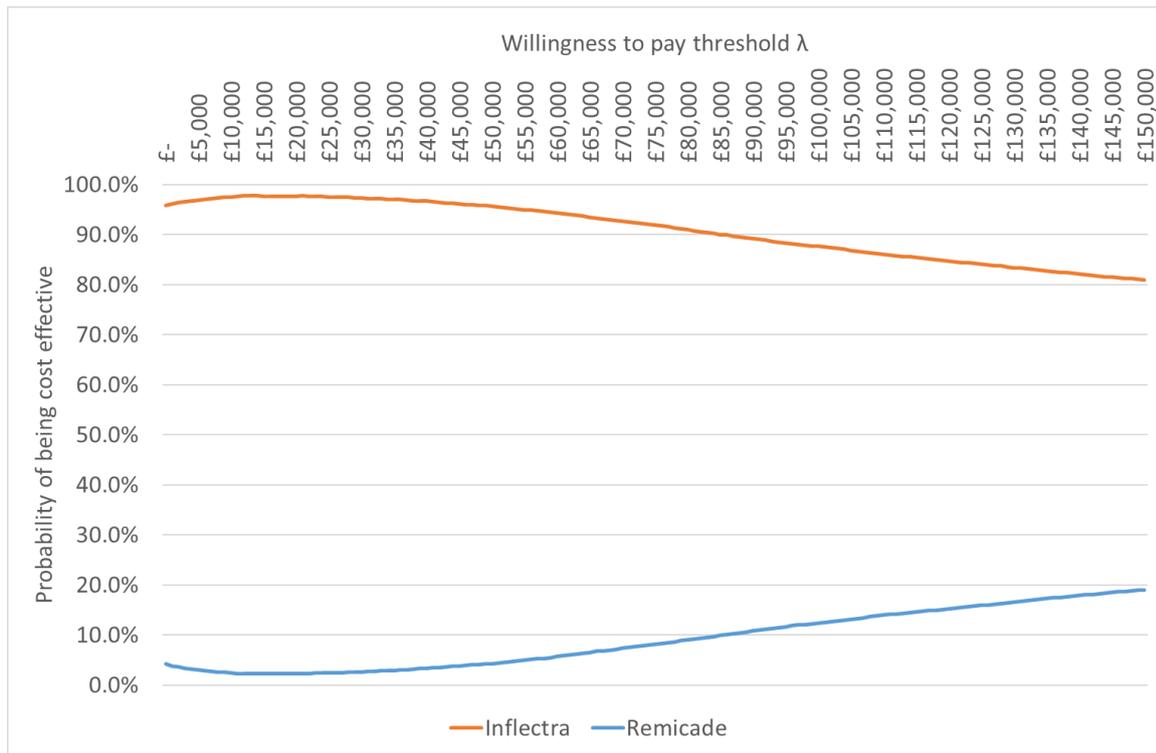
Figure 22: Net-benefit plane resulting from base case probabilistic sensitivity analysis.



NOTE: THE LINE REPRESENTS THE COST-EFFECTIVENESS THRESHOLD OF £30,000 PER QUALITY-ADJUSTED LIFE YEAR (QALY).

This result was robust over a range of threshold values for λ , as shown in the cost-effectiveness acceptability curve (Figure 23). Inflectra dominated Remicade in 50.3% of simulations and was less effective but less costly in 45.5% of simulations. Inflectra was more effective but more costly in 3.3% and was dominated by Remicade in 0.8% of simulations.

Figure 23: Cost-effectiveness acceptability curve resulting from the base case probabilistic sensitivity analysis



5.3.3. Scenario analyses

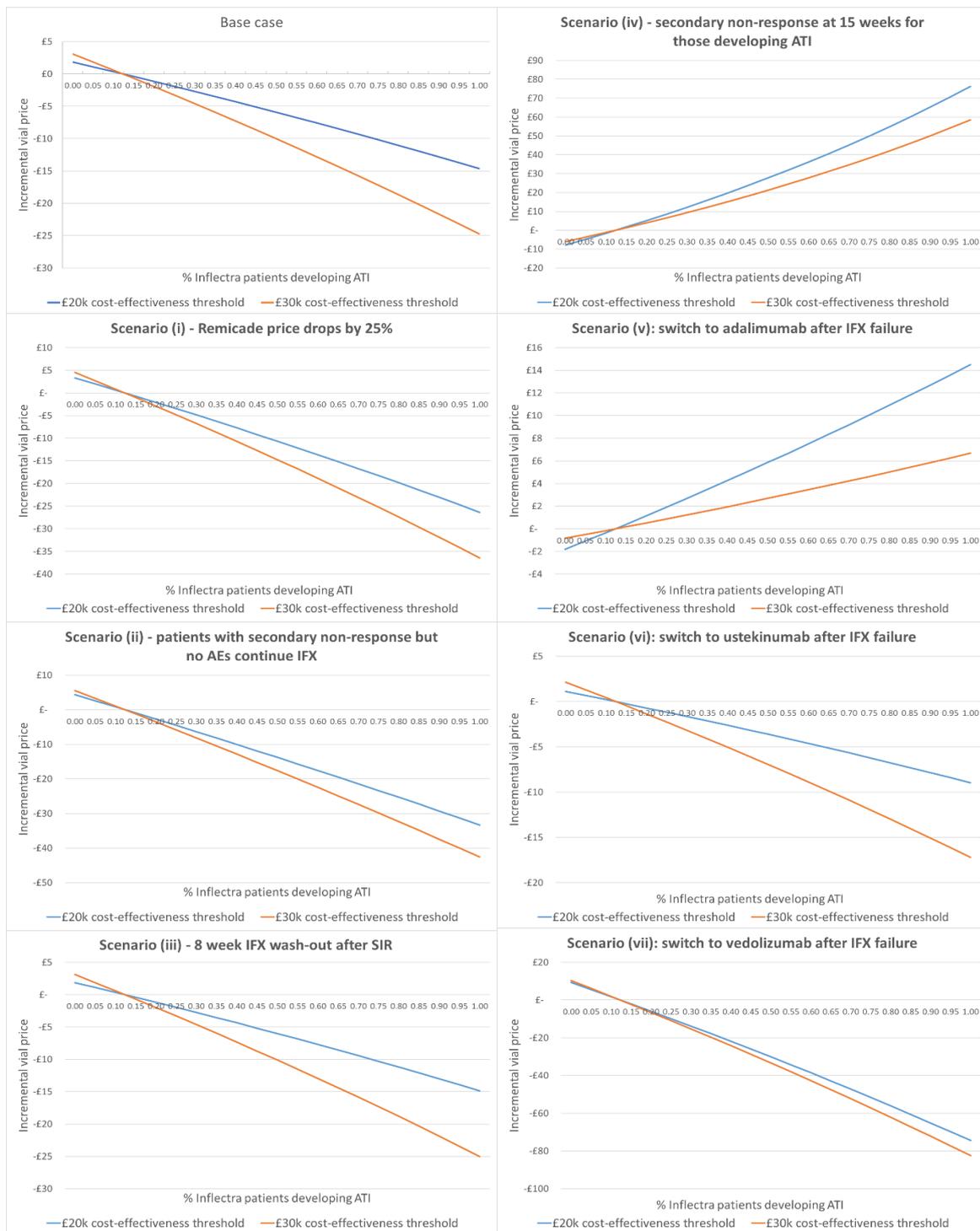
Inflectra is associated with a positive INHB across the scenarios tested, with the exception of scenario (i) where Remicade is the preferred option due to the reduced price (Table 36). Changes in INHB overall were minimal and, in fact, there was no change in INHB in scenarios involving a shorter wash-out of IFX following a SIR (iii), a shorter time to loss of response in patients with ATI (iv) and a switch to another biologic before standard care, (v), (vi) and (vii), as changes affected both biologics equivalently.

The results of the two-way sensitivity analysis reveal the value-based price for Inflectra as they identify the price at which the biosimilar could be marketed based upon the development of ATI and downstream consequences⁴¹⁵. Most scenarios follow a similar pattern to the base case analysis (Figure 24). The price of Inflectra must reduce as ATI_I increases, to remain the optimal choice, but remains below the current market price at all risks of ATI development. Only in

scenario (vii), where patients switch to vedolizumab after IFX failure, is a reduction to below the current market price necessary to remain the optimal choice, and it does so when 60% of Inflectra patients develop ATI.

The relationship is reversed in scenario (iv) and the price of Inflectra can increase as ATI_I risk increases, due to the expected cost savings from the earlier movement to standard care. The cost reduction outweighs the QALY reduction, giving Inflectra an even greater net benefit than in the base case. For illustration, when all Inflectra patients develop ATI (ATI_I=100%), the expected QALY gain is 0.03 less than for Remicade whilst resulting in a cost saving of £1,029. A similar pattern is seen for scenario (v) when patients switch to ADA after IFX failure. In this case, the introduction of a second biologic reduces costs, as it is cheaper than IFX, but also reduces the number of patients moving to standard care in the model and therefore limits the number of expensive surgeries as ATI_I increases.

Figure 24: Results of the two-way analysis of risk of Inflectra antibodies (ATI) against incremental vial price.



NOTE: EACH FIGURE REPRESENTS A SCENARIO. SCENARIO (i), 25% REDUCTION IN VIAL COST OF REMICADE; SCENARIO (ii), PATIENTS WITH SECONDARY NON-RESPONSE BUT NO ADVERSE EVENTS CONTINUE IFX; SCENARIO (iii), 8 WEEK INFlixIMAB WASH OUT PERIOD; SCENARIO (iv), SECONDARY NON-RESPONSE AT 15 WEEKS FOR THOSE DEVELOPING ATI; SCENARIO (v), SWITCH TO ADALIMUMAB AFTER IFX FAILURE; SCENARIO (vi), SWITCH TO USTEKINUMAB AFTER IFX FAILURE; SCENARIO (vii), SWITCH TO VEDOLIZUMAB AFTER IFX FAILURE

5.3.4. Value of information analysis

Using the results of the PSA, the expected value of perfect information (EVPI) in the base model is £7.56 per patient. Based on the number of patients expected to be eligible for Inflectra in England (7,912)⁴¹³, the value of removing the decision uncertainty is £59,775 for one year and £807,332 for the assumed 20-year therapeutic lifetime of the drug. This represents the upper limit on the investment of conducting further research to eliminate uncertainty in model parameters. A more informative expected value of partial perfect information (EVPPI) indicates that there would be no gain from any research to reduce uncertainty in any individual parameters, including the ATI rate of Inflectra. The decision certainty for Inflectra as the optimal choice is so high that there is no value to further researching any individual parameters.

The result of the second VOI analysis, where the price of Remicade is reduced to match that of Inflectra, provides a different result. In this case, the EVPI is now £220.51 per person, equivalent to £25.4 million (discounted) for the assumed 20-year therapeutic lifespan. The EVPPI is now relevant and the highest value is for the initial response rate of Inflectra, where the expected value of reducing uncertainty around the parameter is £196.42 per patient, which is £1.6 million per year, or £22.6 million over 20 years. There is greater value in reducing uncertainty from a range of parameters, including the initial response rate of Remicade, and the rates of sustained remission, sustained response and loss of response in patients who do not develop ATI, than in reducing uncertainty in ATI_I, which has an EVPPI of £7.00 per patient (Table 38).

Table 38: Ten parameters with highest EVPPI when the Remicade price reduces to match Inflectra.

	Per Person EVPPI (£)	Standard Error	Indexed to Overall EVPI = 1.00
Initial response_I	196.42	2.47	0.89
Initial response_R	51.54	3.17	0.23
ATI negative sustained remission_I	23.14	3.65	0.1
ATI negative sustained remission_R	20.69	3.02	0.09
ATI negative sustained response_I	13.36	3.15	0.06
ATI negative sustained response_R	11.37	3.08	0.05
ATI negative LOR_I	11.16	3.07	0.05
ATI negative LOR_R	10.64	2.99	0.05
ATI positive delayed IR_I	7.89	2.86	0.04
ATI_I	7	2.83	0.03

Note: _I/_R suffix indicates Inflectra/Remicade parameter. ATI – antibodies to infliximab. LOR – loss of response.

5.4. Discussion

5.4.1. Summary of evidence

This is the first study to explicitly consider the trade-off between the risk of development of ATI (which is largely unknown at the time of marketing authorisation) and cost advantages, and the value of obtaining further evidence. It positions the problem of assessing the benefit-risk of biosimilars in the context of an economic evaluation framework. For Inflectra, the results align with those found in the extrapolation process of regulators which deemed the new drug biosimilar to the originator^{86,90,91,377,416}. Non-inferiority of the biosimilar to the originator infliximab was demonstrated in a phase III trial for rheumatoid arthritis⁴¹⁷ and extrapolation assumes equivalence in efficacy for Crohn’s disease. Preliminary results from a post-marketing trial of Inflectra and Remicade indicate there is no significant difference between the efficacy and safety of the two drugs at 6 weeks⁴¹⁸. Observational studies and clinical case series have confirmed that Inflectra appears to be safe and efficacious, especially in infliximab-naïve patients^{419–425}. A study of cross immunogenicity identified that ATI developed in patients treated with Remicade react to the biosimilar, further supporting the case that the two drugs are biosimilar⁴²⁶.

In the base case analysis, Inflectra dominated Remicade because the outcomes from both therapies are equivalent, so the advantage is purely based on the lower cost. This was robust to sensitivity analyses, with all parameters – except the drug vial price– having little or no impact on the INHB and the decision outcome. Given the concern and uncertainty around the development of ATIs, the results of the two-way sensitivity analyses of the trade-off between ATIs and the vial price of Inflectra are important. In the base model, increasing the development of ATI would necessitate a reduction in the vial price of Inflectra to remain cost-effective, but even if all patients were to develop ATI_I, the price at which Remicade becomes the preferable option still exceeds the current vial price by £17.21. The only scenarios where the price of Inflectra would fall below the current price to remain the optimal choice as the risk of ATI increases are scenario (i) where the price of Remicade reduces by 25% and scenario (vii) where patients who fail IFX move to vedolizumab. The price of Inflectra would have to be below the current market point at all levels of risk of ATI in scenario (i) and would fall below current market price once the risk of ATI exceeded 60% in scenario (vii).

The PSA highlighted almost no decision uncertainty in the base case and therefore the VOI analysis suggests no value in further research to reduce uncertainty. Inflectra appears to be the most cost-effective with such high probability that there is little value in learning about the parameters, even ATI_I. However, if the price of the originator fell in line with the biosimilar as it entered the market the parameter most worthy of additional research would be the initial response rate of Inflectra, with the expected value of reducing uncertainty around the parameter of £22.6 million over the 20-year lifetime of the drug patent.

5.4.2. Strengths and limitations

A major strength of the work in this chapter is the transparency the approach provides for assessing the value of biosimilars by considering the incremental net health benefit, taking into account both benefits (in terms of cost savings) and the uncertainty of potential harms. Given the

increasing use of biological therapies and the need to restrain costs whilst allowing patients access to these therapies, biosimilars are a rational choice as they open up the opportunity for cost savings or extension of treatment, and given technological advances and improved manufacturing processes they may even result in greater efficacy and less harm. HTA of biosimilars presents a significant challenge due to the assumption of equivalence in outcomes and the lack of comprehensive data at the time of market authorisation. All of this adds to uncertainty in results, but this model overcomes some of these difficulties by making explicit reference to, and characterising the uncertainty of, ATI development as the driver for differences in treatment outcomes. This addresses potential areas of concern relating to the extrapolation exercise while allowing for the uncertainty to be quantified – both in terms of identifying whether the cost savings are sufficient for a health-care payer to accept a potentially inferior product, and the value of conducting further research⁴²⁷.

Modelling the potential impacts using the available evidence and theoretical risks against what is known of the originator could help prevent the rejection of equivalent (or better) biosimilars by health care-payers, which would restrict the opportunity to make cost savings and extend treatment to more patients. Further, having a model which acknowledges and quantifies the uncertainties, explores the risks and identifies key areas requiring further research (or not) could support increased adoption of biosimilars into health care practice by reassuring clinicians and patients⁴²⁷. This is especially relevant in the UK system where biosimilars do not prompt a HTA, but instead existing guidance for originator drugs is applied to the biosimilar once they have gained marketing approval⁴²⁸.

By their nature, models that draw from multiple sources of evidence require many assumptions, which can be considered limitations. Shaping the model to the HTA perspective forced an idealised view of the clinical situation with full adherence to treatment assumed. Further, whilst NICE clinical guidance is to prescribe for only severe disease (CDAI above 300)⁶², the model was

aligned with the population approved by the EMA. Building the model on the basis of previous models^{382,388} and the availability of data for an initial response at 12 weeks shaped the model contrary to UK clinical guidance, which advocates that response should be checked after two doses (week 2) and therapy stopped if there is none⁶². The UK NHS cost framework may eliminate the sensitivity of the model to increased acute infusion reactions as they are managed within the day case cost. Studies in other countries have suggested that infusion costs managed in the outpatient setting could increase the infusion cost by as much as 40%⁴²⁹.

Whilst the one-year timescale was appropriate for simplicity in this proof of concept model, it does not reflect the chronic disease course and fails to capture costs and utilities consequences of long-term outcomes. It is likely that patients who experience LOR are at higher risk of serious infection, due to their active disease, but we could not identify any evidence to support an increased risk due to ATI development. Similarly, we were unable to locate evidence to support modified cancer risk from ATI development. In the interest of parsimony, serious infections and cancers were removed³⁸. However, these are important events with significant costs and health utility impacts and should ideally be incorporated with appropriate methodology.

By necessity, the model is a simplification of reality. All-age, all-cause mortality was applied at week 12 but deaths would take place across the year. Similarly, infusion reactions were all assumed to take place in once period, and on the fourth infusion, occurring only in those who experience a response to treatment. Evidence from studies by Duron et al and Cheifetz et al suggest that infusion reactions take place in the first four infusions^{384,430}, although it is unclear whether this holds for all types of infusion reactions.

Assigning QALYs by 4-week period may fail to reflect the changing condition of patients with Crohn's disease. For instance, the occurrence of a serious infusion reaction is assumed to place a patient in hospital for four days⁴³¹, but causes a detriment to quality of life lasting an entire period. Similarly, the two IFX infusions received in the first period of the model are likely to take effect

before the end of the period, but the quality of life improvement, where experienced, only takes place in period 2.

Sourcing parameter values for the model was a challenge, as was expected. Estimates for ATIs were based on the episodic use of infliximab or were complicated by the absence of a standard definition of ATI, the many factors that can affect ATI test result⁹⁴ and the increasing recognition of transient ATI, which are idiosyncratic and have little impact on outcomes⁴³². More accurate measures of ATI in research would support more accurate modelling of their impact.

Further limitations stemmed from the data available on “standard care” for Crohn’s disease, which do not accurately reflect current clinical management of CD and which we attempted to overcome by including scenarios with other biologics (adalimumab, vedolizumab and ustekinumab)^{59,62,433}. However, more clinically accurate scenarios might include dose escalation or shortening the interval between infusions prior to switching to another drug or a switch to the originator drug⁵⁹. Further, modelling of second line biologics should consider their harms so as not to overstate their benefits. Addressing some of these points might address some of the counterintuitive results in the scenarios where increasing risk of immunogenicity in Inflectra can be accompanied by an increase in price because switching to alternative therapies is seen as more cost-effective. However, accepting these limitations may be appropriate for a model, which is focused not on predicting outcomes, but rather to offer a transparent and structured way to examine a complex decision problem⁴³⁴.

5.4.3. Conclusions

Biosimilars are generally less expensive than originators but achieve similar outcomes. They have been given regulatory approval on the basis of extrapolated evidence with the use of qualitative benefit-risk frameworks, which has led to uncertainty about equivalence in benefits and risks. To date, there has been no attempt to quantitatively assess the benefit-risk balance. This chapter presents a novel framework for the quantitative benefit-risk assessment of biosimilars, the results

of which support the conclusion reached by the regulators of Inflectra through their qualitative approaches. The model is not without limitations in terms of structure and inputs. However, the robustness of the results was tested by identifying potential areas of concern relating to the extrapolation exercise, and conducting a variety of sensitivity and scenario analyses, each of which supported the main findings. It would be appropriate to refine the model to more closely reflect clinical reality and follow the treatment pathway in the UK.

Using knowledge of theoretical risks of biosimilars, the model could be adapted to other therapies. As well as indicating the limits of biosimilarity, the method could help to identify the value of further research and offer reassurance that the extrapolation process is justified. In the absence of trial evidence, the model provides a basis for the quantitative evaluation of biosimilars to support health technology assessment. Value-based pricing using this methodology would be possible to protect health systems such as the NHS in the UK from the potential risks of biosimilars where they are untested in the populations for which they have been approved.

Chapter 6: Discussion and conclusions

All health care interventions carry risk alongside benefit and the availability of good data is vital to allow all decision-makers to assess whether the balance is favourable. Randomised controlled trials (RCTs) remain the gold standard for efficacy data, but they have well understood difficulties in identifying real-world effectiveness, and being able to identify slight increases in common risks and rarer risks occurring, especially with longer-term treatment. Benefit-risk decisions are often at the margin and therefore slight differences in effectiveness, versus efficacy, can alter the benefit-risk balance substantially. Arguably, the greatest uncertainties are in the risks of therapies, which are only well understood long after a drug has been approved for marketing. Even where risks are identified through post-marketing pharmacovigilance, uncertainties remain due to the flaws in spontaneous reporting systems, including the under-reporting of adverse reactions and the difficulties in assigning causation to particular indications or drug-indication combinations.

Further challenges arise from the entrance of biosimilars into market, which introduce additional uncertainty due to the complex manufacturing processes involved and the belief of enough similarity to the originator drug to allow a reduced approval process and extrapolation to a number of indications based upon clinical trial evidence from a single 'sensitive' population. As such, some biosimilars are approved for indications without ever having been tested on patients with those diseases.

These conditions require new approaches to fully characterise the benefit and risks of therapies, which must account for unavailable or uncertain data. As such, this thesis examined methods for understanding what is being measured in clinical trials and what should be measured, additional sources of harms data and the development of a quantitative framework for assessing whether cost savings of biosimilar justify the increased uncertainties regarding efficacy and safety.

6.1. Summary of the main findings from the thesis

The first study of this thesis was a systematic review of RCTS of treatments for Crohn's disease trials in adults. The aim was to identify the outcomes and adverse events reported in RCTs for Crohn's disease, including the measurement tools used and changes over time. The results demonstrate that trialists have adopted a wide and variable approach to outcome measurement with all types of efficacy and safety outcomes increasingly measured over time, with the exception of safety withdrawals reporting, which has reduced. What is clear from the work of this chapter is that clinical and composite-clinical outcomes continue to be the most commonly reported primary and secondary trial endpoints, findings that are confirmed by other recently published reviews of outcomes in Crohn's disease and patients with fistula^{103,104}. In particular, the Crohn's Disease Activity Index (CDAI) is the single most commonly used outcome measurement tool, but its fall from favour with the EMA⁶⁸, alongside increasing interest in objective measures of inflammation and patient reported outcome measures, highlights the need for new outcome measurement tools. The review confirmed the challenge of measuring and categorising harms where it can be difficult to distinguish lack of treatment efficacy from treatment side effects. The results provide a comprehensive inventory of outcomes and adverse events that can support the development of a core outcome set (COS) for Crohn's disease.

The shift towards objective measures of inflammation and patient reported outcomes measures rather than clinical-composite tools requires the design and validation of new measurement tools. Chapter 3 presented a method for disaggregating the discrete outcomes captured within composite outcome measurement tools to make it transparent what is being measured. Overlapping and differential naming of outcomes within the measures necessitated an outcomes classification method, which applied a conceptual framework for developing COS and other validated theoretical frameworks for classifying outcomes. Mapping the categorised data against both a proposed COS for Inflammatory Bowel Disease (IBD) and the commonly used outcome measurement tools identified some inconsistencies between the outcomes identified through

consensus methods with patients and clinicians, and those measured in trials. The method developed in this chapter could be used both to assess which measurement tools currently used in the literature address current COS, but also allows for the indirect assessment of the uptake of COS through the inclusion of the measurement tools.

Chapter 4 examined how to make use of established pharmacovigilance systems to characterise harms that are not captured well in RCTs, such as rare harms or those associated with long-term exposure to treatment. All adverse reactions are recorded in a drug's summary of product characteristics (SPC), which supports benefit-risk assessments that take place beyond the marketing approval of the drug. The initial method in this chapter compared the adverse reactions from the SPCs and adverse events from the trials by drug classes. Whilst there were some findings of interest, overall the complexities of harms data required a more focused method, as there was too much uncertainty in the results. Further, it seemed clear that some of the differences might simply reflect differences in coding of adverse events with the medical dictionary for regulatory activities (MedDRA). An alternative approach was developed to focus on one drug and a limited set of harms.

A literature review identified important and serious harms that result from, or could plausibly result from, the use of the case study drug, Remicade. Grouping queries (SMQs) from the MedDRA data dictionary were used to overcome any risk of inter-coder variability and ensure all terms for the same harm were grouped so that any differences identified did not simply reflect coding differences. This approach identified 17 rare adverse reactions that were not reported in trials but featured in the SPC. Two common or very common adverse events were identified from the SPCs that were not reported by trials: hepatic function abnormal and allergic respiratory symptom. Events occurring with such high frequency would be expected to be detected in trials, but the SMQs helped to identify that similar adverse events had been reported in the trials. This appears to confirm a potential validity to this approach. As up to 91.5% of adverse reactions in

SPCs were not captured in Crohn's disease trials, there is large potential value of approaches to making use of SPC data to characterise harms.

Benefit-risk assessment under conditions of uncertainty was considered further in Chapter 5. A decision-analytic model was constructed to investigate whether the cost savings from biosimilars are sufficient to outweigh the additional uncertainties related to shortened regulatory processes and extrapolation of evidence. The construction of this model extended the theoretical approach to identifying risks that was used in Chapter 4 with a literature search to identify the potential harms from infliximab biosimilars in Crohn's disease. Incremental net health benefit (INHB) was measured to represent the added value of the biosimilar considering both the reduced costs and the increased uncertainty surrounding its clinical performance given societal resource constraints³⁷ and, in effect, represents a quantitative approach to the benefit-risk assessment of biosimilars. This novel approach is the first attempt to quantitatively measure the benefit-risk balance of biosimilar versus originator, to determine whether the cost savings justify the increased uncertainty in efficacy and safety and to assess the value of conducting further trials in CD to reduce uncertainty in parameters. The results of the model support the regulatory decision to approve the infliximab biosimilar. A range of post-marketing studies have provided evidence that supports the drug being biosimilar⁴¹⁸⁻⁴²⁶. The results of the model were robust across a range of sensitivity analyses and even found that the cost reduction was sufficient to outweigh even very high levels of risk of immunogenicity from the drug. Probabilistic sensitivity analysis highlighted almost no decision uncertainty and therefore found no value in further research to reduce uncertainty.

6.2. Implications for practice and research

6.2.1. Implications for practice

The work of this thesis adds to the evidence base on the poor quality of adverse event reporting. The extension to the CONSORT statement requires that all adverse events are reported, but

research suggests this continues to be poor^{333,335,337,339–341,363}. Under-reporting is a significant issue in spontaneous systems too, with estimates as high as 96% of adverse reactions under-reported³⁶⁵. Causality assessment is flawed with incorrect investigator reports estimated at 15.1% and even where correctly reported, 12% of reports coded differently by two coders and 8% were coded incorrectly³⁵³. Improved reporting of adverse events would create a much better data set that would be applicable to benefit-risk assessment at all stages. Current systems for adverse event reporting appear overly simplistic with the result that the outcome data is of little use to fully characterise risk. The results, in common with those in the SPC, are only considered in terms of the drug, but there may be other factors, such as drug-drug and drug-indication interactions that should be considered, especially when supporting patients to take decisions on treatments. Chapter 4 highlights the lack of transparency in the adverse reactions reported in SPCs as it is not clear where the reports come from, as demonstrated when a treatment related adverse event is reported in trials, but is not captured as an adverse reaction in the SPC. To support the richer dataset of harms, ADRs could be identified by source, for example, rule of three calculations or trials in particular indications³⁷². Given the move towards personalised medicine to improve outcomes^{217,435}, it would seem appropriate to begin to personalise harms information.

The hierarchy of evidence is less relevant to harms and pluralist methods are needed that take account of all available evidence to maximise the value of existing data^{347,361}. Adverse events require contextual information, such as the dose taken, how long the drug was taken for, which population is affected, if they are to be a useful source of risk to be included in benefit-risk assessment. However, RCTs deliberately decontextualize information by ensuring that patients, interventions and settings are as similar as possible to remove bias³⁶¹. Risk assessment needs a richer dataset and the triangulation of a variety of sources. Use of systems such as DoTS (dose-time-susceptibility) to incorporate measures of treatment duration and susceptibility factors would support an improved data set on risk⁵⁶.

The evidence from Chapter 3 highlights another issue, selective reporting. Trials and current outcome measurement tools in Crohn's disease appear not to capture some "softer" outcomes such as body image issues, despite them clearly being of enough importance to be included in an IBD COS. The omission of other outcomes and adverse events, related to sexual function and procreation function may reflect both an unwillingness of patients to report these types of adverse events, and a limited focus on trialists on immediate efficacy over wider life impacts. There may be a need for trials to create better guidelines on what should be measured and reported, which would be supported by the development of a COS for Crohn's disease. There may also be value in improving trialists' and patients' understanding of what should be reported as an adverse event.

Trialists could adopt methods developed within this thesis. The results of the mapping exercise in Chapter 3 would help to guide choice of measurement tools by considering which outcomes of the wider life impacts of Crohn's disease they consider the most important to measure in trials. The method in Chapter 4 could help to develop a clinical filter that could be applied to harms reporting in clinical trials as suggested by Lineberry et al³⁶³, and this would be especially useful for drugs in the same class. Such an approach would help to focus reporting on the important known and potential harms and ensure that the information provided in publications can help to accurately characterise harms.

A quantitative benefit-risk model, as developed in Chapter 5, could help to inform regulatory decision processes as well as health technology assessment in the case of biosimilars. Regulators face a difficult path, attempting to allow early access to drugs, whilst ensuring they are safe enough to prevent harm⁴. Being able to explore and quantify key risks via a quantitative model could help prevent the rejection of biosimilars through HTA, but could also support uptake by clinicians and patients by offering reassurance that the extrapolation process was justified, something which is especially important in the UK where biosimilars do not prompt a new HTA^{427,436}.

There is an increasing willingness to consider quantitative approaches to benefit-risk assessment by some organisations^{13,21}, but as yet, there has been no attempt at a regulatory level. There are fundamental difficulties in using economic value for optimising a regulatory decision problem, as regulators cannot consider costs, but it would be possible to strip back the model to remove costs and consider a benefit-risk outcome. The same model could then be passed to HTA organisations following regulatory approval and costs considered within it, as was done in Chapter 5. This would support alignment of the regulatory and HTA processes, as is envisaged in the partnership between the EMA and the European network of health technology assessors (EuNetHTA)²⁶.

6.2.2. Implications for research

The development of a COS for Crohn's disease is a clear research need identified from this thesis as the work in Chapter 2 demonstrates that there is no consensus on what outcome to measure and how to measure them. Whilst there are proposals to develop a COS for inflammatory bowel diseases as a whole¹⁰², Crohn's disease is sufficiently different to other forms of IBD to warrant a separate COS, or at least disease-specific parts to the COS. The first step of any COS is to identify what to measure, that is, which outcomes the key stakeholders consider the most important elements of the disease that should (or should not) be impacted by treatment⁴⁹.

The results in Chapter 2 offer comprehensive listing of both efficacy and safety outcomes to support future COS development, and the lists are supported by recent publications, which adds validity^{103,104}. Adverse event reporting and categorisation is difficult, but the data provided should support attempts to identify disease- and intervention-specific adverse events to standardise safety outcomes as discrete endpoints, within a COS process.

Once a list of outcomes has been generated, consensus methods are used to prioritise the most important outcomes. When agreement is reached on this list of core outcomes, appropriate ways of measuring those outcomes can be identified. The identification of the outcome measurement tools in Chapter 2, and the categorisation of the components of those measurement tools in

Chapter 3 will support these later processes. In particular, the results in Chapter 3 provide a comprehensive and transparent list of the discrete outcomes measured in Crohn's disease trials and highlight the gaps that are apparent, based upon the ICF IBD COS, which has been through a rigorous development process. This list should inform the beginning of the development of new outcome measurement tools to meet the requirements set down by the EMA. A new outcome measurement tool should seek to identify those patients who face a more severe disease pathway and who would benefit from more intensive earlier treatment. This would support benefit-risk assessment and better decision making at the level of clinicians and patients. Understanding the importance of some of the gaps and the importance (or otherwise) of historical outcomes incorporated in the CDAI will be necessary at part of this work – specifically, body image, digestive functions and uveitis outcomes.

The range of harms experienced by a patient is dependent on the treatment. However, as part of a COS development process for Crohn's disease, it would be necessary to consider the harms which are common to all treatments, which could be measured and reported in all trials. The methods in Chapter 4 could provide a refined list of harms that could be prioritised as part of consensus methods in a COS. The approach of linking SPCs and adverse events from trials using evidence of important known and potential risks identified from the literature is efficient research. It could support the inclusion of harms into COS and ensure that clinically important risks are measured and reported.

The complexities involved in recording and categorising harms means that there are a number of areas requiring further research. Chapter 2 highlighted a reduction in study withdrawals over time in Crohn's disease trials. It is hoped that this reflects improved trial management and drug safety, but it could reflect an improvement in patient follow up and this should be understood. The potential selective reporting identified in Chapter 3 indicated that there may be issues for patients and investigators in reporting embarrassing or less clinical issues, or simply bias as investigators

may not report events that appear detrimental to the efficacy found. This should be investigated with trial participants and investigators and inform guidelines for reporting of adverse events. Discrepancies were found in Chapter 4 between adverse events reported as treatment-related in trials and those reported as adverse reactions in SPCs. However, there is a wider issue of causation reporting in general as only 69.1% of trials assessed causation and only 59% reported individual events deemed potential ADRs. An understanding of the causes of these issues is needed to identify methods to improve them.

The methods of characterising harms in Chapter 4 appear to have highlighted some additional serious adverse events that were not reported in trials for infliximab. It would be useful to validate this approach by triangulating the findings with a sample of yellow card spontaneous reports for Crohn's disease, whilst ensuring that methods to deal with multiplicity are used³⁵². Further application of the methods in Chapter 4 should take place when the additional SMQs relevant to infliximab are available – opportunistic infections, autoimmune diseases / autoimmune mediated conditions, and infusion-related reactions³⁵⁸.

There is a need to refine the quantitative benefit-risk model in Chapter 5 to be more clinically realistic and over a longer term due to chronic nature of the disease. Other methodologies might be considered including Multi-Criteria Decision Analysis (MCDA) which is favoured by the IMI-Protect project and the EMA benefit-risk methodology project^{6,21}. It is limited by the need for clinical trial data, which were not available for the biosimilar in Chapter 5. Methods for dealing with uncertainty might support the use of the method in the context of missing clinical data.

6.3. Limitations

The limitations of each area of work have been addressed in each chapter. This section will focus on the overall limitations of the thesis.

A fundamental difficulty for the consideration of harms within economic models is that benefit outcomes are usually specified as primary outcomes in the trial and the power calculation is based

on this. It is therefore possible to obtain a carefully monitored and reasonably precise estimate for benefit, but the harms are always imprecise and uncertain. Added to this, is the fact that there are a small number of major benefits, but the potential risks can run into dozens of possibilities. The selection of which harms to include can be determined using consensus methods, but health economic modelling methods will need to develop to tackle this situation.

A limitation of this thesis is the consideration of trial outcomes and harms, which did not go beyond RCTs. Observational studies contain an array of outcomes and harm information that would be useful to characterise the effects of a product more comprehensively. Given the need for pluralist methods for identifying harms, consideration of observational studies would add another layer to the benefit-risk profile of a drug.

Much of the methodological work in this thesis focused on improving transparency including what is being measured within outcome measurement tools used in trial, alignment of the trials adverse events with adverse reactions in SPCs and the quantification of the uncertainties present in the benefit-risk assessment of biosimilar drugs approved through extrapolation of trial data in other indications. What this has highlighted in many cases, is the clear uncertainties involved in all the sources of information, which can undermine the results. However, novel approaches are required to tackle the issues and the work in this thesis has attempted to do so in an efficient way by making use of existing sources of information.

6.4. Conclusions

The work presented in this thesis is timely as there is a range of work taking place to streamline regulator and HTA processes, to ensure patients are given access to newer forms of biologics, and to ensure that the outcomes of treatments for Crohn's disease are being adequately captured.

A key strength of this thesis is the focus throughout on harms from interventions. Difficulties are extensive in measuring harms – understanding what is caused purely by the intervention, what is related to the drug combined with the indication or other therapies, what is related to treatment

failure. Problems begin at the reporting of causation in trials, where there is evidence that it is not always correct and is prone to variation between investigators and coders. The reporting of adverse events as causally related in trials, which do not appear in the SPC suggest that those reports are either incorrect, or that the grouping of trial data and spontaneous reports with other indications masks an effect that is specific to Crohn's disease. The work in this thesis makes a novel contribution to the literature through methods to triangulate theoretical harms from the literature, adverse events data from trials and adverse reactions data from the SPCs.

A novel contribution is made in Chapter 5, as it is the first attempt to provide a transparent framework for assessing the value of biosimilars by considering the incremental net health benefit, taking into account both benefits and harms. Value-based pricing using this methodology would be possible to protect health systems such as the NHS in the UK from the potential risks of biosimilars where they are untested in the populations for which they have been approved. Future developments on this work could allow a single model to be developed and utilised in both regulatory and health technology assessment decisions.

6.4.1. Recommendations for practice

- The results of the mapping exercise in Chapter 3 should guide trialists in their choice of outcome measurement tools by transparently deciding which wider impacts of the disease are important.
- Trials should have clear guidelines on what should be reported as an adverse event, ensuring that wider life impact adverse events are captured, and patients and investigators are supported to identify such events.
- Improved reporting of adverse events in trials requires more contextual information. Trials should consider the use of the DoTs classification.
- The clinical filter approach to identifying important harms in Chapter 4 could be used by trials in reporting harms.

- SPCs should be more transparent and identify the source of information for each adverse reaction, specifically whether the assessment of frequency is via a rule of three calculation of trials, and if the latter, in which indication.
- Quantitative models, such as in Chapter 5, should be developed to measure a benefit-risk value for regulators, with the ability to add costs in so that they can be passed onto health technology assessors in the post-marketing period. This will support the alignment of regulatory and HTA processes.

6.4.2. Recommendations for future research

- The reduction in study withdrawals found over time should be researched, specifically, whether this reflects a change in the withdrawal from treatment rather than from trial, or whether there has been a change in definition over time due to greater clarity on the requirements of analysis in the CONSORT guidelines.
- Research should be conducted to understand issues around causality of harms assessment, i.e. the absence of causality assessment in trials and the differences in causality between trials and SPCs.
- The outcomes and adverse events data in Chapter 2 should be used as the first stage of a COS in Crohn's disease, to be prioritised through consensus methods.
- Intervention-specific harms should be developed as add-ons to COS. The clinical filter approach to identifying important harms in Chapter 4 might provide a list of intervention-specific harms to include in a consensus process.
- New outcome measurement tools for Crohn's disease should be developed using the results of the categorisation process in Chapter 3.
- Repeat methods in Chapter 4, comparing harms in trials and SPCs to identify new harms as relevant SMQs are made available.

- Validate Chapter 4 results with a sample of MHRA Yellow Card spontaneous reporting data for Crohn's disease using infliximab.
- The quantitative model for benefit-risk assessment of infliximab biosimilar should be refined for a more clinically realistic model, with a longer time horizon to reflect the chronic nature of the disease. MCDA methods should be investigated for the model.

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Appendices

Appendix 1: Full list of benefit-risk methodologies for Chapter 1

Appendix table 1: Full list of benefit-risk methodologies reviewed by Mt-Isa et al (2014) and the abbreviations¹⁷

Methodology	Description	Category
AE-NNT	Adverse event adjusted number needed to treat	Metric indices – threshold indices
ASF	Ashby and Smith Framework	Descriptive framework
BLRA	Benefit-less-risk analysis	Quantitative framework
Beckmann	Beckmann model (AKA evidence based model)	Metric indices – trade-off indices
BRAFO	Benefit-risk analysis for foods	Descriptive framework
BRAT	Benefit-Risk Action Team	Descriptive framework
BRR	Benefit-risk ratio	Metric indices – trade-off indices
CA	Conjoint analysis	Utility survey techniques
CDS	Cross-design synthesis	Estimation techniques
CMR CASS	CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic and Singapore Health Science Authority	Descriptive framework
COBRA	Consortium on benefit-risk assessment	Descriptive framework
CPM	Confidence profile method	Estimation techniques
CUI	Clinical utility index	Quantitative framework
CV	Contingent valuation	Utility survey techniques
DAG	Directed acyclic graphs	Estimation techniques
DALY	Disability-adjusted life years	Metric indices – health indices
DCE	Discrete choice experiment	Utility survey techniques
Decision tree	Decision tree	Quantitative framework
DI	Desirability index	Quantitative framework
FDA BRF	FDA benefit-risk framework	Descriptive framework
GBR	Global benefit-risk	Metric indices – trade-off indices
HALE	Health-adjusted life years	Metric indices – health indices
Impact numbers	Impact numbers	Metric indices – threshold indices
INHB	Incremental net health benefit	Metric indices – trade-off indices
ITC	Indirect treatment comparison	Estimation techniques
MAR	Maximum acceptable risk	Metric indices – threshold indices
MCDA	Multicriteria decision analysis	Quantitative framework
MCE	Minimum clinical efficacy	Metric indices – threshold indices
MDP	Markov decision process	Quantitative framework
MTC	Mixed treatment comparison	Estimation techniques
NCB	Net clinical benefit	Quantitative framework
NEAR	Net efficacy adjusted for risk	Metric indices – threshold indices
NNH	Number needed to harm	Metric indices – threshold indices
NNT	Number needed to treat	Metric indices – threshold indices
OMERACT 3x3	Omeract Measures in Rheumatology 3x3	Descriptive framework

Methodology	Description	Category
Principle of 3s	Principle of threes	Metric indices – trade-off indices
ProACT-URL	Problem, objectives, alternatives, consequences, trade-offs, uncertainty risk, and linked decisions framework	Descriptive framework
PSM	Probabilistic simulation model	Estimation techniques
QALY	Quality-adjusted life years	Metric indices – health indices
Q-TWIST	Quality-adjusted time without symptoms and toxicity	Metric indices – health indices
RV-MCE	Relative value-adjusted minimum clinical efficacy	Metric indices – threshold indices
RV-NNH	Relative value-adjusted number needed to (treat to) harm	Metric indices – threshold indices
SABRE	Southeast Asia benefit-risk evaluation	Descriptive framework
SBRAM	Sarac’s benefit-risk assessment	Quantitative framework
SMAA	Stochastic multicriteria acceptability analysis	Quantitative framework
SPM	Stated preference method	Utility survey techniques
TURBO	Transparent uniform risk-benefit overview	Metric indices – trade-off indices
UMBRA	Unified methodologies for benefit-risk assessment	Descriptive framework
UT-NNT	Utility-adjusted and time-adjusted number needed to treat	Metric indices – trade-off indices

Appendix figure 1: PROSPERO Systematic Review Registered Protocol

UNIVERSITY *of* York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Identifying a core outcome set for Crohn's disease in adults

Heather Catt

Citation

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Review question(s)

To systematically review the literature to identify the important harm and benefit outcomes previously reported in studies of the treatment of inflammatory bowel disease, with a focus on Crohn's disease.

Searches

The following databases are to be searched: Cochrane Library, Cumulative Index to Nursing & Allied Health Literature (CINAHL), EMBASE, and MEDLINE.

The search strategy will be broad to include Crohn's disease and Inflammatory Bowel Diseases and outcomes. The searches will be restricted to records related to adults, where possible.

There will be no date restrictions applied as many important outcomes are reported in early studies.

Types of study to be included

Inclusion: Randomised controlled trials. A sample of prospective studies will be selected for validation of outcomes.

Exclusion: Systematic reviews with or without meta-analyses, clinical trials with or without controls, prospective cohorts, retrospective cohorts, case studies, cases series, letters, editorials and commentaries. Studies related to genetics, aetiology or epidemiology of Crohn's disease.

Condition or domain being studied

Benefit and harm outcomes of treatment for Crohn's disease

Participants/ population

Inclusion: Adults aged 18 years and older with Crohn's disease and other conditions which may include Crohn's disease: inflammatory bowel disease, indeterminate colitis, severe acute colitis and segmental colitis.

Exclusion: Children aged 17 and under. Sub-groups of the population, for example smokers, obese, ethnic groups, etc.

Intervention(s), exposure(s)

Inclusion:

Studies of treatments for inducing or maintaining remission of Crohn's disease and other conditions which may include Crohn's disease: inflammatory bowel disease, indeterminate colitis, severe acute colitis and segmental colitis. Treatments may include medical (e.g. biologics and antibiotics), surgical and other (e.g. supportive care or enteral nutrition).

Studies of treatments of specific bowel or perianal complications of Crohn's disease (fistulae, fissures, perforations, abscesses and strictures).

Exclusion:

Studies of ulcerative colitis and other forms of colitis such as microscopic (lymphocytic and collagenous), intestinal

Behcet's, ischaemic colitis, focal active colitis, cytomegalovirus colitis, diversion colitis, pseudomembranous colitis, etc.

Studies of other bowel conditions such as diverticulitis, familial adenomatous polyposis, polyps, rectal / colorectal cancer, celiac disease, irritable bowel syndrome, collagenous sprue, gastrointestinal tuberculosis, ischaemic bowel disease, peptic ulcer, dyspepsia, etc

Studies of treatments for sequelae of Crohn's disease, e.g. osteoporosis, anaemia, cancer, etc.

Studies of pre-surgery procedures, for example methods of bowel preparation.

Studies of diagnostic techniques for Crohn's disease, e.g. endoscopy, faecal calprotectin test, c-reactive protein test.

Studies of co-morbid conditions, e.g. ankylosing spondylitis, toxic megacolon, etc.

Comparator(s)/ control

Untreated control or other interventions.

Context

Further exclusions:

- Studies of pre-surgery procedures, for example methods of bowel preparation.

- Studies of diagnostic techniques for Crohn's disease, e.g. endoscopy, faecal calprotectin test, c-reactive protein test.

The full articles must be available and they must be reported in English to be included.

Outcome(s)

Primary outcomes

The review will identify all benefit and harm outcomes reported in treatments for Crohn's disease.

Secondary outcomes

None.

Data extraction, (selection and coding)

Two reviewers will independently assess the titles and abstracts of a random sample of 100 studies resulting from the search against the screening inclusion criteria. Assuming good inter-rater reliability, the primary reviewer will review the remaining papers independently with reference to the second reviewer where uncertain of whether they meet the inclusion criteria.

Full copies will be obtained of all studies appearing to meet the inclusion criteria or those where there is insufficient information in the abstract to judge relevance. 10% of the full text papers will be assessed independently by two review authors and any disagreement resolved through discussion. A third reviewer will be consulted if disagreements cannot be resolved. Assuming there is a good degree of inter-reviewer agreement on the initial 10%, the primary reviewer will review the remaining 90% of studies independently. The reference lists of all included studies will be searched for other potentially relevant studies.

Two reviewers will independently extract data from 10% of the eligible studies. The extracted data will then be reviewed together to achieve consensus and ensure all outcomes are identified. Disagreement should be resolved through discussion or, where necessary, through consultation with a third reviewer.

The following data should be extracted from the study:

1. Author details.
2. Year and journal of publication.

3. Study type.
4. Sample size.
5. Participants.
6. Disease behaviour in the study population.
7. Duration of treatment
8. Duration of follow up.
9. Intervention(s) under investigations.
10. Comparator intervention(s).

Outcomes data to be extracted:

1. The outcomes measured, and whether primary, secondary, harm or benefit.
2. The type of measurement (e.g. biomarker, PROM, etc).

Risk of bias (quality) assessment

The review is interested in the outcomes reported in the studies, rather than the results reported. As such, there will not be any synthesis and assessment of risk of bias will not be carried out.

Strategy for data synthesis

Data synthesis will not be carried out as part of this review.

Analysis of subgroups or subsets

None planned.

Dissemination plans

A paper will be submitted to a leading journal in this field. The review will become part of the primary researcher's PhD thesis.

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Anticipated or actual start date

02 November 2015

Anticipated completion date

02 November 2016

Funding sources/sponsors

MRC Network of Hubs for Trials Methodology Research

Conflicts of interest

None known

Language

English

Country

England

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adult; Crohn Disease; Delphi Technique; Humans; Outcome Assessment (Health Care)

Stage of review

Ongoing

Date of registration in PROSPERO

26 April 2016

Date of publication of this revision

26 April 2016

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

PROSPERO

International prospective register of systematic reviews

The information in this record has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record.

any associated files or external websites.

Appendix 3: Systematic review search strategies for Chapter 2

Appendix table 2: Cochrane search strategy for Crohn's disease outcomes in adults (search completed 3rd November 2015)

#	Searches	Results	Search description
1	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees	2,092	Inflammatory bowel disease
2	Inflammatory bowel disease*	1,865	Inflammatory bowel disease
3	#1 or #2	3,240	Inflammatory bowel disease
4	MeSH descriptor: [Crohn disease] explode all trees	1,034	Crohn's disease
5	Crohn*	2,137	Crohn's disease
6	#4 or #5	2,137	Crohn's disease
7	#3 or #6	3,905	Inflammatory bowel disease or Crohn's disease
8	Outcome*	241,924	Outcomes
9	#7 and #8	1,794	Inflammatory bowel disease or Crohn's disease and outcomes
10	Not possible to limit on age		

Appendix table 3: Cumulative Index to Nursing and Allied Health Literature search strategy for Crohn's disease outcomes in adults (search completed 3rd November 2015)

#	Searches	Results	Search description
1	(MH "Inflammatory Bowel Diseases+")	8,376	Inflammatory bowel disease
2	Inflammatory bowel disease*	4,881	Inflammatory bowel disease
3	S1 OR S2	9,322	All inflammatory bowel disease
4	(MH "Crohn Disease")	4,017	Crohn's disease
5	Crohn*	4,884	Crohn's disease
6	S4 or S5	4,884	All Crohn's disease
7	S3 or S6	9,769	Inflammatory bowel disease or Crohn's disease
8	Outcome*	477,077	Outcomes
9	S7 AND S8	1,310	Inflammatory bowel disease or Crohn's disease and outcomes
10	S9 with restriction for adults	529	Inflammatory bowel disease or Crohn's disease and outcomes for adults

Appendix table 4: EMBASE search strategy for Crohn's disease outcomes in adults (search completed 3rd November 2015)

#	Searches	Results	Search description
1	exp INFLAMMATORY BOWEL DISEASE/	98,256	Inflammatory bowel disease
2	Inflammatory AND bowel AND disease.mp	54,886	Inflammatory bowel disease
3	1 OR 2	119,712	Inflammatory bowel disease
4	Exp CROHN DISEASE/	64,317	Crohn's disease
5	Crohn*.mp	72,296	Crohn's disease
6	4 OR 5	72,296	Crohn's disease
7	3 OR 6	123,434	Inflammatory bowel disease or Crohn's disease
8	Outcome*.mp	215,869	Outcomes
9	7 AND 8	16,198	Inflammatory bowel disease or Crohn's disease and outcomes
10	9 [Limit to: (Human Age Groups Adult 18 to 64 years or Aged 64+ years)]	6,394	Inflammatory bowel disease or Crohn's disease and outcomes for adults

Appendix table 5: MEDLINE search strategy for Crohn's disease outcomes in adults (search completed 3rd November 2015)

#	Searches	Results	Search description
1	exp Inflammatory Bowel Diseases/	65,723	Inflammatory bowel disease
2	Inflammatory bowel disease*.mp	32,235	Inflammatory bowel disease
3	1 or 2	73,709	Inflammatory bowel disease
4	exp Crohn disease/	33,044	Crohn's disease
5	Crohn*.mp	41,633	Crohn's disease
6	4 or 5	41,633	Crohn's disease
7	3 or 6	77,739	Inflammatory bowel disease or Crohn's disease
8	outcome*.mp	1,539,674	Outcomes
9	7 and 8	9,153	Inflammatory bowel disease or Crohn's disease and outcomes
10	Limit 9 to "all adult (19 plus years)"	5,710	Inflammatory bowel disease or Crohn's disease and outcomes for adults

Appendix 4: Characteristics of randomised controlled trials identified by the systematic review in Chapter 2

Appendix table 6: Characteristics of Randomised Controlled Trials in Crohn's Disease

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Induction (n=110)					
Medical induction (n=104)					
Greenberg 1988	USA and Canada	51	CDAI >150, refractory	52	Parenteral versus defined formula nutrition
Wright 1990	USA and Canada	11	Patients requiring hospitalisation for acute exacerbation of Crohn's	2	Parenteral versus enteral nutrition
Rigaud 1991	UK and Europe	30	CDAI >150	52	Enteral nutrition: elemental vs polymeric
Ewe 1993	UK and Europe	42	CDAI >150	16	AZA and prednisolone
Singleton 1993	USA and Canada	310	CDAI 150-400	16	Mesalamine
Wright 1993	Rest of world	356	Mild to moderate Crohn's, judged to need oral corticosteroids	4	Fluticasone propionate
Rutgeerts 1994	UK and Europe	176	CDAI >200	10	Budesonide and prednisolone
Tremaine 1994	USA and Canada	38	CDAI 150-450	17	Mesalamine
Royall 1994	USA and Canada	40	CDAI >250	52	Amino acid based defined formula
Greenberg 1994	USA and Canada	258	CDAI >200	10	Budesonide
Jewell 1994	UK and Europe	147	Chronically active Crohn's despite steroid treatment	52	Cyclosporine
Gross 1995	UK and Europe	31	CDAI 150-350	8	5-ASA

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Mansfield 1995	UK and Europe	44	One symptom of active disease, CDAI >150 and one abnormal lab measurement	4	Amino acid versus oligopeptide diet
Middleton 1995	UK and Europe	76	HBI >=6 and elevated ESR, CRP and alpha-1-antichymotrypsin	3	Enteral feeds
Feagan 1995	USA and Canada	141	Chronically active Crohn's despite steroid treatment	16	Methotrexate
Targan 1997	USA and Canada	108	CDAI 220-400	12	Infliximab
Frascio 1997	UK and Europe	14	CDAI >150	2	Enteral and parenteral nutrition
Bar-Meir 1998	Rest of world	201	CDAI 150-350	8	Budesonide and prednisolone
Colombel 1999	UK and Europe	40	CDAI 150-300	6	Ciprofloxacin and mesalazine
Hond 1999	UK and Europe	14	Crohn's with increased intestinal permeability	4	Oral glutamine
D'Haens 1999	UK and Europe	22	CDAI 220-400, refractory	4	infliximab
**Present 1999	USA and Canada	94	Crohn's with single or multiple draining or abdominal fistulas of at least three months' duration	34	infliximab
Sandborn 1999	USA and Canada	96	CDAI 150-450, steroid treated	18	Azathioprine
Verma 2000	UK and Europe	21	CDAI >150, presence of bowel symptoms, at least one raised inflammatory marker and increased bowel activity on leukocyte bowel imaging	4	Elemental versus polymeric diet
Fedorak 2000	USA and Canada	95	CDAI 200-350	24	rhIL-10
Schreiber 2000	UK and Europe	329	CDAI 200-400	8	Tenovil
Leiper 2001	UK and Europe	54	CDAI >200 and serum C-reactive protein 10mg/l	3	Whole protein feed with long chain triglyceride content

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Gordon 2001	UK and Europe	30	CDAI 150-450	12	natalizumab
Schreiber 2001	UK and Europe	78	CDAI 200-400, steroid dependent	26	ISIS-2302
Sandborn 2001	USA and Canada	193	CDAI 220-450	24	CDP571
Lomer 2001	UK and Europe	20	CDAI >150	17.3	Low micro particle diet
Hawkes 2001	UK and Europe	70	CDAI 150-450	12	Glyceryl trinitate (GTN)
Sandborn 2001	USA and Canada	43	CDAI 220-450	8	Etanercept
Carty 2001	UK and Europe	85	CDAI 200-400	12	Ridrogel
Goodgame 2001	USA and Canada	31	Crohn's disease	52	Ethambutol and clarithromycin
Tremaine 2002	USA and Canada	200	CDAI 200-450	10	Budesonide
Steinhart 2002	USA and Canada	134	CDAI 200-400	8	Ciprofloxacin and metronidazole
Yacyshyn 2002	USA and Canada	22	CDAI >220	52	Alicaforsen
Hommes 2002	UK and Europe	12	CDAI 220-450	4	CNI-1493, a guanylhydrazone
Arnold 2002	USA and Canada	47	CDAI >150 CDAI	26	Ciprofloxacin
Sakurai 2002	Rest of world	36	CDAI >150	6	Enteral nutrition with low or high medium-chain triglycerides
Ardizzone 2003	UK and Europe	54	CDAI >200	26	Methotrexate and azathioprine

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Bamba 2003	Rest of world	36	International Organisation of Inflammatory Bowel Disease (IOIBD) rating ≥ 2 and at least one abnormal inflammatory marker	4	Different fat-dose levels of enteral nutrition
Ghosh 2003	UK and Europe	244	CDAI 220-450	12	natalizumab
Ito 2004	Rest of world	36	CDAI >150 and abnormal levels of serum C-reactive protein	12	anti-IL-6R mAb MRA
Joos 2004	UK and Europe	51	CDAI 150-350	12	Traditional acupuncture
Herfarth 2004	UK and Europe	104	CDAI >150	6	Budesonide
Mannon 2004	UK and Europe	79	CDAI 220-450	25	anti-interleukin-12
Sandborn 2004	USA and Canada	396	CDAI 220-450	28	CDP571
**West 2004	UK and Europe	24	Crohn's disease complicated by single or multiple draining perianal fistulae	18	Ciprofloxacin and infliximab
Winter 2004	USA and Canada	92	CDAI 220-450	12	CDP870
Schreiber 2005	UK and Europe	291	CDAI 220-450	20	certolizumab pegol
Lomer 2005	UK and Europe	83	CDAI >150	52	Low microparticle diet
Korzenik 2005	USA and Canada	124	CDAI 220-475	34.3	Granulocyte-macrophage colony-stimulating factor (GM-CSF)
Reinsich 2006	UK and Europe	45	CDAI 250-450	25.1	fontolizumab
Margalit 2006	USA and Canada	31	CDAI 220-400	27	Autologous colonic proteins
Prantera 2006	UK and Europe	83	CDAI 220-400	16	Rifaximin

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Schroder 2006	UK and Europe	19	Refractory to or dependent on corticosteroids	48	infliximab and methotrexate
Hommes 2006	UK and Europe	133	CDAI 250-450	26	fontolizumab
Hanauer 2006	USA and Canada	299	CDAI 220-450	4	Adalimumab
Lemann 2006	UK and Europe	115	CDAI >150, steroid dependent	52	infliximab
Rutgeerts 2006	UK and Europe	207	CDAI 250-400	20	onercept
Schreiber 2006	USA and Canada	284	CDAI 220-450	8	BIRB 796
Herrlinger 2006	UK and Europe	52	CDAI >220	12	rhIL-11 and prednisolone
Reinshagen 2007	UK and Europe	58	CDAI 150-450	24	Azathioprine and azathioprine dose adaption
Mansfield 2007	UK and Europe	84	CDAI 200-400	12	Lenalidomide
Sandborn 2007	USA and Canada	325	CDAI 220-450	4	Adalimumab
Hafer 2007	UK and Europe	31	Active Crohn's	17.3	lactulose syrup
Targan 2007	USA and Canada	509	CDAI 220-450 and elevated CRP	12	natalizumab
Omer 2007	UK and Europe	40	CDAI >170	20	Wormwood
**Hart 2007	UK and Europe	19	Patients with single or multiple draining perianal fistulas or perianal or anal ulcerating disease without fistulas	24	Tacrolimus
Sandborn 2008	USA and Canada	104	CDAI 220-450	28	ustekinumab

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Leiper 2008	UK and Europe	41	CDAI >200	12	Clarithromycin
D'Haens 2008	UK and Europe	133	CDAI >200	104	Immunosuppressives and Infliximab
**Fukuda 2008	Rest of world	62	At least one intractable active anal fistula	8	Spherical carbon adsorbent
Feagan 2008	USA and Canada	185	CDAI 220-400	25.7	vedolizumab
**Thia 2009	USA and Canada	27	Perianal Crohn's with 1 or more open actively draining perianal fistula	10	Ciprofloxacin and metronidazole
Dotan 2010	Rest of world	152	CDAI 250-400	8.1	Semapimod
Steed 2010	UK and Europe	35	CDAI 150-450	26	Synbiotic B.longum and Synergy 1
Van der Woude 2010	UK and Europe	40	CDAI 220-450, elevated CRP and endoscopic confirmation	27.9	NI-0401
Maeda 2010	UK and Europe	74	PCDAI score of >=5	4	Metronidazole
Sands 2010	USA and Canada	220	CDAI 220-450	30.1	Apilimod mesylate
Buchman 2010	USA and Canada	100	CDAI 220-450	24	Teduglutide
Krebs 2010	UK and Europe	20	CDAI >200	6	Wormwood
Tromm 2011	UK and Europe	311	CDAI 200-400	8	Budesonide and mesalamine
Sandborn 2011	USA and Canada	439	CDAI 220-450	6	certolizumab pegol
Benjamin 2011	UK and Europe	103	CDAI >220 and an additional marker of inflammation	4	Prebiotic fructo-oligosaccharides (FOS)
Smith 2011	USA and Canada	34	CDAI >220	24	naltrexone

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Prantera 2012	UK and Europe	402	CDAI 220-400	24	Rifaximin
Hueber 2012	UK and Europe	59	CDAI 220-450	16	Secukinumab
Sands 2013	USA and Canada	235	CDAI 220-450	24	Granulocyte / monocyte apheresis
Naftali 2013	Rest of world	21	CDAI 200-450	10	Cannabis
Suzuki 2013	Rest of world	77	CDAI >200	10	Budesonide
Sandborn 2013	USA and Canada	36	Confirmed diagnosis of Crohn's	26	Trichuris suis ova
Brotherton 2014	USA and Canada	7	partial Harvey Bradshaw Index ≥ 3	4	Whole wheat fibre diet
Sandborn 2014	USA and Canada	139	CDAI 220-450	8	Tofacitinib
**Dewint 2014	UK and Europe	76	Active perianal fistulising Crohn's	24	Adalimumab and ciprofloxacin
**Reinisch 2014	UK and Europe	249	At least one draining perianal fistula, CDAI <400	24	Spherical carbon adsorbant
Sands 2014	USA and Canada	416	CDAI 220-400 and one of the following: elevated C-reactive protein, endoscopy documented ulcerations or elevated faecal calprotectin and features of clinical activity	22	vedolizumab
Dignass 2014	UK and Europe	471	CDAI 200-400	10	Budesonide
Bao 2014	Rest of world	92	CDAI 150-350	24	Acupuncture and moxibustion
D'Haens 2015	UK and Europe	180	CDAI 220-450	12	Laquinimod
Monteleone 2015	UK and Europe	166	CDAI 220-400	12	Mongerson
Vande Casteele 2015	UK and Europe	251	treated with infliximab for at least 14 weeks and in a stable clinical response	52	infliximab

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Surgical induction (n=6)					
Maartense 2006	UK and Europe	60	Patients undergoing elective ilocolonic resection	13	Laparoscopic versus open resection
East 2007	UK and Europe	13	Symptomatic strictures suitable for colonoscopic dilation	52	Intrastricture steroid after balloon dilatation of strictures
McLeod 2009	USA and Canada	170	Patients undergoing elective ilocolonic resection	52	End to end and side to side anastomosis
**Grimaud 2010	UK and Europe	77	CDAI <250 and at least one draining perianal fistula	16	Fibrin glue
Zurbuchen 2013	UK and Europe	67	Crohn's patients with ileitis terminalis who underwent elective ileocecal resection	0	End to end and side to side anastomosis
**Molendijk 2015	UK and Europe	21	Actively draining fistulising Crohn's with 1-2 internal openings and 1-3 fistula tracts and CDAI <250	24	Mesenchymal stromal cells (MSC)
Maintenance (n=71)					
Maintenance studies of medically induced maintenance (n=52)					
Singleton 1979	USA and Canada	89	CDAI >150	26	Prednisone and sulfasalazine
Malchow 1984	UK and Europe	452	Active Crohn's or quiescent	104	Sulfasalazine and / or methylprednisolone
Levenstein 1985	UK and Europe	58	Non-stenosing Crohn's	104	Low residue or normal diet
Bresci 1994	UK and Europe	66	CDAI <150	208	5-ASA
Feagan 1994	USA and Canada	305	Active crohn's with symptoms requiring treatment with steroids or 5-ASA	78	Cyclosporine
Schreiber 1994	UK and Europe	60	CDAI <150 for at least two months	52	4-ASA and 5-ASA
Stange 1995	UK and Europe	182	Stratified: CDAI <200 and CDAI >200	65	Cyclosporine

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Belluzzi 1996	UK and Europe	78	CDAI <150 for 3 months - 2 years plus elevated inflammation marker	52	Fish oil
Greenberg 1996	USA and Canada	105	CDAI <150	52	Budesonide
Sutherland 1997	USA and Canada	293	CDAI <150 with no symptoms for the past 30 days	48	Mesalamine
Ferguson 1998	UK and Europe	75	CDAI <150	52	Budesonide
Arora 1999	USA and Canada	33	Steroid dependent for at least 6 months	52	Methotrexate
Guslandi 2000	UK and Europe	32	CDAI <150 for at least three months	26	Probiotic <i>Saccharomyces boulardii</i>
Green 2001	UK and Europe	141	In remission for at least 1 month (exhibiting no or mild symptoms)	52	Flexible dose budesonide
Mahmud 2001	UK and Europe	328	CDAI <150 for at least one month	52	Olsalazine
Cortot 2001	UK and Europe	120	CDAI <200	22	Budesonide
Hanauer 2002	USA and Canada	335	CDAI 220-400	54	infliximab
Mantzaris 2003	UK and Europe	57	CDAI <150, steroid dependent	52	Budesonide and mesalamine
Keller 2004	UK and Europe	108	At least one active episode of disease in the last 2 years	104	Psychotherapy and relaxation therapy
**Sands 2004	USA and Canada	282	Crohn's with single or multiple draining or abdominal fistulas of at least three months' duration	54	infliximab
Schultz 2004	USA and Canada	11	CDAI 150-300	26	Probiotic <i>Lactobacillus GG</i>
Vilien 2004	UK and Europe	29	Crohn's in remission and on AZA for at least 2 years	52	Azathioprine

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Lemann 2005	UK and Europe	83	In clinical remission induced by azathioprine for ≥ 42 months	78	Azathioprine
Feagan 2005	USA and Canada	71	CDAI < 150 and receiving corticosteroid therapy	16	CDP571
Hanauer 2005	USA and Canada	110	CDAI < 150	52	Budesonide
Sandborn 2005	USA and Canada	905	CDAI 220-450	60	natalizumab
Feagan 2006	USA and Canada	271	CDAI < 150 , steroid dependent	34	CDP571
Takagi 2006	Rest of world	51	CDAI < 150	104	Half elemental diet
Colombel 2007	UK and Europe	778	CDAI 220-450	60	Adalimumab
Sandborn 2007	USA and Canada	55	CDAI < 150	52	Adalimumab
Ng 2007	USA and Canada	32	Mildly active or disease in remission	13	Exercise: walking
Schreiber 2007	UK and Europe	425	CDAI 220-450	26	certolizumab pegol
De Jong 2007	UK and Europe	157	CDAI < 150 for 3-18 months	52	Budesonide
Selby 2007	Rest of world	213	CDAI > 200	52	Clarithromycin, Rifabutin and Clofazimine
Garcia 2008	Rest of world	34	CDAI < 150	13	Probiotic <i>Saccharomyces boulardii</i>
Feagan 2008	USA and Canada	363	CDAI < 150	58	Omega 3 free fatty acids
Mantzaris 2009	UK and Europe	77	CDAI < 150 , steroid dependent	52	Azathioprine and budesonide
Rossi 2009	UK and Europe	67	CDAI < 150	56	IFN beta-la

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Takagi 2009	Rest of world	51	CDAI <150	104	Half elemental diet
Valentine 2009	USA and Canada	156	CDAI 150-450	26	Granulocyte-macrophage colony-stimulating factor (GM-CSF)
Sandborn 2010	USA and Canada	329	CDAI 220-450	26	certolizumab pegol
Jorgensen 2010	UK and Europe	94	CDAI <150 and biochemical signs of quiescent CD	52	Vitamin D3
Prantera 2011	UK and Europe	73	CDAI <150	24	Beclomethasone dipropionate (BDP)
Holtmeier 2011	UK and Europe	82	CDAI <150	64	Boswellia serrata
Watanabe 2012	Rest of world	90	CDAI 220-450	52	Adalimumab
Keefer 2012	USA and Canada	28	CDAI <150	6	Project management
Keshav 2013	UK and Europe	436	CDAI 250-450 and elevated C-reactive protein	52	Vercinon
Bourreile 2013	UK and Europe	165	CDAI <150 after induction therapy	65	Probiotic <i>Saccharomyces boulardii</i>
Jigaranu 2014	UK and Europe	168	CDAI 220-400	48	Rifaximin
Feagan 2014	USA and Canada	126	Active Crohn's being treated with prednisone	50	Methotrexate and infliximab
Piche 2014	UK and Europe	37	Normal global assessment by a clinician, normal C-reactive protein, erythrocyte sedimentation rate, platelet count and white cell count, no use of corticosteroids in the past 12 months, CDAI <150 and normal mucosa	8.6	Osteopathy
Wenzl 2015	UK and Europe	52	CDAI <150 and azathioprine therapy \geq 4 years	104	Azathioprine
Maintenance studies of surgically induced remission (n=19)					

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Brignola 1995	UK and Europe	87	Post curative resection	52	Mesalamine
McLeod 1995	USA and Canada	163	Post-surgical resection	312	Mesalamine
Ewe 1999	UK and Europe	83	Post curative resection for ileal, ileo-colonic or colonic Crohn's	52	budesonide
Hellers 1999	UK and Europe	129	Patients scheduled for resection surgery for ileocolonic Crohn's	52	Budesonide
Lochs 2000	UK and Europe	324	Post-surgical resection	78	Mesalamine
Colombel 2001	UK and Europe	65	First resectional surgery for ileal or ileocolonic Crohn's	16	Tenovil
Prantera 2002	UK and Europe	55	Undergone recent curative resection	52	Probiotic Lactobacillus rhamnosus GG
Caprilli 2003	UK and Europe	206	Post-surgical resection	52	Mesalazine
Hanauer 2004	USA and Canada	131	Patients schedules for resection	104	6-mercaptopurine or mesalamine
Marteau 2006	UK and Europe	98	Undergone recent curative resection	26	Probiotic Lactobacillus johnsonii LA1
D'Haens 2008	UK and Europe	81	Post ileal or ileocolonic resection with ileocolonic anastomosis	52	Metronidazole and azathioprine
Regueiro 2009	USA and Canada	24	Patients with ileal or ileocolonic Crohn's undergoing resection	60	infliximab
Reinisch 2010	UK and Europe	78	CDAI <200 and endoscopic recurrence Rutgeerts grade \geq 2	52	Azathioprine
Savarino 2013	UK and Europe	51	Undergoing resection	104	Adalimumab
Herfarth 2013	USA and Canada	33	Ileal or ileocolonic resection with ileocolonic anastomosis	26	Ciprofloxacin

Reference	Country of study or lead author	Sample size	Disease behaviour	Follow up (weeks)	Intervention
Ren 2013	Rest of world	39	CDAI <150 since resection	52	Tripterygium wilfordii polyglycoside
Armuzzi 2013	UK and Europe	22	Post curative resection	52	Azathioprine and infliximab
Fedorak 2015	USA and Canada	120	Post resection with margins macroscopically free of disease	52	Probiotic VSL#3
Zhu 2015	Rest of world	90	Crohn's undergoing macroscopic disease resection	52	Tripterygium wilfordii Hook f.

Note: CDAI, Crohn's disease activity index; IOIBD, International Organisation of Inflammatory Bowel Disease; HBI, Harvey Bradshaw Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PDAI, perianal disease activity index; **, study involved only patients with fistula.

Appendix 5: Additional tables for Chapter 2

Appendix table 7: Primary and Secondary Clinical and Composite-Clinical Efficacy Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measurement	Measurement tool
Induction (n=101)			
Medical induction (n=95)			
Greenberg 1988	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI >250	CDAI
Wright 1990	Remission	CDAI <150	CDAI
Ewe 1993	Response	Change in CDAI score	CDAI
	Response	Change in Dutch index score	Dutch index
	Response	Change in SAI score	SAI
	Corticosteroid sparing	Steroid dose	
Singleton 1993	Remission	CDAI <150	CDAI
	Response	CDAI decrease by \geq 50 points	CDAI
	Response	Mean CDAI score	CDAI
	Response	Mean HBI score	HBI
	Response	Mean PGA of degree of illness on a Visual Analogue Scale	PGA
	Response	Mean VHAI score	VHAI
Wright 1993	Remission	CDAI <150 and a reduction of \geq 50	CDAI
	Remission	PGA of disease severity	PGA
Rutgeerts 1994	Remission	CDAI <150	CDAI
	Response	CDAI <150 or CDAI 100	CDAI
Tremaine 1994	Response	CDAI <150 or CDAI 70	CDAI
	Disease relapse or worsening	CDAI increase of \geq 100 from baseline	CDAI
	Remission	CDAI <150 and CDAI 70	CDAI
Greenberg 1994	Remission	CDAI <150	CDAI
Jewell 1994	Corticosteroid-free response	Clinician grades response as clinically significant improvement and steroid withdrawal	PGA
	Disease relapse or worsening	Development of new fistula or abscess	

Reference	Outcome	Outcome measurement	Measurement tool
	Disease relapse or worsening	Need for additional therapy or surgery	
	Remission	Clinician grades response as freedom from clinical symptoms	PGA
Gross 1995	Remission	CDAI <150 and a reduction of >=60	CDAI
Middleton 1995	Remission	HBI <=3	HBI
Feagan 1995	Response	Mean CDAI score	CDAI
	Corticosteroid sparing	Mean daily prednisone dose	
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
Targan 1997	Response	CDAI 70	CDAI
Bar-Meir 1998	Response	CDAI <150 or decrease of >=60 with no steroid side effects	CDAI
	Response	CDAI <150 or decrease of >=60 with steroid side effects	CDAI
Colombel 1999	Remission	CDAI <150 and a reduction of >75	CDAI
Present 1999**	Response	Change in CDAI score	CDAI
	Response	Change in PDAI score	PDAI
	Fistula remission	Closure of all active draining anal fistulas at baseline	
	Fistula response	Reduction of 50% in draining fistula	
Sandborn 1999	Response	CDAI 70	CDAI
	Corticosteroid sparing	Mean daily prednisone dose	
	Corticosteroid sparing	Withdrawal of steroids	
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
	Response	Mean CDAI score	CDAI
	Remission	CDAI <150	CDAI
Verma 2000	Remission	CDAI <150 or CDAI 100, no bowel symptoms and normal CRP	CDAI
Fedorak 2000	Combined clinical and endoscopic remission	CDAI <150 and improvement or resolution in endoscopic appearance	CDAI and PGA
Schreiber 2000	Response	CDAI 100	CDAI
	Remission	CDAI <150 and CDAI 100	CDAI
Leiper 2001	Remission	CDAI <150	CDAI
	Response	CDAI 70	CDAI
	Response	HBI <=3	HBI
	Response	Change in VHAI score	VHAI
Gordon 2001	Remission	CDAI <150	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
	Disease relapse or worsening	Need for additional therapy	
	Response	Change in CDAI score	CDAI
Schreiber 2001	Remission	CDAI <150 and low dose corticosteroids	CDAI
	Corticosteroid sparing	Changes from baseline in daily steroids consumed	
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
Sandborn 2001¹⁴³	Fistula response	Reduction of 50% in draining fistula	
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Remission	CDAI <150	CDAI
Lomer 2001	Corticosteroid sparing	Median corticosteroid usage	
	Response	Mean CDAI score	CDAI
Hawkes 2001	Response	Change in CDAI score	CDAI
Sandborn 2001¹⁴⁶	Fistula remission	Closure of all draining fistulas	
	Fistula response	Reduction of 50% in draining fistula	
	Response	CDAI <150 or CDAI 70	CDAI
	Response	CDAI score	CDAI
	Remission	CDAI <150	CDAI
Carty 2001	Response	Mean CDAI score	CDAI
	Response	Mean HBI score	HBI
	Response	PGA of change in clinical condition	PGA
	Remission	CDAI <150	CDAI
Goodgame 2001	Disease relapse or worsening	Need for hospitalisation due to worsening Crohn's	
	Disease relapse or worsening	Need for surgery	
	Response	Change in HBI	HBI
Tremaine 2002	Response	CDAI 100	CDAI
	Remission	CDAI <150	CDAI
	Response	Change in CDAI score	CDAI
Steinhart 2002	Response	Change in CDAI score	CDAI
	Remission	CDAI <150	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
Yacyshyn 2002	Corticosteroid sparing	Corticosteroid use over time	
	Corticosteroid-free remission	CDAI <150 and no need for corticosteroids or immunosuppressives	CDAI
	Disease relapse or worsening	Withdrawal rates for disease progression or lack of efficacy	
	Response	CDAI 70	CDAI
	Response	Change in CDAI score	CDAI
	Remission	CDAI <150 and no increased or new corticosteroids, immunosuppressives or surgery	CDAI
Hommes 2002	Response	CDAI 70 and reduction of $\geq 25\%$ from baseline score	CDAI
	Remission	CDAI <150	CDAI
Arnold 2002	Remission	CDAI <150	CDAI
Sakurai 2002	Remission	CDAI 100 or reduction of 40% from baseline score	CDAI
Ardizzone 2003	Corticosteroid sparing	Mean cumulative steroid dose	
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
	Fistula remission	Closure of draining enterocutaneous and perianal fistulas	
Ghosh 2003	Response	Change in CDAI score	CDAI
	Response	CDAI 70	CDAI
	Remission	CDAI <150	CDAI
Ito 2004	Remission	CDAI <150	CDAI
	Response	CDAI 70	CDAI
Joos 2004	Remission	CDAI <150	CDAI
	Response	CDAI 150-160 (near remission)	CDAI
Herfarth 2004	Remission	CDAI <150	CDAI
	Response	Change in CDAI score	CDAI
Mannon 2004	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Sandborn 2004	Remission	CDAI <150	CDAI
	Fistula remission	Closure of all draining fistulas	
	Fistula response	Reduction of 50% in draining fistula	
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Mean CDAI score	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
West 2004**	Response	Change in PDAI score	PDAI
	Fistula response	Improvement on 3D-HPUS	3D-diagnostic ultrasound system (3D-HPUS)
Winter 2004	Fistula response	50% reduction in draining fistula	
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
Schreiber 2005	Response	CDAI score	CDAI
	Remission	CDAI <150	CDAI
	Remission	CDAI <150	CDAI
Lomer 2005	Response	CDAI 100	CDAI
	Response	CDAI decrease ≥ 60 from baseline	CDAI
	Response	CDAI score	CDAI
Korzenik 2005	Response	Change in VHAI score	VHAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Reinsich 2006	Response	CDAI 70	CDAI
	Remission	CDAI <150	CDAI
	Remission	CDAI <150	CDAI
Margalit 2006	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Prantera 2006	Remission	CDAI <150	CDAI
	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI increase of >100	CDAI
Schroder 2006	Response	CDAI 70	CDAI
	Remission	CDAI <150	CDAI
Hombres 2006	Corticosteroid sparing	Mean daily prednisolone dose	
	Remission	CDAI <150	CDAI
Hanauer 2006	Response	CDAI 100	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
Lemann 2006	Corticosteroid sparing	Median cumulative dose of prednisone	
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
Rutgeerts 2006	Disease relapse or worsening	Need for additional therapy	
	Response	Mean CDAI score	CDAI
	Remission	CDAI <150	CDAI
Sreiber 2006	Fistula response	Reduction of 50% in draining fistula	
	Response	CDAI 70	CDAI
	Response	Change in CDAI from baseline	CDAI
	Remission	CDAI <150	CDAI
Herrlinger 2006	Response	CDAI 100	CDAI
	Remission	CDAI <150	CDAI
Reinshagen 2007	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
Mansfield 2007	Remission	CDAI <150 and CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Mean change in CDAI score	CDAI
Sandborn 2007	Remission	CDAI <150	CDAI
	Fistula response	50% reduction in draining fistula	
	Fistula remission	Closure of all active draining fistulas at baseline	
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Change in CDAI from baseline	CDAI
Hafer 2007	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	Change in SAI score	SAI
Targan 2007	Sustained remission	CDAI <150 over a four week period	CDAI
	Sustained response	CDAI decrease of ≥ 70 for a four week period	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 70	CDAI
Omer 2007	Corticosteroid sparing	Average dose of corticosteroids	
	Response	CDAI 70 or reduction of $\geq 30\%$ from baseline score	CDAI
Hart 2007**	Response	Physician assessment of improvement of ulcers	

Reference	Outcome	Outcome measurement	Measurement tool
	Fistula response	50% reduction in draining fistula	
	Sustained fistula remission	Maintenance of fistula remission for at least 4 weeks	
	Complete response	Physician assessment of complete resolution of all ulcers	
Sandborn 2008	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70 or >=25%	CDAI
Leiper 2008	Remission	CDAI <150 and CDAI 70	CDAI
	Remission	HBI <=4	HBI
	Response	Change in VHAI score	VHAI
D'Haens 2008	Corticosteroid sparing	Daily dose of methylprednisolone	
	Corticosteroid-free remission	CDAI <150, withdrawal of corticosteroids and no surgery	CDAI
	Disease relapse or worsening	proportion given infliximab, methylprednisolone and antimetabolites	
	Disease relapse or worsening	CDAI increase of >=50 points	CDAI
	Response	Mean CDAI score	CDAI
Fukuda 2008**	Fistula response	50% reduction in draining fistula	
	Fistula remission	Closure of all active draining fistulas at baseline	
Feagan 2008	Disease relapse or worsening	Worsening clinical status and need for additional therapy	PGA
	Disease relapse or worsening	Worsening clinical status and CDAI increase of >=100	CDAI and PGA
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Remission	CDAI <150	CDAI
Thia 2009**	Response	Change in CDAI score	CDAI
	Response	Change in PDAI score	PDAI
	Fistula remission	Closure of all active draining anal fistulas at baseline	
	Fistula response	Reduction of 50% in draining fistula	
	Fistula response	Change in mean PGA score of fistula activity	PGA
	Sustained fistula remission	Maintenance of fistula remission for at least 4 weeks	
Dotan 2010	Remission	CDAI <150	CDAI
	Response	CDAI 70	CDAI
	Response	Change in Median CDAI	CDAI
	Response	Mean CDAI score	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
	Response	Median CDAI score	CDAI
Steed 2010	Remission	CDAI <150 or a reduction of ≥ 75	CDAI
Van der Woude 2010	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Maeda 2010	Response	Change in component of PDAI from baseline: degree of induration	PDAI
	Response	Change in component of PDAI from baseline: discharge	PDAI
	Response	Change in component of PDAI from baseline: pain / restriction of activities	PDAI
	Response	Change in component of PDAI from baseline: type of perianal disease	PDAI
	Response	Perianal Disease Activity Index (PDAI) - restriction of sexual activity	PDAI
	Response	Change in PDAI score	PDAI
Sands 2010	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Buchman 2010	Response	CDAI 100	CDAI
	Response	CDAI 100	CDAI
	Remission	CDAI <150	CDAI
	Remission	CDAI <150	CDAI
Krebs 2010	Response	CDAI 70 or reduction of $\geq 30\%$ from baseline score	CDAI
Tromm 2011	Remission	CDAI <150	CDAI
	Remission	PGA of therapeutic success	PGA
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	PGA of therapeutic benefit (category 1, 2, 3 or 4)	PGA
Sandborn 2011	Remission	CDAI <150	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI score	CDAI
	Response	Change in HBI from baseline	HBI
Benjamin 2011	Remission	CDAI <150	CDAI
	Response	CDAI 70	CDAI
	Response	Change in CDAI score	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
Smith 2011	Response	CDAI 70	CDAI
Prantera 2012	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI fail to decrease by at least 70 points from baseline	CDAI
	Disease relapse or worsening	CDAI increase of >100 from baseline	CDAI
	Sustained remission	CDAI <150 sustained for the length of the study	CDAI
	Remission	CDAI <150	CDAI
Hueber 2012	Response	CDAI 100	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Sands 2013	Response	Change in CDAI score	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Naftali 2013	Response	Change in CDAI from baseline	CDAI
	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Suzuki 2013	Remission	CDAI <150	CDAI
	Response	Change in CDAI score	CDAI
Brotherton 2014	Response	Mean pHBI score	pHBI
Sandborn 2014	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
Dewint 2014**	Fistula remission	100% reduction in draining fistula	
	Fistula response	50% reduction in draining fistula	
Reinisch 2014**	Response	Change in CDAI score	CDAI
	Fistula remission	Closure of all draining fistulas	
	Fistula response	Reduction of 50% in draining fistula	
Sands 2014	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
Dignass 2014	Remission	CDAI <150	CDAI
	Response	Mean CDAI score	CDAI
	Response	Change in PGA score	PGA

Reference	Outcome	Outcome measurement	Measurement tool
Bao 2014	Remission	CDAI <150	CDAI
	Disease relapse or worsening	CDAI decreased by <70 or increased CDAI	CDAI
	Response	CDAI 70	CDAI
D'Haens 2015	Remission	CDAI <150 and no treatment failures	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
Monteleone 2015	Remission	CDAI <150	CDAI
	Sustained remission	CDAI <150 maintained for at least 2 weeks	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Change in median CDAI	CDAI
	Response	Mean CDAI score	CDAI
Vande Casteele 2015	Disease relapse or worsening	Need for additional therapy	
	Sustained remission	HBI <=4 and CRP concentration of <=5mg/L throughout study	HBI
	Remission	HBI <=4 and CRP of <=5mg/L	HBI
Surgical induction (n=6)			
Maartense 2006	Post-operative recovery	Duration of hospital stay (days)	
	Post-operative recovery	Morphine requirement	
East 2007	Disease relapse or worsening	Time to repeat dilation or surgery	
McLeod 2009	Combined clinical and endoscopic recurrence	RES >=2 and need for additional therapy or surgery	Rutgeerts endoscopic score
Grimaud 2010**	Response	Occurrence of perianal abscess	
	Fistula remission	Absence of draining fistula, absence of perianal pain and absence of perianal abscess	
	Fistula response	Closure of 50% or more of draining anal fistulas	
Zurbuchen 2013	Recurrence	Need for additional surgery	
	Post-operative recovery	Duration of hospital stay (days)	
	Post-operative recovery	Time (days) to first postoperative stool	
Molendijk 2015**	Fistula response	Reduced number of draining fistulas	
	Response	MRI evaluation of fistula tracts	

Reference	Outcome	Outcome measurement	Measurement tool
	Response	Change in CDAI score	CDAI
	Response	Change in PDAI score	PDAI
Maintenance (n=65)			
Maintenance studies of medically induced remission (n=47)			
Singleton 1979	Response	Change in CDAI score	CDAI
	Disease relapse or worsening	Withdrawn early for severe exacerbation or drug toxicity	
	Disease relapse or worsening	Withdrawn early for surgery	
	Disease relapse or worsening	CDAI > 150 or >40% of initial CDAI	CDAI
	Sustained remission	CDAI <150 for the length of the study	CDAI
	Treatment compliance	Pill count	
	Remission	CDAI <150	CDAI
Malchow 1984	Disease relapse or worsening	Development of a new abscess	
	Disease relapse or worsening	Pending surgery for complication of Crohn's	
	Disease relapse or worsening	CDAI >150 requiring repetition of acute phase treatment	CDAI
	Disease relapse or worsening	CDAI increase of >100, no change or minimal reduction <60	CDAI
Bresci 1994	Disease relapse or worsening	CDAI >150 or increase >=100	CDAI
Feagan 1994	Response	Mean CDAI score	CDAI
	Corticosteroid sparing	Mean dose of prednisone and 5-aminosalicylates	
	Disease relapse or worsening	CDAI increase of >=100	CDAI
Schreiber 1994	Disease relapse or worsening	CDAI >150 and an increase of >=100 points	CDAI
	Sustained remission	CDAI <150 maintained for 12 months	CDAI
Stange 1995	Response	CDAI between 150 and 200	CDAI
	Response	HBI score	HBI
	Response	Change in Present score	Present score
	Response	Change in VHAI score	VHAI
	Disease relapse or worsening	CDAI >200	CDAI
	Remission	CDAI <150	CDAI
Belluzzi 1996	Disease relapse or worsening	CDAI >150 and an increase of >=100 points	CDAI
Greenberg 1996	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI >150 and an increase of >=60 points	CDAI
Sutherland 1997	Disease relapse or worsening	Investigator opinion of relapse	

Reference	Outcome	Outcome measurement	Measurement tool
	Disease relapse or worsening	Need for hospitalisation due to worsening Crohn's	
	Disease relapse or worsening	Need for introduction of corticosteroids	
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 60 points	CDAI
Ferguson 1998	Response	Mean CDAI score	CDAI
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 60 points	CDAI
Arora 1999	Disease relapse or worsening	Withdrew from study due to disease flare or failure to reduce prednisone dose	
Guslandi 2000	Disease relapse or worsening	CDAI >150 and an increase of ≥ 100 points	CDAI
Green 2001	Disease relapse or worsening	Moderate to severe symptoms with either high steroid dose or CDAI >200	
Mahmud 2001	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 60 points	CDAI
Cortot 2001	Response	Change in CDAI score	CDAI
	Disease relapse or worsening	Crohn's Disease Activity Index (CDAI)	CDAI
Hanauer 2002	Disease relapse or worsening	CDAI score >175 and an increase of ≥ 70 points or $\geq 35\%$	CDAI
	Remission	CDAI <150	CDAI
Mantzaris 2003	Response	Change in CDAI score	CDAI
Mantzaris 2003	Disease relapse or worsening	CDAI >150 and an increase of ≥ 100 points	CDAI
Keller 2004	Disease relapse or worsening	Failure of any drug treatment including immunosuppressants, with or without surgery	ECCDS
	Disease relapse or worsening	Failure of standard drug therapy, but effective immunosuppressive therapy	ECCDS
	Remission	Relapse-free course	ECCDS
Sands 2004**	Response	CDAI 70 or by 25% from start of >220	CDAI
	Response	CDAI score	CDAI
	Disease relapse or worsening	Study discontinuation due to perceived inefficacy	
	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	Recurrence of draining fistula	
Schultz 2004	Disease relapse or worsening	CDAI increased by >100 points	CDAI
	Sustained remission	CDAI <150 sustained for the length of the study	CDAI
Vilien 2004	Disease relapse or worsening	Need for additional therapy or surgery	

Reference	Outcome	Outcome measurement	Measurement tool
	Disease relapse or worsening	CDAI >150 or an increase of >=75 points	CDAI
Lemann 2005	Disease relapse or worsening	Need for surgery	
	Disease relapse or worsening	CDAI >250 or CDAI 150-250 and an increase of >=75 points from baseline	CDAI
Feagan 2005	Response	Median CDAI score	CDAI
	Corticosteroid sparing	Withdrawal of corticosteroids, no flare (CDAI >=220) and no study withdrawal	CDAI
	Disease relapse or worsening	CDAI >=220	CDAI
	Response	Mean CDAI score	CDAI
Hanauer 2005	Response	Change in CDAI score	CDAI
	Disease relapse or worsening	CDAI >150 and an increase of >=60 points or clinical deterioration	CDAI
Sandborn 2005	Sustained remission	CDAI <150 sustained for the length of the study	CDAI
	Sustained response	CDAI 70 sustained for the length of the study	CDAI
	Remission	CDAI <150	CDAI
Feagan 2006	Response	Mean CDAI score	CDAI
	Corticosteroid sparing	Withdrawal of corticosteroids and no flare (CDAI >220)	CDAI
	Disease relapse or worsening	Increase in steroids, total steroids taken	
	Fistula remission	Closure of all draining fistulas	
	Fistula response	Reduction of 50% in draining fistula	
Takagi 2006	Disease relapse or worsening	Need for additional therapy	
	Disease relapse or worsening	CDAI >200	CDAI
Colombel 2007	Remission	CDAI <150	CDAI
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
	Sustained corticosteroid-free remission	CDAI<150 and able to discontinue corticosteroid use for >=90days	CDAI
	Fistula remission	Closure of all fistulas that were draining at screening and baseline visits	
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
Sandborn 2007	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
Ng 2007	Response	HBI score	HBI
Schreiber 2007	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
De Jong 2007	Remission	CDAI <150	CDAI
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 60 points	CDAI
Selby 2007	Disease relapse or worsening	Need for additional therapy	
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 60 points	CDAI
	Remission	CDAI <150	CDAI
Feagan 2008	Response	Change in CDAI score	CDAI
	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 70 points	CDAI
Mantzaris 2009	Response	Mean CDAI score	CDAI
	Disease relapse or worsening	CDAI >150 and an increase of ≥ 100 points	CDAI
Rossi 2009	Response	Change in CDAI from baseline	CDAI
	Response	Number of fistulas including new ones and closure of existing ones	
	Disease relapse or worsening	CDAI >220 and increase of ≥ 70 and need for additional therapy	CDAI
Valentine 2009	Corticosteroid-free response	CDAI decrease of ≥ 100 points and withdrawal of corticosteroids	CDAI
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI
	Corticosteroid-free remission	CDAI score <150 and $\geq 25\%$ decrease and withdrawal of corticosteroids	CDAI
	Corticosteroid-free remission	CDAI score <150 and 100 point decrease and withdrawal of corticosteroids	CDAI
	Disease relapse or worsening	Mean daily corticosteroid use at study withdrawal	
	Disease relapse or worsening	Study withdrawal	
	Response	CDAI 100	CDAI
	Response	Change in mean CDAI	CDAI
	Remission	CDAI <150	CDAI
Sandborn 2010	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Mean CDAI score	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
Jorgensen 2010	Disease relapse or worsening	CDAI >150 and an increase of >=70 points	CDAI
Prantera 2011	Response	Change in CDAI score	CDAI
	Disease relapse or worsening	Study withdrawal due to disease deterioration	
	Disease relapse or worsening	CDAI >150 and an increase of >=60 points	CDAI
Holtmeier 2011	Response	Mean change in CDAI score	CDAI
	Disease relapse or worsening	Clinical need for introduction of corticosteroid therapy or hospitalisation for flare-up	
	Disease relapse or worsening	Investigator opinion of relapse	
	Disease relapse or worsening	Surgical intervention for stenosis, fistula or abscesses	
	Disease relapse or worsening	CDAI >150 and an increase of >=70 points	CDAI
	Sustained remission	CDAI <150 maintained for 12 months	CDAI
	Treatment compliance	Pill count	
Watanabe 2012	Remission	CDAI <150	CDAI
	Response	CDAI 100	CDAI
	Response	CDAI 70	CDAI
	Response	Change in CDAI from baseline	CDAI
	Response	Change in IOIBD from baseline	IOIBD
Keshav 2013	Remission	CDAI <150	CDAI
	Sustained remission	CDAI <150 sustained for the length of the study	CDAI
	Response	CDAI 100	CDAI
	Sustained response	CDAI 70 sustained for the length of the study	CDAI
	Response	CDAI 70	CDAI
Bourreile 2013	Response	Mean CDAI score	CDAI
	Disease relapse or worsening	Need for additional therapy or surgery	
	Disease relapse or worsening	Crohn's Disease Activity Index (CDAI)	CDAI
Jigaranu 2014	Sustained remission	CDAI <150 sustained for the length of the study	CDAI
	Sustained response	CDAI 100 sustained for the length of the study	CDAI
Feagan 2014	Sustained corticosteroid-free remission	CDAI <150 and withdrawal of prednisone for length of trial	CDAI
	Corticosteroid-free remission	CDAI <150 and withdrawal of corticosteroids	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
	Disease relapse or worsening	Failure to achieve CDAI<150 and total withdrawal of prednisone or failure to maintain CDAI <150 until the end of the study	CDAI
	Disease relapse or worsening	Failure to achieve CDAI<150 and total withdrawal of prednisone or failure to maintain CDAI <150 until the end of the study	CDAI
	Response	Mean change in CDAI score	CDAI
Wenzl 2015	Disease relapse or worsening	Development of one or more new fistula	
	Disease relapse or worsening	Need for additional surgery	
	Disease relapse or worsening	Need for steroids or anti-TNF	
	Disease relapse or worsening	CDAI >150 and an increase of >=60 points	CDAI
	Disease relapse or worsening	PDAI increase of >4 points	PDAI
	Response	CDAI score	CDAI
Maintenance studies of surgically induced remission (n=18)			
McLeod 1995	Combined clinical and endoscopic recurrence	Investigator assessment of disease activity and radiological or endoscopic evidence	
Ewe 1999	Response	Median CDAI score	CDAI
	Recurrence	Signs and symptoms characteristic of Crohn's	
	Recurrence	CDAI >200 and rise of 60 points	CDAI
Hellers 1999	Response	Mean CDAI score	CDAI
	Response	Change in PGA score	PGA
Lochs 2000	Recurrence	Development of one or more new fistula or septic complication	
	Recurrence	Need for additional surgery	
	Recurrence	CDAI >250	CDAI
	Recurrence	CDAI >200 and rise of 60 points	CDAI
Colombel 2001	Recurrence	Need for additional therapy	
Prantera 2002	Recurrence	CDAI >150	CDAI
Caprilli 2003	Recurrence	CDAI >150	CDAI
Hanauer 2004	Recurrence	Clinical recurrence grading scale	
Marteau 2006	Recurrence	CDAI >=200	CDAI
D'Haens 2008	Recurrence	CDAI >250	CDAI
Regueiro 2009	Recurrence	CDAI >200	CDAI
Reinisch 2010	Response	Mean CDAI change from baseline	CDAI

Reference	Outcome	Outcome measurement	Measurement tool
	Recurrence	CDAI \geq 200 and an increase of \geq 60	CDAI
Savarino 2013	Recurrence	CDAI $>$ 200	CDAI
Herfarth 2013	Recurrence	HBI score \geq 5 or an increase of 3 points since previous visit	HBI
Ren 2013	Response	Change in CDAI score	CDAI
	Combined clinical and endoscopic recurrence	RES \geq 2 and either symptoms and symptoms of Crohn's or CDAI $>$ 150, needing therapy or surgery	Rutgeerts endoscopic score and CDAI
Armuzzi 2013	Recurrence	HBI \geq 8	HBI
Fedorak 2015	Response	Mean CDAI score	CDAI
Zhu 2015	Recurrence	Need for additional therapy or surgery	

Note: CDAI, Crohn's disease activity index; IOIBD, International Organisation of Inflammatory Bowel Disease; HBI, Harvey Bradshaw Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PDAI, perianal disease activity index; **, study involved only patients with fistula.

Appendix table 8: Primary and Secondary Endoscopic Efficacy Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measure	Outcome measurement tool
Induction (n=13)			
Medical induction (n=10)			
Schreiber 2000	Endoscopic response	Change in CDEIS score from baseline	CDEIS
Reinsich 2006	Endoscopic response	Change in CDEIS score from baseline	CDEIS
Lemann 2006	Endoscopic response	Change in CDEIS score from baseline	CDEIS
Schreiber 2006	Endoscopic response	Change in CDEIS score from baseline	CDEIS
D'Haens 2008	Endoscopic mucosal healing	No ulcers identified	SES-CD
	Endoscopic response	Mean SES-CD severity score	SES-CD
Van der Woude 2010	Endoscopic response	Mean change in CDEIS score	CDEIS
Sands 2010	Endoscopic response	Change in CDEIS score from baseline	CDEIS
	Endoscopic response	Change in SES-CD score from baseline	SES-CD
Smith 2011	Endoscopic remission	CDEIS score <6	CDEIS
	Endoscopic response	CDEIS score <3	CDEIS
	Endoscopic response	CDEIS score decrease by ≥5	CDEIS
	Endoscopic response	Change in CDEIS score	CDEIS
Dignass 2014	Endoscopic mucosal healing	Complete mucosal healing: SES-CD score of 0	SES-CD
Bao 2014	Endoscopic response	CDEIS score	CDEIS
Surgical induction (n=3)			
McLeod 2009	Endoscopic recurrence	Rutgeerts endoscopic score ≥2	Rutgeerts endoscopic score
Zurbuchen 2013	Endoscopic recurrence	Rate of endoscopic recurrence	Rutgeerts endoscopic score
Molendijk 2015**	Endoscopic response	Change in CDEIS score	CDEIS
	Endoscopic response	Change in SES-CD score	SES-CD
Maintenance (n=22)			
Maintenance studies of medically induced remission (n=3)			

Reference	Outcome	Outcome measure	Outcome measurement tool
Malchow 1984	Endoscopic recurrence	Endoscopic or radiological results document a worsening of condition	
Selby 2007	Endoscopic response	Change in CDEIS score	CDEIS
Mantzaris 2009	Endoscopic mucosal healing	Change in endoscopic category of mucosal healing	D'Haens endoscopic categories
	Endoscopic response	Change in CDEIS score	CDEIS
Maintenance studies of surgically induced remission (n=19)			
Brignola 1995	Endoscopic recurrence	Rutgeerts endoscopic score >2	Rutgeerts endoscopic score
	Endoscopic recurrence	Rutgeerts endoscopic score >2 or radiological documentation of recurrence	Rutgeerts endoscopic score
	Endoscopic response	Mean Rutgeerts endoscopic score	Rutgeerts endoscopic score
McLeod 1995	Endoscopic recurrence	Rate of endoscopic or radiological recurrence	
Ewe 1999	Endoscopic recurrence	Rutgeerts endoscopic score >=2	Rutgeerts endoscopic score
Hellers 1999	Endoscopic recurrence	Rutgeerts endoscopic score >=2	Rutgeerts endoscopic score
Lochs 2000	Endoscopic recurrence	Rutgeerts score >=2	Rutgeerts endoscopic score
Colombel 2001	Endoscopic recurrence	Rutgeerts endoscopic score >0	Rutgeerts endoscopic score
Prantera 2002	Endoscopic recurrence	Rutgeerts endoscopic score >=2	Rutgeerts endoscopic score
	Endoscopic recurrence	Rutgeerts endoscopic score >2	Rutgeerts endoscopic score
Caprilli 2003	Endoscopic recurrence	Rutgeerts endoscopic score >0	Rutgeerts endoscopic score
	Endoscopic recurrence	Rutgeerts endoscopic score >2	Rutgeerts endoscopic score
Hanauer 2004	Endoscopic recurrence	Radiographic recurrence grading scale >=2	Radiographic grading scale
	Endoscopic recurrence	Rutgeerts endoscopic score >=2	Rutgeerts endoscopic score
Marteau 2006	Endoscopic recurrence	Colonic lesions endoscopic score >1	
	Endoscopic recurrence	Rutgeerts endoscopic score >1	Rutgeerts endoscopic score
	Endoscopic response	Maximum colonic lesions endoscopic score	
	Endoscopic response	Maximum Rutgeerts endoscopic score	Rutgeerts endoscopic score
D'Haens 2008	Endoscopic recurrence	Rutgeerts endoscopic score >=2	Rutgeerts endoscopic score
	Endoscopic recurrence	Rutgeerts endoscopic score >2	Rutgeerts endoscopic score

Reference	Outcome	Outcome measure	Outcome measurement tool
Regueiro 2009	Endoscopic recurrence	Rutgeerts endoscopic score ≥ 2	Rutgeerts endoscopic score
Reinisch 2010	Endoscopic mucosal healing	Median improvement in CDEIS score	CDEIS
	Endoscopic response	≥ 1 point improvement in Rutgeerts score	Rutgeerts endoscopic score
Savarino 2013	Endoscopic recurrence	Rutgeerts endoscopic score ≥ 2	Rutgeerts endoscopic score
Herfarth 2013	Endoscopic recurrence	Martean score $\geq c2$	Martean endoscopic score
	Endoscopic recurrence	Rutgeerts score ≥ 2	Rutgeerts endoscopic score
Ren 2013	Endoscopic recurrence	Rutgeerts endoscopic score ≥ 2	Rutgeerts endoscopic score
Ren 2013	Endoscopic response	Change in Rutgeerts endoscopic score	Rutgeerts endoscopic score
Armuzzi 2013	Endoscopic recurrence	Rutgeerts endoscopic score ≥ 2	Rutgeerts endoscopic score
Fedorak 2015	Endoscopic recurrence	Rutgeerts endoscopic score > 0	Rutgeerts endoscopic score
	Endoscopic recurrence	Rutgeerts endoscopic score > 2	Rutgeerts endoscopic score
Zhu 2015	Endoscopic recurrence	Rutgeerts endoscopic score ≥ 2	Rutgeerts endoscopic score

Note: CDEIS, Crohn's Disease Endoscopic Index of Severity; SES-CD, Simple Endoscopic Score for Crohn's disease;, study involved only patients with fistula.**

Appendix table 9: Primary and Secondary Histology Efficacy Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measure	Outcome measurement tool
Induction (n=5)			
Medical induction (n=5)			
Schreiber 2000	Tissue cytokine, leukocyte, receptor or gene expression	Total concentration of NFκB and IκBα cytokine	
Mannon 2004	Histologic response	D'Haens histologic score	D'Haens histological activity score
Mannon 2004	Tissue cytokine, leukocyte, receptor or gene expression	Mononuclear cell secretion of Interferon-γ cytokine	
Steed 2010	Tissue cytokine, leukocyte, receptor or gene expression	Change in mucosal TNF-alpha cytokines	
Smith 2011	Histologic response	Dieleman histological score	Dieleman histological score
Bao 2014	Histologic response	D'Haens histological activity score of biopsy	D'Haens histological activity score
Maintenance (n=6)			
Maintenance studies of medically induced remission (n=1)			
Mantzaris 2009	Histologic remission	Average histology score (AHS)	Average histology score (AHS)
Maintenance studies of surgically induced remission (n=5)			
Ewe 1999	Histologic recurrence	Histological score of 2 or 1 in conjunction with special findings	Histological Activity Score
Colombel 2001	Histologic recurrence	D'Haens histological activity score of biopsy	D'Haens histological activity score
Regueiro 2009	Histologic recurrence	D'Haens histological activity score and presence of neutrophils	D'Haens histological activity score
Armuzzi 2013	Histologic recurrence	Regueiro histology score of moderate to severe activity	Regueiro histology score
Fedorak 2015	Tissue cytokine, leukocyte, receptor or gene expression	Mucosal inflammatory cytokines expression	

Appendix table 10: Primary and Secondary Biomarker Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measure
Induction studies (n=39)		
Medical induction (n=38)		
Ewe 1993	Serum albumin	Serum albumin
	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum full blood count and subsets	Haematocrit
	Serum full blood count and subsets	Haemoglobin
	Serum full blood count and subsets	Platelet count
	Serum full blood count and subsets	White blood cell count
Greenberg 1994	Serum cortisol level	Plasma cortisol levels
	Serum C-reactive protein	Mean serum C-reactive protein concentration
	Serum protein concentrations	Mean serum orosomucoid concentration
Feagan 1995	Serum protein concentrations	Mean serum orosomucoid concentration
Hond 1999	Intestinal permeability	% of orally administered Cr-EDTA dose permeability
Sandborn 1999	Drug concentration and pharmacokinetics	Mean RBC 6TGN concentrations
	Serum full blood count and subsets	White blood cell count
Verma 2000	Serum C-reactive protein	C-reactive protein
Sandborn 2001	Antidrug antibodies	Presence of anti-drug antibodies
	Autoantibodies	Presence of other antibodies
Hawkes 2001	Serum C-reactive protein	Change in mean C-reactive protein concentrations
	Serum erythrocyte sedimentation rate	Change in mean erythrocyte sedimentation rate
Carty 2001	Serum C-reactive protein	Change in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum full blood count and subsets	Change in platelet count
	Serum protein concentrations	Change in orosomucoid concentration
Goodgame 2001	Intestinal permeability	Lactulose-mannitol test change from baseline
Tremaine 2002	Serum cortisol level	Plasma cortisol levels
Yacyshyn 2002	Drug concentration and pharmacokinetics	Plasma ISIS 2302 concentrations
Ardizzone 2003	Serum C-reactive protein	Decrease in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Ghosh 2003	Serum C-reactive protein	Mean change in C-reactive protein from baseline
Ito 2004	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum lymphocyte count and subset expression	Change in fibrinogen concentration from baseline
	Serum protein concentrations	Change in serum amyloid A protein from baseline
Sandborn 2004	Antidrug antibodies	Presence of anti-drug antibodies
	Serum C-reactive protein	Mean C-reactive protein concentrations
Winter 2004	Serum C-reactive protein	Mean C-reactive protein concentrations
Lomer 2005	Faecal calprotectin	Faecal calprotectin
	Intestinal permeability	% of intestinal permeability
	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate

Reference	Outcome	Outcome measure
Reinsich 2006	Antidrug antibodies	Presence of anti-drug antibodies
	Serum C-reactive protein	Median serum C-reactive protein change from baseline
Hommes 2006	Antidrug antibodies	Presence of anti-drug antibodies
	Drug concentration and pharmacokinetics	Serum fontolizumab concentrations
	Serum C-reactive protein	Mean C-reactive protein concentration change from baseline
Rutgeerts 2006	Serum C-reactive protein	C-reactive protein
Schreiber 2006	Serum C-reactive protein	Change in C-reactive protein concentration from baseline
Sandborn 2007	Serum C-reactive protein	Change in C-reactive protein
Leiper 2008	Serum C-reactive protein	Median serum C-reactive protein
D'Haens 2008	Serum C-reactive protein	Median serum C-reactive protein
Feagan 2008	Serum C-reactive protein	Change in serum C-reactive protein concentrations
Dotan 2010	Serum C-reactive protein	Mean change in C-reactive protein from baseline
Van der Woude 2010	Serum lymphocyte count and subset expression	T-cell receptor (TCR) modulation
Buchman 2010	Serum C-reactive protein	Mean change in serum C-reactive protein from baseline
	Serum full blood count and subsets	Mean change in peripheral blood WBC
	Serum full blood count and subsets	Mean change in platelet count from baseline
Sandborn 2011	Antidrug antibodies	Presence of anti-drug antibodies
	Drug concentration and pharmacokinetics	Serum certolizumab pegol concentrations
	Serum C-reactive protein	Change in C-reactive protein from baseline
Benjamin 2011	Faecal calprotectin	Change in faecal calprotectin
	Serum C-reactive protein	Change in C-reactive protein
Hueber 2012	Drug concentration and pharmacokinetics	Serum secukinumab concentrations
Naftali 2013	Serum C-reactive protein	Reduction of ≥ 0.5 mg C-reactive protein
Suzuki 2013	Serum cortisol level	Plasma cortisol levels
Brotherton 2014	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Bao 2014	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Monteleone 2015	Serum C-reactive protein	Change in C-reactive protein
	Serum cytokine or immunoglobulin levels	Complement activation
Vande Casteele 2015	Antidrug antibodies	Presence of anti-drug antibodies
	Drug concentration and pharmacokinetics	Serum infliximab concentrations
Surgical induction (n=1)		
Molendijk 2015**	Serum C-reactive protein	Changes in C-reactive protein
Maintenance studies (n=22)		
Maintenance studies of medically induced remission (n=16)		

Reference	Outcome	Outcome measure
Bresci 1994	Disease relapse or worsening	Laboratory index ≥ 100
Stange 1995	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum full blood count and subsets	Platelet count
	Serum protein concentrations	Serum orosomucoid concentration
Greenberg 1996	Serum cortisol level	Plasma cortisol levels
	Serum C-reactive protein	Serum C-reactive protein concentration
Ferguson 1998	Serum cortisol level	Plasma cortisol levels
Cortot 2001	Serum cortisol level	Plasma cortisol levels
Schultz 2004	Serum C-reactive protein	C-reactive protein
Vilien 2004	Serum albumin	Serum albumin
	Serum C-reactive protein	C-reactive protein
Feagan 2005	Antidrug antibodies	Presence of anti-drug antibodies
	Autoantibodies	Presence of other antibodies
	Serum C-reactive protein	Median C-Reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Hanauer 2005	Serum cortisol level	Change in plasma cortisol level
Feagan 2006	Serum C-reactive protein	Median serum C-reactive protein concentration
Selby 2007	Serum C-reactive protein	Change in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Garcia 2008	Intestinal permeability	Median urinary lactulose excretion
Rossi 2009	Antidrug antibodies	Presence of anti-drug antibodies
	Serum C-reactive protein	Change in C-reactive protein concentration from baseline
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Bourreile 2013	Serum C-reactive protein	Change in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum full blood count and subsets	Full blood count
Feagan 2014	Antidrug antibodies	Presence of anti-drug antibodies
	Drug concentration and pharmacokinetics	Median serum infliximab concentration
	Serum C-reactive protein	Median change in serum C-reactive protein concentration
Wenzl 2015	Serum C-reactive protein	Median C-reactive protein
	Serum full blood count and subsets	Mean serum haemoglobin
	Serum full blood count and subsets	Platelet count
Maintenance studies of surgically induced remission (n=5)		
Hellers 1999	Serum albumin	Change in serum albumin level
	Serum cortisol level	Plasma cortisol levels
	Serum C-reactive protein	Change in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
	Serum protein concentrations	Change in orosomucoid level
Colombel 2001	Antidrug antibodies	Presence of anti-drug antibodies
Regueiro 2009	Serum C-reactive protein	C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Reinisch 2010	Drug concentration and pharmacokinetics	TPMT and thiopurine metabolites activity
	Serum C-reactive protein	Mean C-reactive protein change from baseline
Ren 2013	Serum C-reactive protein	Change in C-reactive protein
	Serum erythrocyte sedimentation rate	Erythrocyte sedimentation rate
Note: Laboratory index: $-26+(1.3 \times \text{erythrocyte sedimentation rate})+(0.03 \times \text{white blood cell count})+(5.5 \times \text{C-reactive protein})+(0.08 \times \alpha 1\text{-antitrypsin})$		

Appendix table 11: Primary and Secondary Patient Reported Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measure	Outcome measurement tool
Induction studies (n=47)			
Medical induction (n=45)			
Singleton 1993	Defecation functions	Patient diary score of diarrhoea	
	Pain	Mean patient assessment of abdominal pain, diarrhoea and overall well-being	
	Quality of life	Mean patient assessment of abdominal pain, diarrhoea and overall well-being	
Greenberg 1994	Quality of life	Mean IBDQ score	IBDQ
Feagan 1995	Quality of life	Mean IBDQ score	IBDQ
Sandborn 1999	Quality of life	Mean IBDQ score	IBDQ
Verma 2000	Bowel symptoms	Patient report of bowel symptoms such as diarrhoea, rectal bleeding or pain	
Fedorak 2000	Quality of life	IBDQ score	IBDQ
Schreiber 2000	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Change in SF-36 physical scale score	SF-36
Leiper 2001	Quality of life	Improvement in IBDQ score	IBDQ
Schreiber 2001	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Median IBDQ score	IBDQ
Hawkes 2001	Defecation functions	Change in stool frequency	
	Pain	Change in abdominal pain	
	Quality of life	Change in Short-IBDQ score	Short-IBDQ
Sandborn 2001	Quality of life	IBDQ score	IBDQ
Carty 2001	Quality of life	Patient global assessment of changes in clinical condition	Patient Global Assessment
Tremaine 2002	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Change in SF-36 from baseline	SF-36
	Quality of life	Change in SF-36 mental component summary score from baseline	SF-36 MCS
	Quality of life	Change in SF-36 physical component summary score from baseline	SF-36 PCS
Steinhart 2002	Quality of life	Change in IBDQ from baseline	IBDQ
Ghosh 2003	Quality of life	Median IBDQ score	IBDQ

Reference	Outcome	Outcome measure	Outcome measurement tool
Ito 2004	Quality of life	Change in IBDQ from baseline	IBDQ
Joos 2004	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	VAS measure of general wellbeing score	Visual analogue scale
Sandborn 2004	Quality of life	Mean IBDQ score	IBDQ
Lomer 2005	Quality of life	IBDQ score	IBDQ
Korzenik 2005	Quality of life	Change in IBDQ from baseline	IBDQ
Reinsich 2006	Quality of life	Mean IBDQ score	IBDQ
Margalit 2006	Quality of life	Mean IBDQ score	IBDQ
Prantera 2006	Quality of life	Mean IBDQ score	IBDQ
Hanauer 2006	Quality of life	Change in IBDQ from baseline	IBDQ
Schreiber 2006	Quality of life	Change in IBDQ from baseline	IBDQ
Reinshagen 2007	Quality of life	Mean IBDQ score	IBDQ
Sandborn 2007	Quality of life	Change in IBDQ from baseline	IBDQ
Omer 2007	Quality of life	Decrease in HAMD score from baseline	Hamilton Depression Scale
Fukuda 2008**	Defecation functions	Patient diary score of faecal consistency	
	Pain	Change in symptom scores for perianal pain	
	Quality of life	Change in symptom scores for drainage amount (patient diary)	
Leiper 2008	Quality of life	Decrease in inflammatory bowel specific Quality of Life Index	IBD Quality of Life Index
D'Haens 2008	Quality of life	Mean IBDQ score	IBDQ
Feagan 2008	Quality of life	Change in IBDQ from baseline	IBDQ
Thia 2009**	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Change in mean Patient Global Assessment score	Patient Global Assessment
Dotan 2010	Quality of life	Change in median IBDQ	IBDQ
	Quality of life	Mean IBDQ score	IBDQ
	Quality of life	Median IBDQ	IBDQ
Maeda 2010	Pain	Change in perianal pain (VA-Scale) from baseline	Visual analogue scale
	Quality of life	Change in SF12 scores from baseline	SF-12
	Treatment acceptability	Patient global assessment of improvement (Likert scale)	Patient Global Assessment
Sands 2010	Quality of life	Change IBDQ score from baseline	IBDQ
Buchman 2010	Defecation functions	Mean change in number of liquid bowel movements	
	Treatment compliance	Patient diary and pill count	

Reference	Outcome	Outcome measure	Outcome measurement tool
Krebs 2010	Quality of life	Decrease in HAMD score from baseline	Hamilton Depression Scale
Sandborn 2011	Quality of life	IBDQ score >170	IBDQ
Benjamin 2011	Quality of life	Change in IBDQ from baseline	IBDQ
Naftali 2013	Quality of life	Improvement in SF-36 score of at least 50 points	SF-36
Brotherton 2014	Quality of life	Mean IBDQ score	IBDQ
Dignass 2014	Quality of life	SHS value	Short Health Scale
	Quality of life	Total GIQLI score	GIQLI
Bao 2014	Quality of life	IBDQ score	IBDQ
Surgical induction (n=2)			
Maartense 2006	Pain	Pain VAS score	Visual analogue scale
	Pain	SF-36 bodily pain score	SF-36 bodily pain score
	Quality of life	SF-36 emotional score	SF-36
	Quality of life	SF-36 General health perception score	SF-36 general health perception score
	Quality of life	SF-36 mental component scale score	SF-36 MCS
	Quality of life	SF-36 mental health score	SF-36 mental health score
	Quality of life	SF-36 physical component scale score	SF-36
	Quality of life	SF-36 physical function score	SF-36 physical function score
	Quality of life	SF-36 physical role score	SF-36
	Quality of life	SF-36 Social function score	SF-36 social function score
	Quality of life	SF-36 vitality score	SF-36 vitality score
	Quality of life	Total GIQLI score	GIQLI
Molendijk 2015**	Defecation functions	Changes in adapted Vaizey faecal incontinence score	Adapted Vaizey faecal incontinence score
	Quality of life	Change in SF-36 from baseline	SF-36
		Changes in short IBDQ score	Short-IBDQ
Maintenance studies (n=28)			
Maintenance studies of medically induced remission (n=24)			
Feagan 1994	Quality of life	Mean IBDQ score	IBDQ
Greenberg 1996	Quality of life	Mean IBDQ score	IBDQ
Sutherland 1997	Quality of life	Mean IBDQ score	IBDQ
Cortot 2001	Quality of life	Change in IBDQ from baseline	IBDQ

Reference	Outcome	Outcome measure	Outcome measurement tool
Mantzaris 2003	Quality of life	Change in IBDQ from baseline	IBDQ
Sands 2004**	Quality of life	IBDQ score	IBDQ
Keller 2004	Quality of life	Mean depression BDI score	BDI - depression score
	Quality of life	Mean PSKB score	PSKB
	Quality of life	Mean QL score	Quality of Life instrument
	Quality of life	Mean Trait anxiety STAI-X2 score	STAI-X2 - trait anxiety score
Feagan 2005	Quality of life	Median IBDQ score	IBDQ
Feagan 2006	Quality of life	Mean IBDQ score	IBDQ
Colombel 2007	Quality of life	Change in IBDQ from baseline	IBDQ
Sandborn 2007	Quality of life	Change in IBDQ from baseline	IBDQ
Ng 2007	Quality of life	IBD Stress Index Score	IBD Stress Index
	Quality of life	IBDQ score	IBDQ
Selby 2007	Quality of life	Change in Assessment of Quality of Life score	Assessment of Quality of Life Questionnaire
	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Change in SF-36 score	SF-36
Feagan 2008	Quality of life	Change in SF-36 from baseline	SF-36
Mantzaris 2009	Quality of life	Change in IBDQ from baseline	IBDQ
Rossi 2009	Quality of life	Change in IBDQ from baseline	IBDQ
Takagi 2009	Quality of life	Mean IBDQ score	IBDQ
Valentine 2009	Quality of life	Change in IBDQ from baseline	IBDQ
	Quality of life	Change in SF-36 score	SF-36
	Quality of life	Change in VAS score	EuroQOL-derived visual analogue scale
Holtmeier 2011	Quality of life	Change in IBDQ from baseline	IBDQ
Watanabe 2012	Quality of life	Change in SF-36 mental component summary score from baseline	SF-36 MCS
	Quality of life	Change in SF-36 physical component summary score from baseline	SF-36
	Quality of life	IBDQ score	IBDQ
Keefer 2012	Quality of life	Mean IBDQ score	IBDQ
	Quality of life	Mean IBD-SES score	IBD-SES
	Quality of life	Mean PSQ-R score	PSQ-R
	Treatment compliance	Mean MAS score	Medical Adherence Scale

Reference	Outcome	Outcome measure	Outcome measurement tool
Feagan 2014	Quality of life	Change in SF-36 from baseline	SF-36
Piche 2014	Bowel symptoms	IBS severity scoring system	IBS severity scoring system
	Quality of life	BDI severity of depression score	BDI
	Quality of life	FIS severity of fatigue score	Fatigue Impact Scale
	Quality of life	HAD severity of anxiety score	Hospital Anxiety and Depression Scale
	Quality of life	IBDQ score	IBDQ
Wenzl 2015	Quality of life	IBDQ score	IBDQ
Maintenance studies of surgically induced remission (n=4)			
Ewe 1999	Quality of life	Patient global assessment of wellbeing	Patient Global Assessment
Reinisch 2010	Quality of life	Mean IBDQ change from baseline	IBDQ
Savarino 2013	Quality of life	Mean IBDQ score	IBDQ
Fedorak 2015	Quality of life	Mean IBDQ score	IBDQ
<p>Note: IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, Short-Form 36; SF-36 MCS, SF-36 mental component summary score; SF-36 PCS, SF-36 physical component summary score; SF-12, Short-Form 12; GIQLI, Gastrointestinal Quality of Life Index; STAI-X2 State trait Anxiety Inventory instrument; PSKB, Psychiatric and Socio-communicative finding standardised clinical interview; BDI, Beck's Depression Inventory instrument; IBD-SES, Inflammatory Bowel Disease Self-Efficacy Scale; PSQ-R, Perceived Stress Questionnaire-Recent</p>			

Appendix table 12: Primary and Secondary Safety Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Outcome	Outcome measure
Induction studies (n=42)		
Medical induction (n=38)		
Wright 1993	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Corticosteroid-associated side effects
Rutgeerts 1994	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Corticosteroid-associated side effects
Greenberg 1994	Adverse events	Adverse events
Jewell 1994	Adverse events	Study withdrawal due to adverse events
	Death	Death due to Crohn's
Gross 1995	Adverse events	Adverse events
Bar-Meir 1998	Adverse events	Steroid side effects
Sandborn 1999	Adverse events	Adverse events
Fedorak 2000	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Schreiber 2000	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Schreiber 2001	Adverse events	Adverse events
Sandborn 2001 (1737)	Adverse events	Adverse events
Steinhart 2002	Adverse events	Adverse drug reactions
Yacyshyn 2002	Adverse events	Adverse events
Hommes 2002	Adverse events	Adverse events
	Adverse events	Stopping medication because of adverse events
Ardizzone 2003	Abnormal laboratory or ECG parameters	Abnormal laboratory or ECG parameters
	Adverse events	Adverse events
Herfarth 2004	Adverse events	Steroid-associated side effects
Mannon 2004	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Sandborn 2004	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Winter 2004	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
Winter 2004	Adverse events	Adverse events, serious adverse events, infusion reactions and treatment related adverse events
Reinsich 2006	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Prantera 2006	Abnormal laboratory or ECG parameters	Abnormal laboratory or ECG parameters
Schroder 2006	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Hommes 2006	Adverse events	Adverse events
Lemann 2006	Adverse events	Adverse events

Reference	Outcome	Outcome measure
	Adverse events	Steroid side effect score
Reinshagen 2007	Adverse events	AZA related side effects
Feagan 2008	Adverse events	Adverse events
Van der Woude 2010	Adverse events	Adverse events
Buchman 2010	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Tromm 2011	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Prantera 2012	Adverse events	Adverse events
Sands 2013	Adverse events	Adverse events
Suzuki 2013	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
Sandborn 2013	Adverse events	Adverse events
Reinisch 2014**	Adverse events	Treatment-related adverse events
Dignass 2014	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Bao 2014	Abnormal laboratory or ECG parameters	Haemoglobin
D'Haens 2015	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Monteleone 2015	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Surgical induction (n=4)		
Maartense 2006	Adverse events	Post-operative complications: minor and major
	Complications of surgery	Mean blood loss
	Complications of surgery	Mean operating time (min)
	Complications of surgery	Number of conversions to open surgery
	Death	Mortality
Mcleod 2009	Adverse events	Post-operative complications: minor and major
	Complications of surgery	Mean time to complete anastomosis (min)
Grimaud 2010**	Adverse events	Adverse events
Molendijk 2015**	Adverse events	Incidence of surgical interventions and infections
	Adverse events	Serious adverse events
Maintenance studies (n=22)		
Maintenance studies of medically induced remission (n=17)		
Malchow 1984	Adverse events	Adverse events
	Adverse events	Prolonged fever
	Death	Death due to Crohn's
Greenberg 1996	Adverse events	Adverse events
Ferguson 1998	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse corticosteroid-associated effects
Arora 1999	Adverse events	Withdrew from study due to side effects
Cortot 2001	Adverse events	Corticosteroid-associated side effects
Hanauer 2002	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters

Reference	Outcome	Outcome measure
	Adverse events	Adverse events, serious adverse events and infections
Mantzaris 2003	Adverse events	Time to discontinuation of study drug
Schultz 2004	Adverse events	Possible side effects of the study medication
De Jong 2007	Adverse events	Adverse events and corticosteroid-associated side effects
Selby 2007	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Feagan 2008	Adverse events	Adverse events
Mantzaris 2009	Adverse events	Adverse events
Rossi 2009	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events and serious adverse events
Valentine 2009	Adverse events	Adverse events
Prantera 2011	Adverse events	Adverse events
Keshav 2013	Adverse events	Adverse events, serious adverse events and withdrawals due to adverse events
Feagan 2014	Adverse events	Adverse events
Maintenance studies of surgically induced remission (n=5)		
Hellers 1999	Adverse events	Corticosteroid-associated side effects
Colombel 2001	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
D'Haens 2008	Adverse events	Adverse events
Reinisch 2010	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events
Herfarth 2013	Abnormal laboratory or ECG parameters	Abnormal laboratory parameters or ECG parameters
	Adverse events	Adverse events

Appendix table 13: Reporting of Safety Outcomes in Crohn's Disease Randomised Controlled Trials

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to: Adverse events	Treatment failure	Various reasons
Induction studies							
Medical induction studies							
Greenberg 1988	x		x			x	
Wright 1990							
Rigaud 1991						x	
Ewe 1993	x				x	x	
Singleton 1993	x		x		x	x	x
Wright 1993	x		x		x	x	x
Greenberg 1994	x		x		x	x	x
Jewell 1994	x	x	x		x	x	x
Royall 1994							
Rutgeerts 1994		x	x		x	x	x
Tremaine 1994	x				x	x	
Feagan 1995	x		x		x	x	
Gross 1995	x				x	x	x
Mansfield 1995						x	x
Middleton 1995							x
Frascio 1997						x	x
Targan 1997	x	x	x				
Bar-Meir 1998		x	x		x	x	x
Colombel 1999	x				x	x	x
D'Haens 1999	x						
Hond 1999							
Present 1999**	x	x	x		x	x	x
Sandborn 1999	x	x	x		x	x	x
Fedorak 2000	x	x	x		x	x	x
Schreiber 2000	x	x	x		x		x

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Verma 2000							
Carty 2001	x	x			x	x	x
Goodgame 2001	x						
Gordon 2001	x				x		x
Hawkes 2001			x		x		x
Leiper 2001						x	x
Lomer 2001	x				x		x
Sandborn 2001	x	x	x		x	x	x
Sandborn 2001	x	x	x		x	x	x
Schreiber 2001	x	x		x	x		
Arnold 2002	x				x		x
Hommes 2002	x		x		x	x	
Sakurai 2002							
Steinhart 2002	x	x	x		x	x	x
Tremaine 2002	x	x	x		x	x	x
Yacyshyn 2002	x	x	x	x	x	x	
Ardizzone 2003	x		x		x		
Bamba 2003	x					x	x
Ghosh 2003	x	x	x	x	x	x	x
Herfarth 2004		x	x				
Ito 2004	x	x		x	x	x	x
Joos 2004	x	x			x	x	x
Mannon 2004	x	x	x		x		
Sandborn 2004	x	x	x		x		
West 2004**	x		x		x		
Winter 2004	x	x	x		x	x	x
Korzenik 2005	x	x	x	x	x	x	x
Lomer 2005							x
Schreiber 2005	x	x	x	x	x	x	

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Hanauer 2006	x	x	x		x		
Herrlinger 2006	x	x	x		x	x	x
Hommel 2006	x	x					
Lemann 2006	x	x	x	x			
Margalit 2006			x			x	x
Prantera 2006	x	x	x	x	x		
Reinsich 2006	x	x	x				
Rutgeerts 2006	x		x				
Schreiber 2006	x	x		x		x	x
Schroder 2006	x	x	x		x	x	
Hafer 2007	x		x				
Hart 2007**	x		x		x		
Mansfield 2007	x	x	x	x	x	x	x
Omer 2007							
Reinshagen 2007	x						
Sandborn 2007	x	x	x	x	x		x
Targan 2007	x	x	x	x	x		
D'Haens 2008	x	x	x		x		x
Feagan 2008	x	x	x	x			
Fukuda 2008**	x	x			x		x
Leiper 2008	x				x	x	x
Sandborn 2008	x	x	x		x		
Thia 2009**	x		x		x		x
Buchman 2010	x	x	x	x	x	x	x
Dotan 2010	x		x		x		
Krebs 2010						x	
Maeda 2010	x	x					
Sands 2010	x	x	x		x	x	x
Steed 2010	x						x

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Van der Woude 2010	x	x	x	x	x		
Benjamin 2011	x	x				x	
Sandborn 2011	x	x	x	x	x		
Smith 2011	x		x				
Tromm 2011	x		x	x	x		
Hueber 2012	x	x		x	x	x	x
Prantera 2012	x	x	x	x	x		
Naftali 2013	x					x	
Sandborn 2013	x	x	x		x		x
Sands 2013	x	x	x	x	x		
Suzuki 2013	x	x	x	x	x		
Bao 2014	x	x	x			x	x
Brotherton 2014							
Dewint 2014**	x	x			x	x	x
Dignass 2014	x	x	x	x	x		
Reinisch 2014**	x	x			x	x	
Sandborn 2014	x	x	x	x	x		
Sands 2014	x	x	x	x	x		
D'Haens 2015	x	x			x	x	x
Monteleone 2015	x	x					
Vande Casteele 2015	x	x	x		x	x	x
Surgical induction studies							
Maartense 2006	x		x				
East 2007							
Mcleod 2009							
Grimaud 2010**	x	x					
Zurbuchen 2013			x				
Molendijk 2015**	x		x				
Maintenance studies							

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Maintenance studies of medically induced remission							
Singleton 1979	x		x		x	x	x
Malchow 1984	x	x	x		x		x
Levenstein 1985	x						
Bresci 1994	x						x
Feagan 1994	x				x		x
Schreiber 1994	x				x		x
Stange 1995	x	x			x	x	x
Belluzzi 1996	x				x		x
Greenberg 1996	x		x		x	x	
Sutherland 1997	x		x		x		
Ferguson 1998	x		x		x	x	x
Arora 1999	x				x	x	x
Guslandi 2000							
Cortot 2001	x	x	x	x	x	x	x
Green 2001	x	x	x	x	x	x	x
Mahmud 2001	x		x	x	x	x	x
Hanauer 2002	x	x	x	x	x	x	x
Mantzaris 2003	x		x		x	x	
Keller 2004							
Sands 2004**	x	x	x		x		
Schultz 2004	x		x		x		
Vilien 2004							
Feagan 2005	x	x	x		x		
Hanauer 2005			x		x	x	x
Lemann 2005	x						
Sandborn 2005	x	x	x	x	x		
Feagan 2006	x	x	x		x		
Takagi 2006	x						x

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Colombel 2007	x	x	x		x		
De Jong 2007	x	x	x	x		x	x
Ng 2007							
Sandborn 2007	x	x	x		x		
Schreiber 2007	x	x	x	x	x		
Selby 2007	x	x			x		x
Feagan 2008	x				x	x	x
Garcia 2008	x				x		
Mantzaris 2009	x		x				
Rossi 2009	x	x	x	x	x		
Takagi 2009							
Valentine 2009	x	x	x	x	x	x	
Jorgensen 2010	x		x				
Sandborn 2010	x	x	x	x	x	x	
Holtmeier 2011	x	x	x				
Prantera 2011	x		x		x	x	x
Keefer 2012							
Watanabe 2012	x	x	x		x		
Bourreile 2013	x	x	x	x			
Keshav 2013	x	x			x	x	x
Feagan 2014	x	x	x				
Jigarano 2014							x
Piche 2014	x		x				
Wenzl 2015	x		x		x		x
Maintenance studies of surgically induced remission							
Brignola 1995	x				x		
McLeod 1995			x		x		
Ewe 1999		x	x		x		
Hellers 1999	x	x	x		x	x	x

Reference	Adverse events	Serious adverse events	Treatment related adverse events	Treatment related serious adverse events	Discontinuation due to:		Various reasons
					Adverse events	Treatment failure	
Lochs 2000	x	x		x			
Colombel 2001	x	x			x		
Prantera 2002	x		x		x	x	x
Caprilli 2003	x				x	x	x
Hanauer 2004	x	x			x	x	x
Marteanu 2006	x		x		x		x
D'Haens 2008	x				x	x	x
Regueiro 2009	x		x		x		
Reinisch 2010	x	x	x	x	x	x	
Armuzzi 2013	x		x		x		
Herfarth 2013	x	x	x		x		x
Ren 2013	x	x			x		x
Savarino 2013	x					x	
Fedorak 2015	x	x	x		x		x
Zhu 2015	x		x		x	x	x

Note: Discontinuation of treatment due to treatment failure, insufficient therapeutic effect, exacerbation of Crohn's, development of complications of Crohn's, need for additional therapy or surgery, etc.; Discontinuation of treatment due to various reasons, Protocol non-compliance, lost to follow up, prohibited medication use, withdrawal of consent, etc.

Appendix table 14: Safety-related outcomes in Crohn's disease Randomised Controlled Trials, by most commonly reported MedDRA SOCs

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Induction studies												
Medical induction studies												
Greenberg 1988	x			x					x			
Wright 1990												
Rigaud 1991												
Ewe 1993	x			x		x	x					
Singleton 1993	x	x	x	x		x	x	x			x	
Wright 1993	x			x			x				x	
Greenberg 1994	x	x	x		x		x				x	
Jewell 1994	x	x		x	x		x		x			
Royall 1994												
Rutgeerts 1994	x	x	x		x	x	x	x			x	
Tremaine 1994	x	x	x		x		x				x	
Feagan 1995	x	x	x	x	x	x	x					
Gross 1995	x				x							
Mansfield 1995												
Middleton 1995												

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Frascio 1997												
Targan 1997	x	x	x	x	x	x	x		x			
Bar-Meir 1998	x	x			x		x	x	x	x		
Colombel 1999												
D'Haens 1999	x			x					x			
Hond 1999												
Present 1999**	x	x	x	x	x	x						
Sandborn 1999	x	x	x	x	x	x	x	x				
Fedorak 2000	x	x	x	x	x	x	x	x		x	x	
Schreiber 2000	x	x	x	x	x	x		x				
Verma 2000												
Carty 2001	x						x					
Goodgame 2001	x								x			
Gordon 2001	x	x				x		x	x			
Hawkes 2001	x	x	x				x					
Leiper 2001												
Lomer 2001	x							x		x		
Sandborn 2001	x	x	x	x	x	x	x				x	x

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Sandborn 2001	x	x	x				x	x				
Schreiber 2001	x	x	x		x		x		x			
Arnold 2002	x			x	x		x	x	x			
Hommes 2002	x	x	x	x		x	x	x				
Sakurai 2002												
Steinhart 2002	x	x	x	x	x	x	x					
Tremaine 2002	x	x	x	x	x		x	x		x		
Yacyshyn 2002	x	x	x	x	x	x	x				x	
Ardizzone 2003	x	x	x			x		x				
Bamba 2003												
Ghosh 2003	x	x	x	x	x	x	x		x		x	
Herfarth 2004					x							
Ito 2004	x	x	x	x		x				x		
Joos 2004	x	x	x		x			x	x			
Mannon 2004	x	x	x	x	x	x			x	x		x
Sandborn 2004	x	x	x	x	x	x	x				x	x

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
West 2004**	x	x		x	x		x				x	
Winter 2004	x	x	x	x	x		x				x	
Korzenik 2005	x	x	x	x	x	x		x		x		
Lomer 2005												
Schreiber 2005	x	x	x	x	x	x	x	x				x
Hanauer 2006	x	x	x	x		x						x
Herrlinger 2006	x	x	x	x	x		x	x				
Hommel 2006	x	x	x	x	x	x			x			x
Lemann 2006	x	x	x	x	x	x	x				x	
Margalit 2006												
Prantera 2006	x	x	x	x	x	x	x		x	x		
Reinsich 2006	x	x	x		x	x						
Rutgeerts 2006	x	x	x	x	x	x		x				x
Schreiber 2006	x	x	x	x	x	x	x					
Schroder 2006		x	x	x		x	x					x

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Hafer 2007	x											
Hart 2007**			x	x			x					
Mansfield 2007	x	x	x			x	x	x				
Omer 2007												
Reinshagen 2007	x		x		x							
Sandborn 2007	x	x	x	x	x	x				x		x
Targan 2007	x	x	x	x		x	x				x	x
D'Haens 2008	x	x	x	x	x	x	x	x	x	x		
Feagan 2008	x	x	x	x		x		x				x
Fukuda 2008**	x		x			x						
Leiper 2008	x	x		x								
Sandborn 2008	x	x	x	x	x	x	x				x	x
Thia 2009**	x	x		x	x							
Buchman 2010	x	x	x	x	x	x		x		x		x
Dotan 2010	x	x	x	x	x	x	x	x				
Krebs 2010												
Maeda 2010	x	x	x	x					x			x
Sands 2010	x	x	x	x	x					x		
Steed 2010		x	x									

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Van der Woude 2010	x	x	x	x	x	x	x			x		x
Benjamin 2011	x										x	
Sandborn 2011	x	x	x	x	x	x		x			x	x
Smith 2011	x	x	x	x		x	x			x		
Tromm 2011	x	x	x	x	x	x	x			x		
Hueber 2012	x	x	x	x	x	x		x		x		
Prantera 2012	x	x	x	x		x						
Naftali 2013	x	x	x									
Sandborn 2013	x	x		x	x				x	x	x	
Sands 2013	x	x	x	x		x			x		x	
Suzuki 2013	x		x	x		x	x	x		x	x	
Bao 2014			x								x	
Brotherton 2014												
Dewint 2014**	x	x	x	x							x	
Dignass 2014	x	x		x								
Reinisch 2014**	x	x	x	x	x		x					
Sandborn 2014	x	x	x	x		x						

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Sands 2014	x	x	x	x	x	x		x				x
D'Haens 2015	x	x	x		x	x						
Monteleone 2015	x	x	x	x	x	x			x		x	
Vande Castele 2015	x	x	x	x	x	x	x		x		x	
Surgical induction studies												
Maartense 2006	x		x	x					x		x	
East 2007												
Mcleod 2009												
Grimaud 2010**				x								
Zurbuchen 2013				x					x		x	
Molendijk 2015**	x	x	x	x	x	x	x		x	x	x	x
Maintenance studies												
Maintenance studies of medically induced remission												
Singleton 1979	x	x		x	x		x	x		x		
Malchow 1984	x	x	x	x	x		x	x		x		

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Levenstein 1985	x		x		x				x		x	
Bresci 1994	x		x						x			
Feagan 1994		x	x			x	x					x
Schreiber 1994			x									
Stange 1995	x	x		x	x	x	x					
Belluzzi 1996	x											
Greenberg 1996	x	x	x				x	x		x		
Sutherland 1997	x	x	x	x	x	x						
Ferguson 1998	x				x	x	x	x	x	x		
Arora 1999			x	x		x						
Guslandi 2000												
Cortot 2001	x	x	x		x	x	x		x			
Green 2001	x	x	x	x	x	x	x					
Mahmud 2001	x				x							
Hanauer 2002	x	x	x	x	x	x	x		x		x	x
Mantzaris 2003	x	x		x	x		x					
Keller 2004												

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Sands 2004**	x	x	x	x	x	x			x			x
Schultz 2004	x			x					x			
Vilien 2004												
Feagan 2005	x	x	x	x	x	x	x		x			x
Hanauer 2005		x			x		x	x		x		
Lemann 2005			x				x	x				x
Sandborn 2005	x	x	x	x	x	x	x				x	
Feagan 2006	x	x	x	x	x	x	x	x	x		x	x
Takagi 2006	x										x	
Colombel 2007	x	x	x	x	x							x
De Jong 2007	x	x	x	x	x		x		x	x	x	
Ng 2007												
Sandborn 2007	x	x	x	x	x	x						x
Schreiber 2007	x	x	x	x	x	x		x			x	x
Selby 2007	x			x	x	x						
Feagan 2008	x	x	x	x	x	x						
Garcia 2008	x											
Mantzaris 2009	x	x		x		x	x	x				
Rossi 2009	x	x	x	x	x	x	x	x		x		

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Takagi 2009												
Valentine 2009	x	x	x	x	x	x	x		x	x		
Jorgensen 2010	x									x		
Sandborn 2010	x	x	x	x	x							x
Holtmeier 2011	x	x	x	x	x	x	x	x		x		
Prantera 2011	x	x	x	x	x	x	x	x				
Keefer 2012												
Watanabe 2012	x	x	x	x	x	x				x		x
Bourreile 2013	x			x	x							
Keshav 2013	x	x	x	x	x	x						
Feagan 2014	x	x	x	x	x	x	x	x	x		x	x
Jigaranu 2014												
Piche 2014			x									
Wenzl 2015	x	x	x	x	x	x		x	x	x	x	x
Maintenance studies of surgically induced remission												
Brignola 1995	x					x	x					
McLeod 1995	x	x					x					

Reference	Gastro-intestinal disorders	Nervous system disorders	General disorders and administration conditions	Infections and infestations	Musculo-skeletal and connective tissue disorders	Investigations	Skin and sub-cutaneous tissue disorders	Blood and lymphatic system disorders	Surgical and medical procedures	Metabolism and nutrition disorders	Injury, poisoning and procedural complications	Neoplasms benign, malignant and unspecified
Ewe 1999	x	x				x	x		x			
Hellers 1999	x	x		x	x	x	x	x		x		
Lochs 2000	x	x	x	x			x				x	x
Colombel 2001	x	x	x		x	x		x	x		x	
Prantera 2002	x			x		x	x					
Caprilli 2003	x		x		x	x			x			x
Hanauer 2004	x	x			x	x	x	x	x			
Marteau 2006	x		x									x
D'Haens 2008	x	x		x	x	x	x					
Regueiro 2009	x		x	x	x	x	x					
Reinisch 2010	x	x	x	x	x	x		x	x	x	x	
Armuzzi 2013	x								x		x	
Herfarth 2013				x					x		x	
Ren 2013	x					x		x				
Savarino 2013	x	x	x	x	x	x	x		x			
Fedorak 2015	x		x	x					x		x	

Appendix 6: Additional tables for Chapter 3

Appendix table 15: Outcomes measured in Crohn's disease trials in adults identified by systematic review, listed by frequency of reporting

Outcome	Studies measuring outcome	
	No.	% (of 181)
Abdominal pain	169	93.4%
Faecal consistency	169	93.4%
Fistula / fissure / abscess	168	92.8%
Frequency of defecation	168	92.8%
Abdominal mass	164	90.6%
Wellbeing	164	90.6%
Arthralgia	163	90.1%
Extra-intestinal lesions	163	90.1%
Fever	163	90.1%
Arthritis	162	89.5%
Need for additional steroids, therapy or surgery	162	89.5%
Uveitis	162	89.5%
Body mass	157	86.7%
Blood abnormalities	156	86.2%
Inflammation	100	55.2%
Depression	83	45.9%
Energy levels	82	45.3%
Happy	82	45.3%
Relaxed	82	45.3%
Condition affects attending events	82	45.3%
Condition affects leisure or sports activities	82	45.3%
Condition prevents going out	82	45.3%
Activities limited due to health problems (education)	82	45.3%
Activities limited due to health problems (work and employment)	82	45.3%
Appetite	78	43.1%
Blood with stool	78	43.1%
Faecal continence	78	43.1%
Flatulence	78	43.1%
Nausea	78	43.1%
Abdominal bloating	77	42.5%
Angry	77	42.5%
Embarrassment	77	42.5%
Feel lack of sympathy	77	42.5%
Feeling generally well	77	42.5%
Frustration	77	42.5%
Irritable	77	42.5%
Needing to keep close to a toilet	77	42.5%
Needing to rush to the toilet	77	42.5%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Sex life affected	77	42.5%
Unable to sleep	77	42.5%
Upset	77	42.5%
Wanting to go back to the toilet	77	42.5%
Worries about being admitted to hospital	77	42.5%
Worry	77	42.5%
Lesions / ulcers	63	34.8%
Perceived tolerability of treatment	57	31.5%
Disease activity	25	13.8%
Withdrawal or tapered steroids	22	12.2%
Steroid dose	19	10.5%
Anxiety	16	8.8%
Bodily pain	15	8.3%
Absorption of nutrients	14	7.7%
Bathing or dressing yourself	14	7.7%
Bending, kneeling or stooping	14	7.7%
Climbing stairs	14	7.7%
Condition interferes with social life	14	7.7%
Lifting or carrying groceries	14	7.7%
Moderate activities	14	7.7%
Patient perception of health	14	7.7%
Vigorous activities	14	7.7%
Walking	14	7.7%
Perianal pain	12	6.6%
Fistula discharge	10	5.5%
General quality of life	10	5.5%
Perianal disease	10	5.5%
Perianal induration	10	5.5%
Restriction of sexual activity	10	5.5%
Resection	7	3.9%
Temperature	7	3.9%
Intestinal permeability	6	3.3%
Need for hospitalisation	6	3.3%
Prolonged fever	4	2.2%
Calorie intake	3	1.7%
Costs of health care	3	1.7%
Faecal output	3	1.7%
Death due to Crohn's	2	1.1%
Liver function	2	1.1%
Maintenance of full oral diet	2	1.1%
Pancreas function	2	1.1%
Utility	2	1.1%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Ability to cope with the disease	1	0.6%
Acid reflux	1	0.6%
Defecation functions	1	0.6%
Diarrhoea	1	0.6%
Improvement in psychological status	1	0.6%
Influence on interpersonal relationships	1	0.6%
Perceived credibility of treatment	1	0.6%
Perceived efficacy of treatment	1	0.6%
Perceived stress	1	0.6%
Return to full diet	1	0.6%
Return to liquid diet	1	0.6%
Rumbling gut	1	0.6%
Vomiting	1	0.6%

Appendix table 16: Adverse events reported in Crohn's disease trials in adults identified by systematic review, listed by frequency of reporting

Outcome	Studies measuring outcome	
	No.	% (of 181)
Discrete adverse events		
Abdominal pain	102	56.4%
Headache	96	53.0%
Crohn's disease	89	49.2%
Nausea	88	48.6%
Vomiting	67	37.0%
Diarrhoea	59	32.6%
Arthralgia	58	32.0%
Pyrexia	56	30.9%
Infection	53	29.3%
Death	48	26.5%
Fatigue	37	20.4%
Nasopharyngitis	35	19.3%
Drug specific antibody present	33	18.2%
Anal abscess	33	18.2%
Rash	31	17.1%
Dizziness	29	16.0%
Acne	28	15.5%
Upper respiratory tract infection	27	14.9%
Back pain	24	13.3%
Intestinal obstruction	22	12.2%
Urinary tract infection	21	11.6%
Hospitalisation	21	11.6%
Injection site reaction	20	11.0%
Cushingoid	20	11.0%
Pneumonia	20	11.0%
Myalgia	19	10.5%
Dyspepsia	18	9.9%
Asthenia	18	9.9%
Insomnia	17	9.4%
Flatulence	17	9.4%
Influenza	17	9.4%
Pain	16	8.8%
Abdominal distension	16	8.8%
Abscess	16	8.8%
Anaemia	15	8.3%
Opportunistic infection	15	8.3%
Pancreatitis	14	7.7%
Injection site pain	13	7.2%
Infusion related reaction	13	7.2%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Leukopenia	13	7.2%
Pruritus	13	7.2%
Surgery	13	7.2%
Depression	12	6.6%
Cough	12	6.6%
Alopecia	12	6.6%
Neoplasm malignant	12	6.6%
Tuberculosis	12	6.6%
Decreased appetite	11	6.1%
Abdominal pain upper	11	6.1%
Hypersensitivity	11	6.1%
Alanine aminotransferase increased	11	6.1%
Chills	11	6.1%
Fistula	11	6.1%
Double stranded DNA antibody	10	5.5%
Transaminases increased	10	5.5%
Hirsutism	10	5.5%
Sinusitis	10	5.5%
Viral infection	10	5.5%
Influenza like illness	10	5.5%
C-reactive protein increased	9	5.0%
Thrombocytopenia	9	5.0%
Ileus	9	5.0%
Constipation	9	5.0%
Lipohypertrophy	9	5.0%
Skin striae	9	5.0%
Paraesthesia	9	5.0%
Abdominal abscess	9	5.0%
Dysgeusia	8	4.4%
Proctalgia	8	4.4%
Antinuclear antibody positive	8	4.4%
Lupus-like syndrome	8	4.4%
Flushing	8	4.4%
Pharyngitis	8	4.4%
Sepsis	8	4.4%
Oedema	8	4.4%
Chest pain	7	3.9%
Laryngeal pain	7	3.9%
Increased tendency to bruise	7	3.9%
Lymphoma	7	3.9%
Gastroenteritis	7	3.9%
Respiratory tract infection	7	3.9%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Oedema peripheral	7	3.9%
Hypertension	6	3.3%
Weight decreased	6	3.3%
Liver function test abnormal	6	3.3%
Blood creatinine increased	6	3.3%
Dehydration	6	3.3%
Cushing's syndrome	6	3.3%
Pregnancy	6	3.3%
Joint swelling	6	3.3%
Urticaria	6	3.3%
Intestinal resection	6	3.3%
Injection site erythema	5	2.8%
Post procedural complication	5	2.8%
Tachycardia	5	2.8%
Hypotension	5	2.8%
Haemoglobin decreased	5	2.8%
Platelet count decreased	5	2.8%
Systematic lupus erythematosus	5	2.8%
Demyelination	5	2.8%
Dyspnoea	5	2.8%
Abdominal mass	5	2.8%
Small intestinal obstruction	5	2.8%
Aspartate aminotransferase increased	5	2.8%
Liver function test increased	5	2.8%
Blood cortisol decreased	5	2.8%
Nephrolithiasis	5	2.8%
Arthritis	5	2.8%
Muscle spasms	5	2.8%
Hypertrichosis	5	2.8%
Aphthous ulcer	5	2.8%
Rectal haemorrhage	5	2.8%
Anal fistula	5	2.8%
Adenocarcinoma	5	2.8%
Clostridium difficile infection	5	2.8%
Bronchitis	5	2.8%
Gastroenteritis viral	5	2.8%
Injection site bruising	4	2.2%
Injection site irritation	4	2.2%
Injection site pruritus	4	2.2%
Overdose	4	2.2%
Malaise	4	2.2%
Cataract	4	2.2%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Vision blurred	4	2.2%
Pulmonary embolism	4	2.2%
Deep vein thrombosis	4	2.2%
Lymphopenia	4	2.2%
Neutropenia	4	2.2%
Type IV hypersensitivity reaction	4	2.2%
White blood cell count decreased	4	2.2%
White blood cell count increased	4	2.2%
Weight increased	4	2.2%
Blood alkaline phosphatase increased	4	2.2%
Hepatic enzyme increased	4	2.2%
Renal impairment	4	2.2%
Tremor	4	2.2%
Gastrointestinal haemorrhage	4	2.2%
Squamous cell carcinoma	4	2.2%
Vulvovaginal candidiasis	4	2.2%
Conjunctivitis	4	2.2%
Peritonitis	4	2.2%
Rhinitis	4	2.2%
Herpes zoster	4	2.2%
Injection site inflammation	3	1.7%
Drug intolerance	3	1.7%
Syncope	3	1.7%
Confusional state	3	1.7%
Mood swings	3	1.7%
Completed suicide	3	1.7%
Vertigo	3	1.7%
Migraine	3	1.7%
Chest discomfort	3	1.7%
Musculoskeletal pain	3	1.7%
Oropharyngeal pain	3	1.7%
Bone pain	3	1.7%
Haematocrit decreased	3	1.7%
Subileus	3	1.7%
Diarrhoea haemorrhagic	3	1.7%
Gastrointestinal sounds abnormal	3	1.7%
Amylase increased	3	1.7%
Lipase increased	3	1.7%
Hyperglycaemia	3	1.7%
Adrenal disorder	3	1.7%
Muscular weakness	3	1.7%
Dermatitis	3	1.7%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Eczema	3	1.7%
Erythema	3	1.7%
Skin disorder	3	1.7%
Hyperhidrosis	3	1.7%
Hair growth abnormal	3	1.7%
Anal fissure	3	1.7%
Haematochezia	3	1.7%
Enteritis	3	1.7%
Intestinal perforation	3	1.7%
Hepatotoxicity	3	1.7%
Basal cell carcinoma	3	1.7%
Stenosis	3	1.7%
Oral candidiasis	3	1.7%
Gastrointestinal infection	3	1.7%
Peritoneal abscess	3	1.7%
Vaginal infection	3	1.7%
Herpes simplex	3	1.7%
Herpes virus infection	3	1.7%
Oral herpes	3	1.7%
Progressive multifocal leukoencephalopathy	3	1.7%
Fistula repair	3	1.7%
Infusion site reaction	2	1.1%
Injection site haemorrhage	2	1.1%
Injection site rash	2	1.1%
Thermal burn	2	1.1%
Anastomic leak	2	1.1%
Procedural pain	2	1.1%
Serum sickness	2	1.1%
Increased appetite	2	1.1%
Amnesia	2	1.1%
Affect lability	2	1.1%
Mood altered	2	1.1%
Psychotic disorder	2	1.1%
Oral pain	2	1.1%
Pain in extremity	2	1.1%
Palpitations	2	1.1%
Myocardial infarction	2	1.1%
Cardiac failure congestive	2	1.1%
Venous thrombosis	2	1.1%
Hot flush	2	1.1%
Phlebitis	2	1.1%
Iron deficiency anaemia	2	1.1%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Thrombocytosis	2	1.1%
Red blood cell sedimentation rate increased	2	1.1%
Hypersensitivity vasculitis	2	1.1%
Leukocytosis	2	1.1%
Eosinophil count increased	2	1.1%
Lymphocyte count decreased	2	1.1%
Lymphocyte count increased	2	1.1%
Monocyte count increased	2	1.1%
Neutrophil count increased	2	1.1%
Interleukin level increased	2	1.1%
Multiple sclerosis	2	1.1%
Pneumothorax	2	1.1%
Dry mouth	2	1.1%
Ileus paralytic	2	1.1%
Abdominal tenderness	2	1.1%
Gamma-glutamyltransferase increased	2	1.1%
Blood albumin decreased	2	1.1%
Hyperamylasemia	2	1.1%
Bone density decreased	2	1.1%
Blood calcium decreased	2	1.1%
Hypokalaemia	2	1.1%
Iron deficiency	2	1.1%
Body temperature increased	2	1.1%
Hyperthyroidism	2	1.1%
Blood cortisol abnormal	2	1.1%
Dysmenorrhoea	2	1.1%
Menstrual disorder	2	1.1%
Skin lesion	2	1.1%
Erythema nodosum	2	1.1%
Rosacea	2	1.1%
Night sweats	2	1.1%
Tooth disorder	2	1.1%
Pulmonary mass	2	1.1%
Gastric ulcer	2	1.1%
Anorectal swelling	2	1.1%
Anal fistula	2	1.1%
Melaena	2	1.1%
Intestinal stenosis	2	1.1%
Haemorrhoids thrombosed	2	1.1%
Colon cancer	2	1.1%
Nephropathy toxic	2	1.1%
Breast cancer	2	1.1%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Prostate cancer	2	1.1%
Anogenital warts	2	1.1%
Face oedema	2	1.1%
Neoplasm	2	1.1%
Furuncle	2	1.1%
Candida infection	2	1.1%
Oral fungal infection	2	1.1%
Abdominal wall abscess	2	1.1%
Appendicitis	2	1.1%
Ear infection	2	1.1%
Pelvic abscess	2	1.1%
Postoperative wound infection	2	1.1%
Psoas abscess	2	1.1%
Pyelonephritis	2	1.1%
Skin infection	2	1.1%
Tonsillitis	2	1.1%
Wound infection	2	1.1%
Anogenital warts	2	1.1%
Hepatitis C	2	1.1%
Colectomy	2	1.1%
Ileostomy	2	1.1%
Abscess drainage	2	1.1%
Antibiotic therapy	2	1.1%
Elective surgery	2	1.1%
Contusion	2	1.1%
Road traffic accident	2	1.1%
Stab wound	2	1.1%
Infusion site erythema	1	0.6%
Infusion site irritation	1	0.6%
Infusion site pain	1	0.6%
Infusion site phlebitis	1	0.6%
Injection site haematoma	1	0.6%
Vessel puncture site bruise	1	0.6%
Subcutaneous haematoma	1	0.6%
Feeding tube complication	1	0.6%
Intestinal anastomosis complication	1	0.6%
Post procedural haematoma	1	0.6%
Post procedural haemorrhage	1	0.6%
Postoperative ileus	1	0.6%
Procedural complication	1	0.6%
Procedural intestinal perforation	1	0.6%
Stomal hernia	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Sudden cardiac death	1	0.6%
Feeling abnormal	1	0.6%
Diabetic coma	1	0.6%
Loss of consciousness	1	0.6%
Seizure	1	0.6%
Hyperphagia	1	0.6%
Substance abuse	1	0.6%
Lethargy	1	0.6%
Somnolence	1	0.6%
Abnormal dreams	1	0.6%
Sleep disorder	1	0.6%
Disturbance in attention	1	0.6%
Agitation	1	0.6%
Ataxia	1	0.6%
Anxiety	1	0.6%
Nervousness	1	0.6%
Depression suicidal	1	0.6%
Irritability	1	0.6%
Suicide attempt	1	0.6%
Photophobia	1	0.6%
Amblyopia	1	0.6%
Visual acuity reduced	1	0.6%
Visual impairment	1	0.6%
Dry eye	1	0.6%
Tinnitus	1	0.6%
Facial pain	1	0.6%
Biliary colic	1	0.6%
Musculoskeletal chest pain	1	0.6%
Renal colic	1	0.6%
Breast pain	1	0.6%
Neuralgia	1	0.6%
Post herpetic neuralgia	1	0.6%
Sciatica	1	0.6%
Tendon pain	1	0.6%
Sensory loss	1	0.6%
Sinus tachycardia	1	0.6%
Ventricular extrasystoles	1	0.6%
Ventricular fibrillation	1	0.6%
Cyanosis	1	0.6%
Angina pectoris	1	0.6%
Coronary artery disease	1	0.6%
Myocardial ischaemia	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Cardiac failure	1	0.6%
Electrocardiogram QT prolonged	1	0.6%
Cerebrovascular accidents	1	0.6%
Superior sagittal sinus thrombosis	1	0.6%
Peripheral coldness	1	0.6%
Circulatory collapse	1	0.6%
Thrombosis	1	0.6%
Flushing	1	0.6%
Haematoma	1	0.6%
Haemorrhage	1	0.6%
Blood pressure diastolic decreased	1	0.6%
Blood pressure diastolic increased	1	0.6%
Blood pressure increased	1	0.6%
Orthostatic hypotension	1	0.6%
Hypertensive crisis	1	0.6%
Hyperbilirubinaemia	1	0.6%
Anaemia macrocytic	1	0.6%
Cytopenia	1	0.6%
Pancytopenia	1	0.6%
Hypercoagulation	1	0.6%
Blood disorder	1	0.6%
Haemolytic anaemia	1	0.6%
Splenomegaly	1	0.6%
Eosinophilia	1	0.6%
Granulocytopenia	1	0.6%
Activated partial thromboplastin time prolonged	1	0.6%
Prothrombin time shortened	1	0.6%
Reticulocyte count increased	1	0.6%
Myelodysplastic syndrome	1	0.6%
Natural killer-cell lymphoblastic lymphoma	1	0.6%
Rhinitis allergic	1	0.6%
Lymphoedema	1	0.6%
Lymphocytosis	1	0.6%
Neutrophilia	1	0.6%
Drug hypersensitivity	1	0.6%
Seasonal allergy	1	0.6%
Autoimmune disorder	1	0.6%
Cytokine release syndrome	1	0.6%
T-lymphocyte count decreased	1	0.6%
Optic neuritis	1	0.6%
Multiple sclerosis relapse	1	0.6%
Central nervous system lesion	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Asthma	1	0.6%
Bronchospasm	1	0.6%
Acute pulmonary oedema	1	0.6%
Pneumonitis	1	0.6%
Dyspnoea exertional	1	0.6%
Retching	1	0.6%
Megacolon	1	0.6%
Large intestinal obstruction	1	0.6%
Abdominal adhesions	1	0.6%
Frequent bowel movements	1	0.6%
Rectal tenesmus	1	0.6%
Abnormal faeces	1	0.6%
Mucous stools	1	0.6%
Abnormal loss of weight	1	0.6%
Malnutrition	1	0.6%
Obesity	1	0.6%
Gastrooesophageal disease	1	0.6%
Gastrooesophageal reflux disease	1	0.6%
Abdominal symptom	1	0.6%
Blood creatine phosphokinase increased	1	0.6%
Pancreatic enzymes increased	1	0.6%
Alanine aminotransferase abnormal	1	0.6%
Blood bilirubin increased	1	0.6%
Hepatic enzyme abnormal	1	0.6%
Blood triglycerides decreased	1	0.6%
Low density lipoprotein	1	0.6%
Blood glucose abnormal	1	0.6%
Retinol binding protein decreased	1	0.6%
Protein total decreased	1	0.6%
Hyperlipidaemia	1	0.6%
Hyperuricaemia	1	0.6%
Blood potassium decreased	1	0.6%
Serum ferritin decreased	1	0.6%
Hyperphosphataemia	1	0.6%
Hypocalcaemia	1	0.6%
Fluid retention	1	0.6%
Apoptosis	1	0.6%
Vitamin D deficiency	1	0.6%
Osteoporosis	1	0.6%
Adrenal suppression	1	0.6%
Hypoglycaemia	1	0.6%
Chromaturia	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Haematuria	1	0.6%
Libido decreased	1	0.6%
Sexual dysfunction	1	0.6%
Metrorrhagia	1	0.6%
Abortion spontaneous	1	0.6%
Ectopic pregnancy	1	0.6%
Unintended pregnancy	1	0.6%
Joint stiffness	1	0.6%
Polyarthriti	1	0.6%
Muscle atrophy	1	0.6%
Muscle contractions involuntary	1	0.6%
Neurological symptom	1	0.6%
Dermatitis atopic	1	0.6%
Dry skin	1	0.6%
Lichen planus	1	0.6%
Photosensitivity reaction	1	0.6%
Rash erythematous	1	0.6%
Rash generalised	1	0.6%
Rash maculo-papular	1	0.6%
Skin ulcer	1	0.6%
Ecchymosis	1	0.6%
Purpura	1	0.6%
Anal pruritus	1	0.6%
Anorectal discomfort	1	0.6%
Paraesthesia oral	1	0.6%
Glossodynia	1	0.6%
Burning sensation	1	0.6%
Skin burning sensation	1	0.6%
Parkinson's disease	1	0.6%
Ependymoma	1	0.6%
Neuropathy peripheral	1	0.6%
Polyneuropathy	1	0.6%
Eyelid oedema	1	0.6%
Laryngeal oedema	1	0.6%
Nasal mucosal ulcer	1	0.6%
Sinus congestion	1	0.6%
Tooth discolouration	1	0.6%
Gingival hyperplasia	1	0.6%
Glossitis	1	0.6%
Mouth ulceration	1	0.6%
Lung neoplasm malignant	1	0.6%
lung cyst	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Haematological malignancy	1	0.6%
Gastritis	1	0.6%
Peptic ulcer	1	0.6%
Peptic ulcer haemorrhage	1	0.6%
Stomatitis	1	0.6%
Anal inflammation	1	0.6%
Colonic fistula	1	0.6%
Anal haemorrhage	1	0.6%
Haematemesis	1	0.6%
Lower gastrointestinal haemorrhage	1	0.6%
Colitis	1	0.6%
Anal stenosis	1	0.6%
Large intestinal stenosis	1	0.6%
Small intestinal stenosis	1	0.6%
Duodenal ulcer	1	0.6%
Ileal ulcer	1	0.6%
Small intestinal ulcer haemorrhage	1	0.6%
Colorectal cancer	1	0.6%
Rectal adenocarcinoma	1	0.6%
Rectal cancer	1	0.6%
Pancreatitis acute	1	0.6%
Hepatitis acute	1	0.6%
Hepatomegaly	1	0.6%
Cholelithiasis	1	0.6%
Papillary thyroid cancer	1	0.6%
Renal cell carcinoma	1	0.6%
Glomerulonephritis	1	0.6%
Renal infarct	1	0.6%
Ureteric obstruction	1	0.6%
Bladder cancer	1	0.6%
Ovarian cancer	1	0.6%
Ovarian cyst	1	0.6%
Cervix carcinoma	1	0.6%
Breast hyperplasia	1	0.6%
Bartholin's cyst	1	0.6%
Benign neoplasm of epididymis	1	0.6%
Testis cancer	1	0.6%
Scrotal oedema	1	0.6%
Prostatitis	1	0.6%
Inguinal hernia	1	0.6%
Hernia	1	0.6%
Melanocytic naevus	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Neoplasm skin	1	0.6%
Skin cancer	1	0.6%
Multiple organ dysfunction syndrome	1	0.6%
Adenoma benign	1	0.6%
Carcinoma in situ	1	0.6%
Campylobacter infection	1	0.6%
Cellulitis	1	0.6%
Clostridia infection	1	0.6%
Escherichia infection	1	0.6%
Legionella infection	1	0.6%
Listeriosis	1	0.6%
Nocardiosis	1	0.6%
Staphylococcal sepsis	1	0.6%
Aspergillus infection	1	0.6%
Blastomycosis	1	0.6%
Coccidioidomycosis	1	0.6%
Fungal infection	1	0.6%
Histoplasmosis	1	0.6%
Histoplasmosis disseminated	1	0.6%
Mucocutaneous candidiasis	1	0.6%
Oesophageal candidiasis	1	0.6%
Onychomycosis	1	0.6%
Pneumocystis jirovecii pneumonia	1	0.6%
Abdominal infection	1	0.6%
Abscess intestinal	1	0.6%
Abscess jaw	1	0.6%
Appendiceal abscess	1	0.6%
Bacteraemia	1	0.6%
Catheter site infection	1	0.6%
Device related sepsis	1	0.6%
Ear lobe infection	1	0.6%
Eye infection	1	0.6%
Hordeolum	1	0.6%
Infectious colitis	1	0.6%
Liver abscess	1	0.6%
Mesenteric abscess	1	0.6%
Otitis media	1	0.6%
Pelvic inflammatory disease	1	0.6%
Perirectal abscess	1	0.6%
Pilonidal cyst	1	0.6%
Pyuria	1	0.6%
Rectal abscess	1	0.6%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Scrotal infections	1	0.6%
Subcutaneous abscess	1	0.6%
Urosepsis	1	0.6%
Vaginal infections	1	0.6%
Vulval abscess	1	0.6%
Pulmonary tuberculosis	1	0.6%
Cytomegalovirus hepatitis	1	0.6%
Cytomegalovirus infection	1	0.6%
Epstein-Barr virus	1	0.6%
HIV infection	1	0.6%
Lower respiratory tract infection viral	1	0.6%
Meningitis viral	1	0.6%
Respiratory tract infection viral	1	0.6%
Varicella zoster pneumonia	1	0.6%
Abdominal hernia repair	1	0.6%
Appendicectomy	1	0.6%
Hernia repair	1	0.6%
Ileostomy closure	1	0.6%
Small intestinal resection	1	0.6%
Transfusion	1	0.6%
Dental operation	1	0.6%
Tooth extraction	1	0.6%
Toothache	1	0.6%
Adhesiolysis	1	0.6%
Bed rest	1	0.6%
Drain placement	1	0.6%
Vasodilation procedure	1	0.6%
Swelling	1	0.6%
Swelling face	1	0.6%
Concomitant disease aggravated	1	0.6%
Fracture	1	0.6%
Hand fracture	1	0.6%
Spinal compression fracture	1	0.6%
Arthropod sting	1	0.6%
Adverse event categories		
Discontinuation of treatment due to adverse events	102	56.4%
Total adverse events	93	51.4%
Discontinuation of treatment due to various reasons (Protocol non-compliance, lost to follow up, prohibited medication use, withdrawal of consent)	83	45.9%
Total serious adverse events	76	42.0%

Outcome	Studies measuring outcome	
	No.	% (of 181)
Discontinuation of treatment due to treatment failure (insufficient therapeutic effect, exacerbation of Crohn's, development of complications of Crohn's, need for additional therapy or surgery)	75	41.4%
Total treatment related adverse events	66	36.5%
Total treatment related serious adverse events	31	17.1%
Discontinuation of treatment due to treatment related adverse events	25	13.8%
Discontinuation of treatment due to serious adverse events	7	3.9%
Discontinuation of treatment due to treatment related serious adverse events	2	1.1%

Appendix table 17: Crohn's disease activity index constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description		ICF outcome code level			Outcome	Domain
			1 st	2 nd	3 rd		
1	No. of liquid or very soft stools per day (liquid or very soft stools)				b5251	Faecal consistency	ICF b525: Defecation functions
1	No. of liquid or very soft stools per day (frequency of stools)				b5252	Frequency of defecation	ICF b525: Defecation functions
1-A	Adjustment if using diarrhoea-control medications					Need for additional therapy	Individual resource use
2	Abdominal pain rating (0-3)				b28012	Pain in stomach or abdomen	ICF b28012: Pain in stomach or abdomen
3	General well-being rating (0-4)					Wellbeing	Quality of life
4	No. of 6 types, other occasional Crohn's findings	The presence of joint pains (arthralgia) or frank arthritis			b28016	Pain in joints	ICF b28016: Pain in joints
				s770		Additional musculoskeletal structures related to movement	ICF s770: Additional musculoskeletal structures related to movement
		Inflammation of the iris or uveitis			s2202	Iris	ICF s220: Structure of eyeball
		Presence of erythema nodosum, pyoderma gangrenosum or aphthous ulcers			s810	Structure of areas of skin	ICF s810: Structure of areas of skin
		Anal fissures, fistulae or abscesses			s540	Structure of intestine	ICF s540: Structure of intestine
		Other fistulae			s540	Structure of intestine	ICF s540: Structure of intestine
		Fever during the previous week			b5500	Body temperature	ICF b5500: Body temperature
5	Abdominal mass (CDAI = 0, 2, 5; HBI = 1-4)				s540	Structure of intestine	ICF s540: Structure of intestine
6	Haematocrit, % decrease from expected				b430	Haematological system functions	ICF b430: Haematological system functions

Item no.	Item description	ICF outcome code level			Outcome	Domain
		1 st	2 nd	3 rd		
7	Body weight, % decrease from expected		b530		Weight maintenance functions	ICF b530: Weight maintenance functions

Appendix table 18: Inflammatory Bowel Disease Questionnaire constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description	IBDQ score	ICF code level			Outcome	Domain
			1 st	2 nd	3 rd		
1	Runny bowel movements	Bowel			b5251	Faecal consistency	ICF b525: Defecation functions
5	Frequent bowel movements	Bowel			b5252	Frequency of defecation	ICF b525: Defecation functions
9	Bowels open accidentally	Bowel			b5253	Faecal continence	ICF b525: Defecation functions
13	Abdominal pain	Bowel			b28012	Pain in stomach or abdomen	ICF b28012: Pain in stomach or abdomen
17	Problems with wind	Bowel			b5254	Flatulence	ICF b525: Defecation functions
20	Bloated abdomen	Bowel			b5351	Feeling bloated	ICF b535: Sensations associated with the digestive system
22	Notice blood with bowel movement	Bowel		b525		Defecation functions	ICF b525: Defecation functions
24	Want to go back to the toilet immediately after emptying bowel	Bowel			d5301	Regulating defecation	ICF d5301: Regulating defecation
26	Have to rush to toilet	Bowel			d5301	Regulating defecation	ICF d5301: Regulating defecation
29	Feeling sick	Bowel			b5350	Sensation of nausea	ICF b535: Sensations associated with the digestive system
3	Feeling frustrated	Emotion		b152		Emotional functions	ICF b152: Emotional functions
7	Worried about being admitted to hospital	Emotion		b152		Emotional functions	ICF b152: Emotional functions
11	Need to keep close to a toilet	Emotion			d5301	Regulating defecation	ICF d5301: Regulating defecation
15	Feeling depressed	Emotion		b152		Emotional functions	ICF b152: Emotional functions
19	Feeling worried	Emotion		b152		Emotional functions	ICF b152: Emotional functions
21	Feeling relaxed	Emotion		b152		Emotional functions	ICF b152: Emotional functions
23	Feeling embarrassed by bowel problem	Emotion		b152		Emotional functions	ICF b152: Emotional functions

Item no.	Item description	IBDQ score	ICF code level			Outcome	Domain
			1 st	2 nd	3 rd		
25	Feeling upset	Emotion		b152		Emotional functions	ICF b152: Emotional functions
27	Feeling angry	Emotion		b152		Emotional functions	ICF b152: Emotional functions
30	Feeling irritable	Emotion		b152		Emotional functions	ICF b152: Emotional functions
31	Feeling lack of sympathy from others	Emotion		b152		Emotional functions	ICF b152: Emotional functions
32	Feeling happy	Emotion		b152		Emotional functions	ICF b152: Emotional functions
4	Unable to attend school or work	Social		d810- d839 d840- d859		Education Work and employment	ICF d810-d839: Education ICF d840-d859: Work and employment
8	Prevent going out	Social		d920		Recreation and leisure	ICF d9: Community, social and civic life
12	Leisure or sports activities affected	Social		d920		Recreation and leisure	ICF d9: Community, social and civic life
16	Avoid attending events	Social		d910		Community life	ICF d9: Community, social and civic life
28	Sex life affected	Social		d640		Sexual functions	ICF d640: Sexual functions
2	Feeling tired	Systemic			b1300	Energy level	ICF b130: Energy and drive functions
6	Feeling full of energy	Systemic			b1300	Energy level	ICF b130: Energy and drive functions
10	Feeling generally unwell	Systemic				Feeling generally well	Patient perception of health
14	Unable to sleep	Systemic		b134		Sleep functions	ICF b134: Sleep functions
18	Feeling off food	Systemic			b1302	Appetite	ICF b130: Energy and drive functions

Appendix table 19: Short Form-36 constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description	ICF code level			Outcome	Domain
		1 st	2 nd	3 rd		
GENERAL HEALTH						
1	In general, how would you rate your health?				Perception of health	Patient perception of health
2	Compared to one year ago, how would you rate your health in general now?				Perception of health	Patient perception of health
LIMITATIONS OF ACTIVITIES						
Does your health limit you in these activities? If so, how much?						
3	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			d9201	Sports	ICF d9: Community, social and civic life
			d430		Lifting and carrying objects	ICF d4: Mobility
4	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			d9201	Sports	ICF d9: Community, social and civic life
			d640		Doing housework	ICF d640: Doing housework
5	Lifting or carrying groceries		d430		Lifting and carrying objects	ICF d4: Mobility
6	Climbing several flights of stairs			d4551	Climbing	ICF d4: Mobility
7	Climbing one flight of stairs			d4551	Climbing	ICF d4: Mobility
8	Bending, kneeling, or stooping		d410		Changing basic body position	ICF d4: Mobility
9	Walking more than a mile			d4501	Walking long distances	ICF d4: Mobility
10	Walking several blocks		d450		Walking	ICF d4: Mobility
11	Walking one block			d4500	Walking short distances	ICF d4: Mobility
12	Bathing or dressing yourself (bathing)		d510		Washing oneself	ICF d5: Self care
	Bathing or dressing yourself (dressing)		d540		Dressing	ICF d5: Self care
PHYSICAL HEALTH PROBLEMS						
Have you had any of the following problems with your work or other regular daily activities as a result of your physical health?						

Item no.	Item description	ICF code level			Outcome	Domain
		1 st	2 nd	3 rd		
13	Cut down the amount of time you spent on work or other activities		d810- d839		Education Work and employment	ICF d810-d839: Education ICF d840-d859: Work and employment
14	Accomplished less than you would like		d840- d859			
15	Were limited in the kind of work or other activities					
16	Had difficulty performing the work or other activities (for example, it took extra effort)					
EMOTIONAL HEALTH PROBLEMS						
Have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?						
17	Cut down the amount of time you spent on work or other activities		d810- d839		Education Work and employment	ICF d810-d839: Education ICF d840-d859: Work and employment
18	Accomplished less than you would like		d840- d859			
19	Didn't do work or other activities as carefully as usual					
SOCIAL ACTIVITIES						
20	Emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?	d9			Community, social and civic life	Community, social and civic life
PAIN						
21	How much bodily pain have you had during the past 4 weeks?		b280		Sensation of pain	ICF b280: Sensation of pain
22	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?		b280		Sensation of pain	ICF b280: Sensation of pain
ENERGY AND EMOTIONS						
23	Did you feel full of pep?			b1300	Energy level	ICF b130: Energy and drive functions

Item no.	Item description	ICF code level			Outcome	Domain
		1 st	2 nd	3 rd		
24	Have you been a very nervous person?		b152		Emotional functions	Emotional functions
25	Have you felt so down in the dumps that nothing could cheer you up?		b152		Emotional functions	Emotional functions
26	Have you felt calm and peaceful?		b152		Emotional functions	Emotional functions
27	Did you have a lot of energy?			b1300	Energy level	ICF b130: Energy and drive functions
28	Have you felt downhearted and blue?		b152		Emotional functions	Emotional functions
29	Did you feel worn out?			b1300	Energy level	ICF b130: Energy and drive functions
30	Have you been a happy person?		b152		Emotional functions	Emotional functions
31	Did you feel tired?			b1300	Energy level	ICF b130: Energy and drive functions
SOCIAL ACTIVITIES						
32	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	d9			Community, social and civic life	Community, social and civic life
GENERAL HEALTH						
33	I seem to get sick a little easier than other people				Perception of health	Patient perception of health
34	I am as healthy as anybody I know				Perception of health	Patient perception of health
35	I expect my health to get worse				Perception of health	Patient perception of health
36	My health is excellent				Perception of health	Patient perception of health

Appendix table 20: Harvey Bradshaw Index (HBI) constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description		ICF outcome code level			Outcome	Domain
			1 st	2 nd	3 rd		
1	No. of liquid or very soft stools per day (liquid or very soft stools)				b5251	Faecal consistency	ICF b525: Defecation functions
1	No. of liquid or very soft stools per day (frequency of stools)				b5252	Frequency of defecation	ICF b525: Defecation functions
1-A	Adjustment if using diarrhoea-control medications					Need for additional therapy	Individual resource use
2	Abdominal pain rating (0-3)				b28012	Pain in stomach or abdomen	ICF b28012: Pain in stomach or abdomen
3	General well-being rating (0-4)					Wellbeing	Quality of life
4	No. of 6 types, other occasional Crohn's findings	The presence of joint pains (arthralgia) or frank arthritis			b28016	Pain in joints	ICF b28016: Pain in joints
				s770		Additional musculoskeletal structures related to movement	ICF s770: Additional musculoskeletal structures related to movement
		Inflammation of the iris or uveitis			s2202	Iris	ICF s220: Structure of eyeball
		Presence of erythema nodosum, pyoderma gangrenosum or aphthous ulcers			s810	Structure of areas of skin	ICF s810: Structure of areas of skin
		Anal fissures, fistulae or abscesses			s540	Structure of intestine	ICF s540: Structure of intestine
		Other fistulae			s540	Structure of intestine	ICF s540: Structure of intestine
		Fever during the previous week			b5500	Body temperature	ICF b5500: Body temperature
5	Abdominal mass (CDAI = 0, 2, 5; HBI = 1-4)				s540	Structure of intestine	ICF s540: Structure of intestine

Appendix table 21: Perianal Disease Activity Index (PDAI) constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description	ICF code level			Outcome	Domain
		1 st	2 nd	3 rd		
1	Discharge		b525		Defecation functions	ICF b525: Defecation functions
2	Pain /restriction of activities		b280		Sensation of pain	ICF b280: Sensation of pain
3	Restriction of sexual activities		b640		Sexual functions	ICF b640: Sexual functions
4	Type of perianal disease		s540		Structure of the intestine	ICF s540: Structure of the intestine
5	Degree of induration		S810		Structure of areas of skin	ICF s810: Structure of areas of skin

Appendix table 22: Van-Hees Activity Index (VHAI) constituent outcomes and mapped Filter 2.0 domains

Item no.	Item description	ICF code level			Outcome	Domain
		1 st	2 nd	3 rd		
1	Albumin		b430		Haematological system functions	ICF b430: Haematological system functions
2	ESR				Inflammation	Biomarker
3	BMI		b530		Weight maintenance functions	ICF b530: Weight maintenance functions
4	Abdominal mass		s540		Structure of intestine	ICF s540: Structure of intestine
5	Sex					
6	Temperature		b5500		Body temperature	ICF b5500: Body temperature
7	Stool consistency		b5251		Faecal consistency	ICF b525: Defecation functions
8	Resection				Need for surgery	Individual resource use
9	Extraintestinal lesion		s810		Structure of areas of skin	ICF s810: Structure of areas of skin

Appendix table 23: Filter 2.0 domains, outcomes and outcome measures within the endpoints of 181 trials in adults with Crohn's disease

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: DEATH					
Death	2		2	Death due to Crohn's	Death due to Crohn's
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: ECONOMIC IMPACT					
Individual resource use	83	156	163	Disease activity, need for additional steroids, therapy or surgery, need for hospitalisation, steroid dose, withdrawal or tapered steroids and resection.	CDAI, VHA1 and physician assessment. Physician global assessments of disease activity, partial Harvey Bradshaw index, Severity and Activity index, Present score and European cooperative Crohn's Disease Study (ECCDS) based grading. Patient global ratings, impressions and evaluations of disease activity.
Health care cost	3		3	Costs of health care	Drug cost per patient, monthly cost of medical treatment, overall cost of surgery, Cost per QALY, cost to utility ratio of treatment, incremental cost effectiveness ratio (ICER)
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: LIFE IMPACT					
Quality of life	16	163	167	Wellbeing and general quality of life	VAS assessment, CDAI, HBI, diary card assessments and patient global assessments of wellbeing. Assessment of Quality of Life Questionnaire, Gastrointestinal Quality of Life Index, IBD

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
					Quality of Life questionnaires, Inflammatory Bowel Disease Self-Efficacy Scale, Inflammatory Bowel Disease Stress Index, Quality of Life instrument, Short Form 12 Health Survey, Short Health Scale and Short Inflammatory Bowel disease Questionnaire (short-IBDQ)
ICF d9: Community, social and civic life	1	82	82	Condition interferes with social life, education, work and employment, prevents going out, attending social events and leisure and sports affected.	SF-36, IBDQ
Patient perception of health	2	82	82	Perception of health and feeling generally well	EuroQOL visual analogue scale, SF-36 and IBDQ
ICF d5301: Regulating defecation		77	77	Wanting to go back to the toilet, needing to rush to the toilet and needing to keep close to a toilet.	IBDQ
Utility of treatment	71		71	Perceived credibility, efficacy and tolerability of treatment, perceived disease activity and utility.	Pill counts, patient diaries, duration of therapy, stool pH test, Patient ratings, Investigator / physician assessment, changes in laboratory values deemed serious, EQ-5D, EuroQOL derived VAS, QALY.

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
ICF d4: Mobility		14	14	Bending, kneeling or stooping, climbing stairs, lifting or carrying groceries, vigorous activities and walking	SF-36
ICF d5: Self-care		14	14	Bathing or dressing yourself	SF-36
ICF d640: Doing housework		14	14	Moderate activities	SF-36
ICF d810-d839: Education		14	14	Activities limited due to emotional or physical health problems	SF-36
ICF d840-d859: Work and employment	1	14	14	Activities limited due to emotional or physical health problems	Work limitation questionnaire and SF-36
ICF d240: Handling stress and other psychological demands	2		2	Ability to cope with the disease, perceived stress and improvement in psychological status.	Patient self-rating and perceived stress questionnaire
ICF d7: Interpersonal interactions and relationships	1		1	Influence on interpersonal relationships	Patient self-rating and Psychiatric and Socio-communicative finding (PSKB) standardised clinical interview
CONCEPT: PATHOPHYSIOLOGICAL MANIFESTATIONS; CORE AREA: PATHOPHYSIOLOGICAL MANIFESTATIONS					
ICF s540: Structure of intestine	85	166	174	Fistulae, fissures, abscesses, abdominal masses, lesions, ulcers and perianal disease.	CDAI, HBI, VHAI, PDAI, Crohn's disease Endoscopic Index of Severity (CDEIS), D'Haens endoscopic scores, Rutgeerts scores, Simple Endoscopic Score for Crohn's disease (SES-CD), Marteau endoscopic score, other endoscopic classifications and scores, endoscopic

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
					visual analogue scales, Dieleman histological score, Regueiro histology score, other histology scores and grading, barium x-ray appearance, 3D ultrasound and physician assessments.
ICF b525: Defecation functions	19	170	172	Faecal output, faecal consistency, frequency of defecation, faecal continence, flatulence, diarrhoea, blood with stool and fistula discharge.	CDAI, HBI, VHAI, IBDQ, PDAI, adapted Vaizey faecal incontinence score, IBS severity scoring system and diary card assessments.
ICF b28012: Pain in abdomen or stomach	7	168	169	Abdominal pain	CDAI, HBI and IBDQ.
ICF s810: Structure of areas of skin	2	166	166	Extra intestinal lesions and perianal induration.	CDAI, HBI, VHAI and PDAI.
ICF b28012: Pain in joints		163	163	Arthralgia	CDAI and HBI.
ICF b5500: Body temperature	4	163	163	Fever and prolonged fever	CDAI, HBI and VHAI.
ICF s220: Structure of eyeball		162	162	Uveitis	CDAI and HBI.
ICF s770: Additional musculoskeletal structures related to movement		162	162	Arthritis	CDAI and HBI.
ICF b530: Weight maintenance functions	15	156	157	Body mass	CDAI, VHAI, body weight, BMI, creatinine-height index, mid-arm muscle circumference and triceps skinfold thickness.

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
ICF b430: Haematological system functions	23	156	156	Blood abnormalities	CDAI, VHAI, albumin, abnormal blood cell count, complete blood count, full blood count, haematocrit, haemoglobin, platelet count, red blood cell count, white blood cell count.
Biomarkers	102	7	102	Inflammation and intestinal permeability	VHAI, C-reactive protein, erythrocyte sedimentation rate, faecal calprotectin, serum orosomucoid concentration, α -1 acid glycoprotein and presence of cytokines and bacteria in mucosal tissues and plasma. Urine permeability tests and stool α 1-antitrypsin clearance.
ICF b152: Emotional functions	6	82	83	Depression, frustration, anxiety, worry, embarrassment, upset, angry, irritable, happy, relaxed, feel lack of sympathy and worries about being admitted to hospital.	Beck's depression inventory, Hamilton Depression Scale, Hospital Anxiety and Depression Scale, SF-36, State trait Anxiety Inventory instrument and IBDQ.
ICF b640: Sexual functions	1	83	83	Restriction of sexual activity and sex life affected.	IBDQ and PDAI.
ICF b130: Energy and drive functions	3	82	82	Energy levels and appetite.	Fatigue impact scale, side effect questionnaire, IBDQ and SF-36.
ICF b535: Sensations associated with the digestive system	2	77	78	Nausea, abdominal bloating, rumbling gut and acid reflux.	IBDQ and patient diary.
ICF b134: Sleep functions		77	77	Unable to sleep	IBDQ

Outcome domain	Studies measuring outcomes in domain			Outcomes	Outcome measures
	Individually	Within an index	Total		
ICF b280: Sensation of pain	8	23	25	Bodily pain and perianal pain.	Clinical scales, patient diary, PDAI, Physician assessment, SF-36, side effect questionnaire and visual analogue scale.
ICF b515: Digestive functions	14		14	Absorption of nutrients	Important outcomes include albumin (also an indicator of inflammation), transferrin and retinol-binding protein. Numerous other outcome measures including fatty acid fractions, linoleic acid and phospholipids
ICF b510: Ingestion functions	6		6	Vomiting, calorie intake, maintenance of full diet, return to full diet and return to liquid diet	Patient diary scores.
ICF b540: General metabolic functions	2		2	Liver or kidney function	Abnormal alkaline phosphatase, AST, amylase, lipase or serum creatinine levels and elevated liver enzyme
Note: CDAI – Crohn’s disease activity index; VHAI – Van Hees activity index; VAS – visual analogue scale; HBI – Harvey Bradshaw index; SF-36 – Short form 36; IBDQ – inflammatory bowel disease questionnaire; QALY – quality-adjusted life-years; PDAI – perianal disease activity index; BMI – body mass index; AST – aspartate aminotransferase					

Appendix table 24: Filter 2.0 domains and adverse events reported in the 181 trials in adults with Crohn's disease

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: DEATH					
	Death	49	2	Fatal outcomes	Death, sudden cardiac death
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: ECONOMIC IMPACT					
	Individual resource use	38	15	Gastrointestinal therapeutic procedures, Haematological and lymphoid tissue therapeutic procedures, Therapeutic procedures and supportive care NEC	Hospitalisation, surgery, intestinal repair, colectomy, ileostomy, abscess drainage, antibiotic therapy, elective surgery, ileostomy closure, small intestinal resection, transfusion, adhesiolysis, bed rest, drain placement
CONCEPT: IMPACT OF HEALTH CONDITIONS; CORE AREA: LIFE IMPACT					
	Utility of treatment	160	43	Administration site reactions, Injuries by physical agents, Injuries NEC, Procedural related injuries and complications NEC, Product use issues, Therapeutic and nontherapeutic effects (excl. toxicity),	Injection site reaction, injection site pain, infusion related reaction, injection site erythema, post-procedural complication, injection site bruising, injection site irritation, injection site pruritus, overdose, injection site inflammation, drug intolerance, infusion site reaction, injection site haemorrhage, injection site rash, infusion site erythema, infusion site irritation, infusion site pain,

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
					infusion site phlebitis, injection site haematoma
	Patient perception of health	5	2	General system disorders NEC	Malaise, feeling abnormal
CONCEPT: PATHOPHYSIOLOGICAL MANIFESTATIONS; CORE AREA: PATHOPHYSIOLOGICAL MANIFESTATIONS					
	Infections	106	100	Bacterial infectious disorders, Fungal infectious disorders, General system disorders NEC, Infections - pathogen unspecified, Mycobacterial infectious disorders, Viral infectious disorders,	Infection, nasopharyngitis, anal abscess, upper respiratory tract infection, urinary tract infection, urinary tract infection, pneumonia, influenza, abscess, opportunistic infection, tuberculosis, sinusitis, viral infection, influenza like illness
b280	Sensation of pain	105	24	Anal and rectal conditions NEC, bile duct disorders, Bone disorders (excl congenital and fractures), Breast disorders, General system disorders NEC, Headaches, Muscle disorders, Musculoskeletal and connective tissue disorders NEC, Neurological disorders NEC, Oral soft tissue conditions, Respiratory disorders NEC, Spinal cord and nerve root disorders, Tendon, ligament	Headache, back pain, myalgia, pain, proctalgia, chest pain, laryngeal pain, bone pain, chest discomfort, migraine, musculoskeletal pain, oropharyngeal pain, oral pain, pain in extremity, biliary colic, breast pain, facial pain, musculoskeletal chest pain, neuralgia, post herpetic neuralgia, renal colic, sciatica, sensory loss, tendon pain

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
				and cartilage disorders, Urinary tract signs and symptoms	
s540	Structure of intestine	96	62	Anal and rectal conditions NEC, Gastrointestinal conditions NEC, Gastrointestinal haemorrhages NEC, Gastrointestinal inflammatory conditions, Gastrointestinal neoplasms malignant and unspecified, Gastrointestinal stenosis and obstruction, Gastrointestinal ulceration and perforation, Gastrointestinal vascular conditions, General system disorders NEC, Musculoskeletal and connective tissue disorders NEC	Crohn's disease, fistula, rectal haemorrhage, anal fistula, gastrointestinal haemorrhage, anal fissure, haematochezia, enteritis, intestinal perforation, stenosis, anorectal swelling, melaena, intestinal stenosis, haemorrhoids thrombosed, colon cancer, anal inflammation, colonic fistula, anal haemorrhage, haematemesis, lower gastrointestinal haemorrhage, colitis, anal stenosis, large intestinal stenosis, small intestinal stenosis, duodenal ulcer, ileal ulcer, small intestinal ulcer haemorrhage, colorectal cancer, rectal adenocarcinoma, rectal cancer
b28012	Pain in stomach or abdomen	90	2	Gastrointestinal signs and symptoms	Abdominal pain, abdominal pain upper
b535	Sensations associated with the digestive system	90	8	Gastrointestinal motility and defaecation conditions, Gastrointestinal signs and symptoms	Nausea, dyspepsia, abdominal distension, gastrointestinal sounds abnormal, abdominal tenderness, gastrooesophageal disease,

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
					gastroesophageal reflux disease, abdominal symptom
b8	Functions of the skin and related structures	76	35	Anal and rectal conditions NEC, Angioedema and urticaria, Cornification and dystrophic skin disorders, Epidermal and dermal conditions, General system disorders NEC, Neurological disorders NEC, Oral soft tissue conditions, Skin and subcutaneous tissue disorders NEC, Skin appendage conditions, Skin vascular abnormalities, Tongue conditions	Rash, acne, pruritus, alopecia, skin striae, paraesthesia, flushing, urticaria, hypertrichosis, dermatitis, eczema, erythema, skin disorder, hyperhidrosis, hair growth abnormal, skin lesion, erythema nodosum, rosacea, night sweats, dermatitis atopic, dry skin, lichen planus, photosensitivity reaction, rash erythematous, rash generalised, rash maculo-papular, skin ulcer, ecchymosis, purpura, anal pruritus, anorectal discomfort, paraesthesia oral, glossodynia, burning sensation, skin burning sensation
b435	Immunological system functions	65	36	Allergic conditions, Autoimmune disorders, Connective tissue disorders (excl congenital), Cranial nerve disorders (excl neoplasms), Demyelinating disorders, Haematology investigations (incl blood groups), Immune disorders NEC, Immunology and allergy investigations,	Drug specific antibody present, leukopenia, hypersensitivity, double stranded DNA antibody, antinuclear antibody present, lupus-like syndrome, lymphoma, systematic lupus erythematosus, demyelination, lymphopenia, neutropenia, type IV hypersensitivity reaction, white blood cell

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
				Lymphomas NEC, Lymphomas non-Hodgkin's T-cell, Neurological disorders NEC, Skin vascular abnormalities, Spleen, lymphatic and reticuloendothelial system disorders, Toxicology and therapeutic drug monitoring, Upper respiratory tract disorders (excl infections), White blood cell disorders	count decreased / increased, hypersensitivity vasculitis, leucocytosis, eosinophil count increased, lymphocyte count increased / decreased, monocyte count increased, neutrophil count increased, interleukin level increased, multiple sclerosis / MS relapse, rhinitis allergic, natural killer-cell lymphoblastic lymphoma, lymphoedema, lymphocytosis, neutrophilia, drug hypersensitivity, seasonal allergy, autoimmune disorder, cytokine release syndrome, T-lymphocyte count decreased, optic neuritis, central nervous system lesion
b525	Defecation functions	65	8	Anal and rectal conditions NEC, Gastrointestinal motility and defaecation conditions, Gastrointestinal signs and symptoms	Diarrhoea, flatulence, constipation, diarrhoea haemorrhagic, frequent bowel movements, rectal tenesmus, abnormal faeces, mucous stools
b510	Ingestion functions	59	3	Gastrointestinal signs and symptoms, Salivary gland conditions	Vomiting, dry mouth, retching
b28016	Pain in joints	58	1	Joint disorders	Arthralgia

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b540	General metabolic functions	50	26	Enzyme investigations, Enzyme investigations NEC, Gastrointestinal investigations, Hepatobiliary investigations, Lipid analyses, Lipid metabolism disorders, Metabolic, nutritional and blood gas investigations, Metabolism disorders NEC, Protein and chemistry analyses NEC, Purine and pyrimidine metabolism disorders, Renal and urinary tract investigations and urinalyses	Alanine aminotransferase increased / abnormal, transaminases increased, lipohypertrophy, liver function test abnormal / increased, blood creatinine increased, aspartate aminotransferase increased. Blood alkaline phosphatase increased, hepatic enzyme abnormal / increased, amylase increased, lipase increased, gamma-glutamyltransferase increased, blood albumin decreased, hyperamylasemia, blood creatine phosphokinase increased, pancreatic enzymes increased, blood bilirubin increased, blood triglycerides decreased, low density lipoprotein, blood glucose abnormal, retinol binding protein decreased, protein total decreased, hyperlipidaemia, hyperuricemia
b130	Energy and drive functions	47	6	Appetite and general nutrition disorders, general system disorders NEC, neurological disorders NEC, psychiatric disorders NEC	Fatigue, decreased / increased appetite, lethargy, substance abuse, hyperphagia

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b5500	Body temperature	47	3	Body temperature conditions, General system disorders NEC, Physical examination and organ system status topics	Pyrexia, chills, body temperature decreased
b430	Haematological system functions	39	23	Anaemias nonhaemolytic and marrow depression, Coagulopathies and bleeding diatheses (excl thrombocytopenic), Haematological disorders NEC, Haematology investigations (incl blood groups), Haemolyses and related conditions, Hepatic and hepatobiliary disorders, Leukaemias, Platelet disorders, Spleen, lymphatic and reticuloendothelial system disorders, White blood cell disorders	Anaemia, thrombocytopenia, increased tendency to bruise, haemoglobin decreased, platelet count decreased, haematocrit decreased, iron deficiency anaemia, thrombocytosis, red blood cell sedimentation rate increased, hyperbilirubinaemia, anaemia macrocytic, cytopenia, pancytopenia, hypercoagulation, blood disorder, haemolytic anaemia, splenomegaly, eosinophilia, granulocytopenia, activated partial thromboplastin time prolonged, prothrombin time shortened, reticulocyte count increased, myelodysplastic syndrome
b515	Digestive functions	35	9	Gastrointestinal motility and defaecation conditions, Gastrointestinal signs and symptoms, Gastrointestinal stenosis and	Intestinal obstruction, ileus, abdominal mass, small intestinal obstruction, subileus, ileus paralytic, megacolon, large intestinal obstruction, abdominal adhesions

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
				obstruction, Peritoneal and retroperitoneal conditions	
b7	Neuromusculoskeletal and movement-related functions	33	11	General system disorders NEC, Joint disorders, Movement disorders (incl parkinsonism), Muscle disorders, Neurological disorders NEC, Neuromuscular disorders	Asthenia, joint swelling, arthritis, muscle spasms, tremor, muscular weakness, joint stiffness, polyarthritis, muscle atrophy, muscle contractions involuntary, neurological symptom
b240	Sensations associated with hearing and vestibular function	31	3	Inner ear and VIIIth cranial nerve disorders, Neurological signs and symptoms NEC	Dizziness, tinnitus, vertigo
b555	Endocrine gland functions	25	9	Adrenal gland disorders, Endocrine disorders of gonadal function, Endocrine investigations (incl sex hormones), Glucose metabolism disorders (incl diabetes mellitus), Thyroid gland disorders	Cushingoid, hirsutism, Cushing's syndrome, blood cortisol decreased / abnormal, adrenal disorder / suppression, hyperthyroidism, hypoglycaemia
b415	Blood vessel functions	24	13	Arteriosclerosis, stenosis, vascular insufficiency and necrosis, Central nervous system vascular disorders, Decreased and nonspecific blood pressure disorders and shock, Embolism and thrombosis, Pulmonary vascular disorders, Vascular	Pulmonary embolism, deep vein thrombosis, venous thrombosis, hot flush, phlebitis, cerebrovascular accidents, superior sagittal sinus thrombosis, peripheral coldness, circulatory collapse, thrombosis, flushing, haematoma, haemorrhage

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
				disorders NEC, Vascular haemorrhagic disorders, Vascular inflammations	
b152	Emotional functions	22	11	Anxiety disorder and symptoms, Depressed mood disorders and disturbances, Mood disorders and disturbances NEC, Schizophrenia and other psychotic disorders, Suicidal and self-injurious behaviours NEC	Depression, mood swings, completed suicide, affect lability, mood altered, psychotic disorder, anxiety, nervousness, depression suicidal, irritability, suicide attempt
b6	Genitourinary and reproductive functions	22	13	Abortions and stillbirths, Maternal complications of pregnancy, Menstrual cycle and uterine bleeding disorders, Pregnancy, labour, delivery and postpartum conditions, Renal disorders (excl nephropathies), Sexual dysfunctions, disturbances and gender identity disorders, Sexual function and fertility disorders, Urinary tract signs and symptoms, Urolithiasis	Pregnancy, nephrolithiasis, renal impairment, dysmenorrhoea, menstrual disorder, chromaturia, haematuria, libido decreased, sexual dysfunction, metrorrhagia, abortion spontaneous, ectopic pregnancy, unintended pregnancy
	Unspecified: cancer	20	5	Miscellaneous and site unspecified neoplasms malignant and unspecified	Neoplasm malignant, adenocarcinoma, neoplasm, adenoma benign, carcinoma in situ

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b440- b460	Respiratory functions	20	8	Bronchial disorders (excl neoplasms), Lower respiratory tract disorders (excl obstruction and infection), Pleural disorders, Respiratory disorders NEC	Cough, dyspnoea, pneumothorax, asthma, bronchospasm, acute pulmonary oedema, pneumonitis, dyspnoea exertional
s6	Structures related to the genitourinary and reproductive systems	20	18	Breast disorders, Breast neoplasms malignant and unspecified (incl nipple), Cutaneous neoplasms benign, Male reproductive tract infections and inflammations, Nephropathies, Ovarian and fallopian tube disorders, Penile and scrotal disorders (excl infections and inflammations), Renal and urinary tract neoplasms malignant and unspecified, Renal disorders (excl nephropathies), Reproductive neoplasms female malignant and unspecified, Reproductive neoplasms male malignant and unspecified, Ureteric disorders, Vulvovaginal disorders (excl infections and inflammations)	Nephropathy toxic, breast cancer, prostate cancer, anogenital warts, renal cell carcinoma, glomerulonephritis, renal infarct, ureteric obstruction, bladder cancer, ovarian cancer, ovarian cyst, cervix carcinoma, breast hyperplasia, Bartholin's cyst, benign neoplasm of epididymis, testis cancer, scrotal oedema, prostatitis
b134	Sleep functions	19	4	Neurological disorders NEC, sleep disorders and disturbances	Insomnia, sleep disorder, somnolence and abnormal dreams

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b410	Heart functions	18	13	Cardiac and vascular investigations (excl enzyme tests), Cardiac arrhythmias, Cardiac disorders signs and symptoms, Coronary artery disorders, Heart failures	Tachycardia, palpitations, myocardial infarction, cardiac failure congestive, sinus tachycardia, ventricular extrasystoles, ventricular fibrillation, cyanosis, angina pectoris, coronary artery disease, myocardial ischaemia, cardiac failure, electrocardiogram QT prolonged
b545	Water, mineral and electrolyte balance functions	18	14	Bone disorders (excl congenital and fractures), Bone, calcium, magnesium and phosphorus metabolism disorders, Electrolyte and fluid balance conditions, Glucose metabolism disorders (incl diabetes mellitus), Iron and trace metal metabolism, Metabolism disorders NEC, Musculoskeletal and soft tissue investigations (excl enzyme tests), Vitamin related disorders, Water, electrolyte and mineral investigations	Dehydration, hyperglycaemia, bone density decreased, blood calcium decreased, hypokalaemia, iron deficiency, blood potassium decreased, serum ferritin decreased, hyperphosphataemia, hypocalcaemia, fluid retention, apoptosis, vitamin D deficiency, osteoporosis
	Unspecified: general system conditions	18	5	Angioedema and urticaria, General system disorders NEC	Oedema, oedema peripheral, multiple organ dysfunction syndrome, swelling, swelling face

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b420	Blood pressure functions	16	7	Cardiac and vascular investigations (excl enzyme tests), Decreased and nonspecific blood pressure disorders and shock, Vascular hypertensive disorders	Hypertension, hypotension, blood pressure diastolic increased / decreased, blood pressure increased, orthostatic hypotension, hypertensive crisis
s550-580	Structures related to the metabolic and endocrine systems	16	7	Endocrine neoplasms malignant and unspecified, Exocrine pancreas conditions, Gallbladder disorders, Hepatic and hepatobiliary disorders	Pancreatitis, hepatotoxicity, pancreatitis acute, hepatitis acute, hepatomegaly, cholelithiasis, papillary thyroid cancer
b530	Weight maintenance functions	13	5	Appetite and general nutritional disorders, Physical examination and organ system status topics	Weight decreased / increased, abnormal loss of weight, malnutrition, obesity
s3	Structures involved in voice and speech	12	9	Dental and gingival conditions, Oral soft tissue conditions, Tongue conditions, Upper respiratory tract disorders (excl infections)	Aphthous ulcer, tooth disorder, laryngeal oedema, nasal mucosal ulcer, sinus congestion, tooth discolouration, gingival hyperplasia, glossitis, mouth ulceration
b210-b220	Seeing functions and sensations associated with the eye	11	7	Anterior eye structural change, deposit and degeneration, eye disorders NEC, ocular sensory symptoms NEC, Vision disorders	Cataract, vision blurred, photophobia, amblyopia, visual acuity reduced, visual impairment, dry eye

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
b110-b147	Other mental functions	10	9	Deliria (incl confusion), Mental impairment disorders, Neurological disorders NEC, Seizures (incl subtypes)	Syncope, confusional state, amnesia, diabetic coma, loss of consciousness, seizure, disturbance in attention, agitation, ataxia
s8	Skin and related structures	10	6	Cutaneous neoplasms benign, General system disorders NEC, Miscellaneous and site unspecified neoplasms malignant and unspecified, Skin neoplasms malignant and unspecified	Squamous cell carcinoma, basal cell carcinoma, face oedema, melanocytic naevus, neoplasm skin, skin cancer
	Biomarkers	9	1	Protein and chemistry analyses NEC	C-reactive protein increased
b250	Taste function	8	1	Neurological disorders NEC	Dysguesia
s4	Structures of the cardiovascular, immunological and respiratory systems	5	4	Haematopoietic neoplasms (excl leukaemias and lymphomas), Lower respiratory tract disorders (excl obstruction and infection), Respiratory and mediastinal neoplasms malignant and unspecified, Respiratory disorders NEC	Pulmonary mass, haematological malignancy, lung cyst, lung neoplasm malignant
s530	Structure of stomach	5	5	Gastrointestinal inflammatory conditions, Gastrointestinal ulceration and perforation, Oral soft tissue conditions	Gastric ulcer, gastritis, peptic ulcer, peptic ulcer haemorrhage, stomatitis

ICF code	Domain	Number of trials reporting adverse events in domain	Number of adverse events reported in domain	MedDRA Higher Level Group Terms for adverse events reported (in alphabetical order)	MedDRA Preferred Terms for adverse events reported (in order of frequency reported)
s1	Structures of the nervous system	4	4	Movement disorders (incl parkinsonism), Nervous system neoplasms malignant and unspecified NEC, Peripheral neuropathies	Parkinson's disease, ependymoma, neuropathy peripheral, polyneuropathy
s7	Structures related to movement	2	2	Abdominal hernias and other abdominal wall conditions, General system disorders NEC	Inguinal hernia, hernia
s2	The eye, ear and related structures	1	1	Ocular infections, irritations and inflammations	Eyelid oedema
Note: NEC – not elsewhere classified					

Appendix table 25: Filter 2.0 domains and key outcome measurement tools mapped against the ICF comprehensive core set for IBD

Comprehensive set		Brief set?	Filter 2.0?		CDAI?	IBDQ?	SF-36?	HBI?	PDAI?	VHAI?	Adverse events?
Code	Name		Code	Domains							
b130	Energy and drive functions	yes	yes			yes	yes				yes
b134	Sleep functions	yes	yes			yes					yes
b152	Emotional functions	yes	yes			yes	yes				yes
b1801	Body image	yes									
b28012	Pain in stomach or abdomen	yes	yes	Plus b280-sensation of pain	yes	yes	b280 - sensation of pain	yes	b280 - sensation of pain		yes
b28016	Pain in joints		yes		yes			yes			yes
b430	Haematological system functions		yes		yes					yes	yes
b435	Immunological system functions										yes
b515	Digestive functions	yes	yes								yes
b525	Defecation functions	yes	yes		yes	yes		yes	yes	yes	yes
b530	Weight maintenance functions		yes		yes					yes	yes
b535	Sensations associated with the digestive system		yes			yes					yes
b545	Water, mineral and electrolyte balance functions										Yes
b640	Sexual functions		yes			yes			yes		
b660	Procreation functions										
b810	Protective functions of the skin		s810	Structures of areas of skin	yes - s810			yes - s810	yes - s810	yes - s810	
s540	Structure of intestine	yes	yes		yes			yes	yes	yes	yes

Comprehensive set Code	Name	Brief set?	Filter 2.0? Code	Domains	CDAI?	IBDQ?	SF-36?	HBI?	PDAI?	VHAI?	Adverse events?
s770	Additional musculoskeletal structures related to movement	yes	yes		yes			yes			
d230	Carrying out daily routine										
d5301	Regulating defecation	yes	yes			yes					
d570	Looking after one's health	yes	d5	Quality of life Self-care	yes - quality of life		yes - self care	yes - quality of life			
d7	Interpersonal interactions and relationships	yes	yes			yes					
d810- d839	Education	yes	yes			yes	yes				
d840- d859	Work and employment	yes	yes			yes	yes				
d920	Recreation and leisure		d9	Community, social and civic life		Yes	yes				
Additional domains not in the ICF core set						yes	yes				
			d4	Mobility			yes				
			d640	Doing housework			yes				
			d240	Handling stress and other psychological demands							

Comprehensive set Code	Name	Brief set?	Filter 2.0? Code	Domains	CDAI?	IBDQ?	SF-36?	HBI?	PDAI?	VHAI?	Adverse events?
				Utility							
				Surrogate: disease activity	yes			yes		yes	
			b5500	Body temperature	yes			yes		yes	
			s220	Structure of eyeball	yes			yes			
				Biomarkers							
				Surrogate: treatment acceptability							
			b510	Ingestion functions							
			b540	General metabolic function							

Note: CDAI – crohn’s disease activity index; IBDQ – inflammatory bowel disease questionnaire; SF-36 – short form 36; HBI – Harvey Bradshaw Index; PDAI – perianal disease activity index; VHAI – van Hees activity index

Appendix 7: Additional tables for Chapter 4

Appendix table 26: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) - antibiotics: macrolides

SOC	HLGT	PT	Frequency	Not reported in trials
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea	Common	
	Gastrointestinal signs and symptoms	Abdominal pain	Common	
		Dyspepsia	Common	x
		Nausea	Common	
		Vomiting	Common	
Investigations	Hepatobiliary investigations	Liver function test abnormal	Common	
Nervous system disorders	Headaches	Headache	Common	x
	Neurological disorders NEC	Dysgeusia	Common	
	Sleep disturbances (incl subtypes)	Insomnia	Common	x
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Rash	Common	x
	Skin appendage conditions	Hyperhidrosis	Common	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified
Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

Appendix table 27: Very common and common adverse reactions recorded in SPCs - antibiotics: quinolones

SOC	HLGT	PT	Frequency	Not reported in trials
Gastrointestinal disorders	Gastrointestinal motility and defecation conditions	Diarrhoea	Common	
	Gastrointestinal signs and symptoms	Nausea	Common	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified
Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

Appendix table 28: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) – corticosteroids

SOC	HLGT	PT	Frequency	Not reported in trials
Cardiac disorders	Cardiac disorders signs and symptoms	Palpitations	Common	
Endocrine disorders	Adrenal gland disorders	Cushingoid	Common	
		Cushing's syndrome	Common	
Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract subcapsular	Common	X
	Vision disorders	Vision blurred	Common	
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Dyspepsia	Common	
	Gastrointestinal ulceration and perforation	Peptic ulcer	Common	X
General disorders and administration site conditions	Tissue disorders NEC	Impaired healing	Common	X
Infections and infestations	Infections - pathogen unspecified	Infection	Common	
		Infection susceptibility increased	Common	X
Investigations	Water, electrolyte and mineral investigations	Blood potassium decreased	Common	
Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Fluid retention	Common	
		Hypokalaemia	Common	
		Sodium retention	Common	X
Musculoskeletal and connective tissue disorders	Bone disorders (excl congenital and fractures)	Osteoporosis	Common	X
	Joint disorders	Arthralgia	Common	X
	Muscle disorders	Muscle spasms	Common	
		Muscle twitching	Common	X
		Muscular weakness	Common	
		Myalgia	Common	X

SOC	HLGT	PT	Frequency	Not reported in trials
	Musculoskeletal and connective tissue disorders NEC	Growth retardation	Common	
Nervous system disorders	Headaches	Headache	Common	
	Sleep disturbances (incl subtypes)	Insomnia	Common	
Psychiatric disorders	Anxiety disorders and symptoms	Nervousness	Common	X
	Depressed mood disorders and disturbances	Depression	Common	
	Mood disorders and disturbances NEC	Affective disorder	Common	X
		Euphoric mood	Common	X
		Irritability	Common	X
		Mood swings	Common	
Reproductive system and breast disorders	Menstrual cycle and uterine bleeding disorders	Menstrual disorder	Common	
Skin and subcutaneous tissue disorders	Cornification and dystrophic skin disorders	Skin atrophy	Common	X
		Allergic exanthema	Common	X
	Epidermal and dermal conditions	Dermatitis contact	Common	X
		Skin reaction	Common	X
	Skin appendage conditions	Acne	Common	
		Ecchymosis	Common	X
Petechiae		Common	X	
Vascular disorders	Vascular hypertensive disorders	Hypertension	Common	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

Appendix table 29: Very common and common adverse reactions recorded in summary of product characteristics (SPCs) - immunosuppressives: methotrexate

SOC	HLGT	PT	Frequency	Not reported in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	Common	x
	Platelet disorders	Thrombocytopenia	Common	
	White blood cell disorders	Leukopenia	Common	
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea	Common	
		Abdominal pain	Very common	
		Dyspepsia	Very common	
		Nausea	Very common	
	Gastrointestinal signs and symptoms	Vomiting	Very common	
	Oral soft tissue conditions	Stomatitis	Very common	x
General disorders and administration site conditions	General system disorders NEC	Fatigue	Common	
Infections and infestations	Viral infectious disorders	Herpes zoster	Common	x
Investigations	Hepatobiliary investigations	Hepatic enzyme increased	Very common	
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite	Very common	x
Nervous system disorders	Headaches	Headache	Common	
	Neurological disorders NEC	Somnolence	Common	x
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Alveolitis	Common	x
		Interstitial lung disease	Common	x
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Erythema	Common	x
		Pruritus	Common	x
		Rash	Common	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, affecting more than or equal to one in ten patients exposed to the drug; COMMON, affecting more than or equal to one in 100, but fewer than one in ten patients.

Appendix table 30: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - 5-ASAs

SOC	HLGT	PT	Frequency	Not reported in trials	
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	very rare		
		Aplastic anaemia	rare	X	
		Aplastic anaemia	very rare	X	
		Pancytopenia	very rare		
	Platelet disorders	Thrombocytopenia	Rare	X	
		Thrombocytopenia	very rare	X	
	White blood cell disorders	agranulocytosis	Rare	X	
		agranulocytosis	very rare	X	
		Eosinophilia	very rare	X	
		Leukopenia	Rare	X	
		Leukopenia	very rare	X	
		Neutropenia	Rare	X	
	Cardiac disorders	Myocardial disorders	Myocarditis	rare	X
		Pericardial disorders	Pericarditis	rare	X
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Vertigo	rare	X	
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis	Rare		
		Pancreatitis acute	very rare	X	
	Gastrointestinal inflammatory conditions	Colitis	very rare	X	
	Gastrointestinal motility and defaecation conditions	Diarrhoea	Rare		
	Gastrointestinal signs and symptoms	Abdominal pain	Rare		
Flatulence		Rare	X		

SOC	HLGT	PT	Frequency	Not reported in trials
		Nausea	Rare	
		Vomiting	Rare	
General disorders and administration site conditions	Body temperature conditions	Pyrexia	rare	
		Pyrexia	very rare	
	Fatal outcomes	Death	very rare	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis	very rare	X
		Hepatic function abnormal	rare	X
		Hepatitis	rare	X
		Hepatitis	very rare	X
		Hepatitis cholestatic	very rare	X
		Hepatotoxicity	Rare	X
Immune system disorders	Allergic conditions	Hypersensitivity	very rare	X
	Autoimmune disorders	Systemic lupus erythematosus	Rare	X
Investigations	Gastrointestinal investigations	Amylase increased	Rare	X
	Hepatobiliary investigations	Blood bilirubin increased	very rare	X
		Hepatic enzyme increased	very rare	X
		Liver function test abnormal	rare	X
		Transaminases increased	very rare	
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	very rare	
	Muscle disorders	Myalgia	very rare	
Nervous system disorders	Headaches	Headache	Rare	
	Neurological disorders NEC	Dizziness	Rare	
	Peripheral neuropathies	Neuropathy peripheral	rare	X

SOC	HLGT	PT	Frequency	Not reported in trials
Renal and urinary disorders	Nephropathies	Neuropathy peripheral	very rare	X
		Nephropathy toxic	rare	
		Nephrotic syndrome	rare	X
		Tubulointerstitial nephritis	rare	X
		Tubulointerstitial nephritis	very rare	X
	Renal disorders (excl nephropathies)	Renal failure	rare	X
		Renal failure	very rare	X
		Renal impairment	Rare	
	Urinary tract signs and symptoms	Chromaturia	Rare	X
	Reproductive system and breast disorders	Sexual function and fertility disorders	Oligospermia	very rare
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	Bronchospasm	rare	X
		Bronchospasm	very rare	X
	Lower respiratory tract disorders (excl obstruction and infection)	allergic alveolitis	Rare	X
		Alveolitis	very rare	X
		Eosinophilic pneumonia	rare	X
		Lung infiltration	Rare	X
		Lung infiltration	very rare	X
		Pneumonitis	Rare	X
		Pneumonitis	very rare	X
		Pulmonary eosinophilia	Rare	X
	Pulmonary eosinophilia	very rare	X	
	Respiratory disorders NEC	Cough	Rare	X
		Cough	very rare	X

SOC	HLGT	PT	Frequency	Not reported in trials
		Dyspnoea	Rare	X
		Dyspnoea	very rare	X
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis bullous	rare	X
		Erythema multiforme	very rare	X
		Rash	rare	
		Stevens-Johnson syndrome	very rare	
	Skin appendage conditions	Alopecia	rare	
		Alopecia	very rare	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

Appendix table 31: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - antibiotics: nitroimidazole derivatives

SOC	HLGT	PT	Frequency	Not in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Pancytopenia	Very rare	x
	Platelet disorders	Thrombocytopenia	Very rare	x
	White blood cell disorders	Agranulocytosis	Very rare	x
		Neutropenia	Very rare	x
Eye disorders	Vision disorders	Diplopia	Very rare	x
		Myopia	Very rare	x
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis	Very rare	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatitis cholestatic	Very rare	x
		Jaundice	Very rare	x
Immune system disorders	Allergic conditions	Anaphylactic reaction	Rare	x
Investigations	Hepatobiliary investigations	Liver function test abnormal	Very rare	x
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	Very rare	
	Muscle disorders	Myalgia	Very rare	
Nervous system disorders	Encephalopathies	Encephalopathy	Very rare	x
	Headaches	Headache	Very rare	
	Neurological disorders NEC	Cerebellar syndrome	Very rare	x
		Dizziness	Very rare	
		Somnolence	Very rare	x
	Seizures (incl subtypes)	Seizure	Very rare	x
Psychiatric disorders	Schizophrenia and other psychotic disorders	Psychotic disorder	Very rare	x
Renal and urinary disorders	Urinary tract signs and symptoms	Chromaturia	Very rare	x
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Pruritus	Very rare	x
		Rash	Very rare	

SOC	HLGT	PT	Frequency	Not in trials
		Rash pustular	Very rare	x
	Skin vascular abnormalities	Flushing	Very rare	x

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

Appendix table 32: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - antibiotics: quinolones

SOC	HLGT	PT	Frequency	Not in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	rare	
		Bone marrow failure	very rare	x
		Pancytopenia	very rare	x
	Haemolyses and related conditions	Haemolytic anaemia	very rare	x
		Platelet disorders	Thrombocytopenia	rare
	White blood cell disorders	Thrombocytosis	rare	x
		agranulocytosis	very rare	x
		Leukocytosis	rare	x
		Leukopenia	rare	x
		Neutropenia	rare	x
Cardiac disorders	Cardiac arrhythmias	Tachycardia	rare	x
Ear and labyrinth disorders	Hearing disorders	Hypoacusis	rare	x
		Inner ear and VIIIth cranial nerve disorders	Tinnitus	rare
			Vertigo	rare
Eye disorders	Vision disorders	Visual impairment	rare	x
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis	very rare	
General disorders and administration conditions	General system disorders NEC	Oedema	rare	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic necrosis	very rare	x
		Hepatitis	rare	x
		Jaundice cholestatic	rare	x
		Liver disorder	rare	x
Immune system disorders	Allergic conditions	Allergic oedema	rare	x

SOC	HLGT	PT	Frequency	Not in trials
		Anaphylactic reaction	very rare	x
		Anaphylactic shock	very rare	x
		Hypersensitivity	rare	x
Infections and infestations	Bacterial infectious disorders	Clostridium difficile colitis	rare	
Injury, poisoning and procedural complications	Injuries NEC	Tendon rupture	very rare	x
	Procedural related injuries and complications NEC	Serum sickness	very rare	x
Investigations	Gastrointestinal investigations	Amylase increased	rare	x
Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemia	rare	x
		Hypoglycaemia	rare	x
Musculoskeletal and connective tissue disorders	Joint disorders	Arthritis	rare	x
	Muscle disorders	Hypertonia	rare	x
		Muscle spasms	rare	x
		Muscular weakness	very rare	x
		Myalgia	rare	
		Myasthenia gravis	very rare	x
	Tendon, ligament and cartilage disorders	Tendonitis	very rare	x
Nervous system disorders	Cranial nerve disorders (excl neoplasms)	Olfactory nerve disorder	very rare	x
	Headaches	Migraine	very rare	x
	Increased intracranial pressure and hydrocephalus	Intracranial pressure increased	very rare	x
		Benign intracranial hypertension	very rare	x
	Movement disorders (incl parkinsonism)	Tremor	rare	x
	Neurological disorders NEC	Coordination abnormal	very rare	x
		Dysaesthesia	rare	x

SOC	HLGT	PT	Frequency	Not in trials
		Gait disturbance	very rare	x
		Hypoaesthesia	rare	x
		Paraesthesia	rare	x
	Seizures (incl subtypes)	Seizure	rare	x
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety	rare	x
	Deliria (incl confusion)	Confusional state	rare	x
	Depressed mood disorders and disturbances	Depression	rare	x
	Disturbances in thinking and perception	Hallucination	rare	x
	Schizophrenia and other psychotic disorders	Psychotic disorder	very rare	x
	Sleep disorders and disturbances	Abnormal dreams	rare	x
Renal and urinary disorders	Nephropathies	Tubulointerstitial nephritis	rare	x
	Renal disorders (excl nephropathies)	Renal failure	rare	x
	Urinary tract signs and symptoms	Crystalluria	rare	x
		Haematuria	rare	x
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Dyspnoea	rare	x
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Photosensitivity reaction	rare	
		Stevens-Johnson syndrome	very rare	x
		Toxic epidermal necrolysis	very rare	x
	Skin and subcutaneous tissue disorders NEC	Erythema nodosum	very rare	x
	Skin appendage conditions	Hyperhidrosis	rare	x
	Skin vascular abnormalities	Petechiae	very rare	x
	Epidermal and dermal conditions	Erythema multiforme	very rare	x
Surgical and medical procedures	Vascular therapeutic procedures	Vasodilation procedure	rare	x
Vascular disorders		Hypotension	rare	x

SOC	HLGT	PT	Frequency	Not in trials
	Decreased and nonspecific blood pressure disorders and shock	Syncope	rare	x
	Vascular inflammations	Vasculitis	very rare	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

Appendix table 33: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) – corticosteroids

SOC	HLGT	PT	Frequency	Not in trials
Blood and lymphatic system disorders	White blood cell disorders	Granulocytosis	Rare	X
		Lymphopenia	Rare	X
		Monocytopenia	Rare	X
Endocrine disorders	Adrenal gland disorders	Adrenal suppression	Rare	
		Cushingoid	Rare	
		Cushing's syndrome	very rare	
Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract	Rare	X
		Cataract	very rare	X
	Glaucoma and ocular hypertension	Glaucoma	Rare	X
		Glaucoma	very rare	X
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis	very rare	
	Gastrointestinal motility and defaecation conditions	Constipation	very rare	
	Gastrointestinal signs and symptoms	Dyspepsia	very rare	
	Gastrointestinal ulceration and perforation	Gastroduodenal ulcer	very rare	X
General disorders and administration site conditions	General system disorders NEC	Asthenia	very rare	X
		Fatigue	very rare	X
		Malaise	very rare	X
		Oedema peripheral	very rare	X
Immune system disorders	Allergic conditions	Anaphylactic reaction	very rare	X
Infections and infestations	Fungal infectious disorders	Oropharyngeal candidiasis	Rare	X
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Obesity	Rare	
Musculoskeletal and connective tissue disorders	Bone disorders (excl congenital and fractures)	Osteonecrosis	very rare	X
		Osteoporosis	Rare	X

SOC	HLGT	PT	Frequency	Not in trials
		Osteoporosis	very rare	X
	Muscle disorders	Myalgia	very rare	X
Nervous system disorders	Increased intracranial pressure and hydrocephalus	Benign intracranial hypertension	Rare	X
		Benign intracranial hypertension	very rare	X
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders NEC	Lipodystrophies	Rare	X
	Skin appendage conditions	Rosacea	Rare	
Vascular disorders	Vascular inflammations	Vasculitis	very rare	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified
Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

Appendix table 34: Rare and very rare adverse reactions recorded in summary of product characteristics (SPCs) - immunosuppressives: methotrexate

SOC	HLGT	PT	Frequency	Not in trials
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia megaloblastic	Rare	x
		Aplastic anaemia	Very rare	x
		Bone marrow failure	Very rare	x
	Haematopoietic neoplasms (excl leukaemias and lymphomas)	Lymphoproliferative disorder	Very rare	x
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphadenopathy	Very rare	x
	White blood cell disorders	Eosinophilia	Very rare	x
		Neutropenia	Very rare	
Cardiac disorders	Pericardial disorders	Cardiac tamponade	Rare	x
		Pericardial effusion	Rare	x
		Pericarditis	Rare	x
Eye disorders	Eye disorders NEC	Lacrimation increased	Very rare	x
		Periorbital oedema	Very rare	x
	Ocular infections, irritations and inflammations	Blepharitis	Very rare	x
		Conjunctivitis	Very rare	x
	Ocular sensory symptoms NEC	Photophobia	Very rare	x
	Retina, choroid and vitreous haemorrhages and vascular disorders	Retinopathy	Very rare	x
	Vision disorders	Blindness	Very rare	x
		Vision blurred	Rare	
Visual impairment		Rare	x	
Gastrointestinal disorders	Dental and gingival conditions	Gingivitis	Rare	x
	Gastrointestinal haemorrhages NEC	Haematemesis	Very rare	x

SOC	HLGT	PT	Frequency	Not in trials
		Melaena	Rare	x
	Gastrointestinal inflammatory conditions	Enteritis	Rare	x
	Gastrointestinal motility and defaecation conditions	Megacolon	Very rare	x
General disorders and administration site conditions	Body temperature conditions	Pyrexia	Very rare	
	General system disorders NEC	Pain	Very rare	
	Tissue disorders NEC	Impaired healing	Very rare	x
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Acute hepatic failure	Very rare	x
		Chronic hepatitis	Very rare	x
		Hepatic failure	Very rare	x
		Hepatitis acute	Rare	
		Hepatotoxicity	Rare	x
		Herpes simplex hepatitis	Very rare	x
Immune system disorders	Immunodeficiency syndromes	Hypogammaglobulinaemia	Very rare	x
		Immunosuppression	Very rare	x
Infections and infestations	Bacterial infectious disorders	Furuncle	Very rare	x
		Nocardiosis	Very rare	x
	Fungal infectious disorders	Pneumocystis jirovecii pneumonia	Very rare	x
	Infections - pathogen unspecified	Opportunistic infection	Very rare	x
		Pharyngitis	Rare	x
		Pneumonia	Very rare	
		Sepsis	Very rare	x
	Viral infectious disorders	Cytomegalovirus infection	Very rare	
Investigations	Renal and urinary tract investigations and urinalyses	Blood creatinine increased	Rare	x
		Blood urea increased	Rare	x

SOC	HLGT	PT	Frequency	Not in trials
Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus	Rare	x
	Purine and pyrimidine metabolism disorders	Hyperuricaemia	Rare	x
Musculoskeletal and connective tissue disorders	Fractures	Stress fracture	Rare	x
	Muscle disorders	Muscular weakness	Very rare	x
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm related morbidities	Tumour lysis syndrome	Very rare	x
Nervous system disorders	Movement disorders (incl parkinsonism)	Paresis	Rare	x
	Neurological disorders NEC	Dysgeusia	Very rare	x
		Meningism	Very rare	x
		Paraesthesia	Very rare	x
	Sleep disturbances (incl subtypes)	Insomnia	Very rare	
	Central nervous system infections and inflammations	Meningitis aseptic	Very rare	x
	Psychiatric disorders	Cognitive and attention disorders and disturbances	Cognitive disorder	Very rare
Mood disorders and disturbances NEC		Mood altered	Rare	x
Sexual dysfunctions, disturbances and gender identity disorders		Loss of libido	Very rare	x
Renal and urinary disorders	Renal disorders (excl nephropathies)	Anuria	Rare	x
		Azotaemia	Rare	x
		Oliguria	Rare	x
		Renal failure	Rare	x
	Urinary tract signs and symptoms	Proteinuria	Very rare	x
Reproductive system and breast disorders	Breast disorders	Gynaecomastia	Very rare	x
	Menstrual cycle and uterine bleeding disorders	Menstrual disorder	Very rare	x

SOC	HLGT	PT	Frequency	Not in trials
	Sexual function and fertility disorders	Erectile dysfunction	Very rare	x
		Infertility	Very rare	x
		Oligospermia	Very rare	x
	Vulvovaginal disorders (excl infections and inflammations)	Vaginal discharge	Very rare	x
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	Asthma	Rare	x
		Chronic obstructive pulmonary disease	Very rare	x
	Pleural disorders	Pleural effusion	Very rare	x
	Respiratory disorders NEC	Apnoea	Rare	x
Dyspnoea		Very rare	x	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Erythema multiforme	Rare	x
		Rash erythematous	Rare	x
	Pigmentation disorders	Pigmentation disorder	Rare	x
	Skin and subcutaneous tissue infections and infestations	Paronychia	Very rare	x
	Skin appendage conditions	Acne	Rare	
	Skin vascular abnormalities	Ecchymosis	Rare	x
		Petechiae	Rare	x
Telangiectasia		Very rare	x	
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Hypotension	Rare	x
	Embolism and thrombosis	Embolism	Rare	X

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: RARE, affecting more than or equal to one in 10,000 patients, but fewer than one in 1,000; VERY RARE, affecting less than one in 10,000.

Appendix table 35: All adverse reactions reported in the summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - 5-ASAs

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia megaloblastic						x	
		Aplastic anaemia				x	x	x	
		Pancytopenia						x	
	Coagulopathies and bleeding diatheses (excl thrombocytopenic)	Hypoprothrombinaemia						x	
	Haematological disorders NEC	Methaemoglobinaemia						x	
	Haemoglobinopathies	Anaemia Heinz body						x	
	Haemolyses and related conditions	Haemolytic anaemia						x	
	Platelet disorders	Thrombocytopenia			x	x	x		
	Red blood cell disorders	Macrocytosis						x	
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphadenopathy						x	
	White blood cell disorders	agranulocytosis					x	x	x
		Eosinophilia						x	x
		Leukopenia		x			x	x	x
		Neutropenia					x	x	x
Cardiac disorders	Cardiac disorders signs and symptoms	Cyanosis						x	
		Palpitations						x	
	Myocardial disorders	Allergic myocarditis						x	
		Myocarditis				x		x	
	Pericardial disorders	Pericarditis				x		x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Vertigo			x	x		
Eye disorders	Eye disorders NEC	Periorbital oedema						x
	Ocular infections, irritations and inflammations	Scleritis		x				
Gastrointestinal disorders	Anal and rectal conditions NEC	Anorectal disorder		x				
	Exocrine pancreas conditions	Pancreatitis acute					x	
	Gastrointestinal inflammatory conditions	Colitis					x	
		Colitis ulcerative						x
	Gastrointestinal signs and symptoms	Flatulence		x		x		
	Oral soft tissue conditions	Stomatitis		x				
	Salivary gland conditions	Parotitis						x
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis					x	
		Hepatic failure						x
		Hepatic function abnormal				x		
		Hepatitis				x	x	x
		Hepatitis cholestatic					x	
		Hepatitis fulminant						x
		Hepatotoxicity				x		
Immune system disorders	Allergic conditions	Anaphylactic reaction						x
		Hypersensitivity					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Autoimmune disorders	Systemic lupus erythematosus				x		
	Immune disorders NEC	Polyarteritis nodosa						x
Infections and infestations	Bacterial infectious disorders	Pseudomembranous colitis						x
	Infections - pathogen unspecified	Respiratory tract infection		x				
		Rhinitis			x			
		Sinusitis			x			
Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Serum sickness					x	
Investigations	Gastrointestinal investigations	Amylase increased				x		
	Hepatobiliary investigations	Blood bilirubin increased					x	x
		Hepatic enzyme increased			x		x	
		Liver function test abnormal					x	
	Immunology and allergy investigations	Autoantibody positive						x
Musculoskeletal and connective tissue disorders	Connective tissue disorders (excl congenital)	Systemic lupus erythematosus						x
Nervous system disorders	Central nervous system infections and inflammations	Meningitis aseptic						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Cranial nerve disorders (excl neoplasms)	Parosmia						x
	Encephalopathies	Encephalopathy						x
	Neurological disorders NEC	Ataxia						x
		Dysgeusia		x				
	Peripheral neuropathies	Neuropathy peripheral				x	x	x
Psychiatric disorders	Disturbances in thinking and perception	Hallucination						x
Renal and urinary disorders	Nephropathies	Nephrotic syndrome				x		x
		Tubulointerstitial nephritis				x	x	x
	Renal disorders (excl nephropathies)	Renal failure				x	x	
	Urinary tract signs and symptoms	Chromaturia				x		
		Crystalluria						x
		Haematuria						x
		Proteinuria		x				
Reproductive system and breast disorders	Sexual function and fertility disorders	Oligospermia					x	x
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	Bronchospasm				x	x	
	Lower respiratory tract disorders (excl obstruction and infection)	allergic alveolitis				x		
		Alveolitis					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Eosinophilic pneumonia				x		
		Idiopathic pulmonary fibrosis						x
		Interstitial lung disease	x					x
		Lung infiltration				x	x	
		Pneumonitis				x	x	
		Pulmonary eosinophilia				x	x	x
	Respiratory disorders NEC	Cough		x		x	x	
		Dyspnoea			x	x	x	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema						x
		Urticaria			x			
	Epidermal and dermal conditions	Acute generalised exanthematous pustulosis						x
		Dermatitis bullous				x		
		Dermatitis exfoliative						x
		Drug reaction with eosinophilia and systemic symptoms						x
		Erythema						x
		Erythema multiforme					x	
		Lichen planus						x
		Photosensitivity reaction			x			x
		Skin discolouration						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Toxic epidermal necrolysis						x
Vascular disorders	Vascular inflammations	Vasculitis			x			

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified
Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Appendix table 36: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - antibiotics: macrolides

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Blood and lymphatic system disorders	Platelet disorders	Thrombocytosis			x			
	White blood cell disorders	agranulocytosis						x
		Eosinophilia			x			
		Leukopenia			x			
		Neutropenia			x			
Cardiac disorders	Cardiac arrhythmias	Torsade de pointes						x
		Ventricular tachycardia						x
	Cardiac disorders signs and symptoms	Palpitations			x			
Ear and labyrinth disorders	Hearing disorders	Deafness						x
		Hypoacusis			x			
	Inner ear and VIIIth cranial nerve disorders	Tinnitus			x			
		Vertigo			x			
Gastrointestinal disorders	Anal and rectal conditions NEC	Proctalgia			x			
	Exocrine pancreas conditions	Pancreatitis acute						x
	Gastrointestinal inflammatory conditions	Gastritis			x			
	Gastrointestinal motility and defaecation conditions	Constipation			x			
		Gastrooesophageal reflux disease			x			
	Gastrointestinal signs and symptoms	Dyspepsia		x				
	Eructation			x				

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Flatulence			x			
	Oral soft tissue conditions	Stomatitis			x			
	Salivary gland conditions	Dry mouth			x			
	Tongue conditions	Glossitis			x			
		Tongue discolouration						x
General disorders and administration site conditions	General system disorders NEC	Asthenia			x			
		Chest pain			x			
		Chills			x			
		Fatigue			x			
		Malaise			x			
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis			x			
		Hepatic failure						x
		Hepatitis			x			
		Jaundice hepatocellular						x
Immune system disorders	Allergic conditions	Anaphylactic reaction						x
		Hypersensitivity			x			
Infections and infestations	Bacterial infectious disorders	Erysipelas						x
		Pseudomembranous colitis						x
	Fungal infectious disorders	Candida infection			x			
	Infections - pathogen unspecified	Gastroenteritis			x			
Vaginal infection				x				
Investigations	Cardiac and vascular investigations (excl enzyme tests)	Electrocardiogram QT prolonged			x			

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Enzyme investigations NEC	Blood alkaline phosphatase increased			x			
		Blood lactate dehydrogenase increased			x			
	Haematology investigations (incl blood groups)	International normalised ratio increased						x
		Prothrombin time prolonged						x
	Hepatobiliary investigations	Alanine aminotransferase increased			x			
		Aspartate aminotransferase increased			x			
		Gamma-glutamyltransferase increased			x			
Metabolism and nutrition disorders	Appetite and general nutrition disorders	Decreased appetite			x			
musculoskeletal and connective tissue disorders	Muscle disorders	Myopathy						x
		Rhabdomyolysis						x
Nervous system disorders	Cranial nerve disorders (excl neoplasms)	Anosmia						x
		Parosmia						x
	Headaches	Headache		x				

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Movement disorders (incl parkinsonism)	Tremor			x			
	Neurological disorders NEC	Dizziness			x			
		Paraesthesia						x
		Somnolence			x			
	Seizures (incl subtypes)	Seizure						x
	Sleep disturbances (incl subtypes)	Insomnia		x				
	Neurological disorders NEC	Ageusia						x
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety			x			
	Deliria (incl confusion)	Confusional state						x
		Disorientation						x
	Depressed mood disorders and disturbances	Depression						x
	Dissociative disorders	Depersonalisation/ derealisation disorder						x
	Disturbances in thinking and perception	Hallucination						x
	Schizophrenia and other psychotic disorders	Psychotic disorder						x
	Sleep disorders and disturbances	Abnormal dreams						x
Nephropathies	Tubulointerstitial nephritis						x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Renal and urinary disorders	Renal disorders (excl nephropathies)	Renal failure						x	
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract disorders (excl infections)	Epistaxis			x				
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema						x	
		Urticaria			x				
	Epidermal and dermal conditions	Drug reaction with eosinophilia and systemic symptoms							x
		Pruritus			x				
		Rash		x					
		Stevens-Johnson syndrome							x
		Toxic epidermal necrolysis							x
Skin appendage conditions	Acne							x	
	Hyperhidrosis		x						
Vascular disorders	Vascular haemorrhagic disorders	Haemorrhage						X	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified
Frequency: VERY COMMON, ≥ 1/10; COMMON, ≥ 1/100 to < 1/10; UNCOMMON ≥ 1/1,000 to < 1/100; RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000; and frequency not known, cannot be estimated from the available data.

Appendix table 37: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - antibiotics: nitroimidazole derivatives

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Bone marrow failure						x
		Pancytopenia					x	
	Platelet disorders	Thrombocytopenia					x	
	White blood cell disorders	agranulocytosis					x	
		Leukopenia						x
	Neutropenia					x		
Eye disorders	Vision disorders	Diplopia					x	
	Vision disorders	Myopia					x	
Gastrointestinal disorders	Gastrointestinal conditions NEC	Gastrointestinal disorder						x
	Gastrointestinal signs and symptoms	Abdominal pain						x
		Vomiting						x
	Oral soft tissue conditions	Stomatitis						x
	Tongue conditions	Dysgeusia						x
Tongue coated								x
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatitis cholestatic					x	
		Jaundice					x	
Immune system disorders	Allergic conditions	Anaphylactic reaction				x		
Investigations	Hepatobiliary investigations	Liver function test abnormal					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Metabolism and nutrition disorders	Appetite and general nutrition disorders	Decreased appetite						x
Nervous system disorders	Encephalopathies	Encephalopathy					x	
	Neurological disorders NEC	Cerebellar syndrome					x	
		Somnolence					x	
	Peripheral neuropathies	Peripheral sensory neuropathy						x
	Seizures (incl subtypes)	Epilepsy						
Seizure							x	
Psychiatric disorders	Depressed mood disorders and disturbances	Depression						x
	Schizophrenia and other psychotic disorders	Psychotic disorder					x	
Renal and urinary disorders	Urinary tract signs and symptoms	Chromaturia					x	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema						x
		Urticaria						x
	Epidermal and dermal conditions	Pruritus					x	
		Rash pustular					x	
		Erythema multiforme						x
Skin vascular abnormalities	Flushing					x		

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified. Frequency: VERY COMMON, ≥ 1/10; COMMON, ≥ 1/100 to < 1/10; UNCOMMON ≥ 1/1,000 to < 1/100; RARE, 1/10,000 to < 1/1,000; VERY RARE, < 1/10,000; and frequency not known, cannot be estimated from the available data.

Appendix table 38: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - antibiotics: quinolones

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Bone marrow failure					x		
		Pancytopenia					x		
	Haemolyses and related conditions	Haemolytic anaemia					x		
	Platelet disorders	Thrombocytopenia					x		
		Thrombocytosis					x		
	White blood cell disorders	agranulocytosis						x	
		Eosinophilia			x				
		Leukocytosis					x		
		Leukopenia					x		
		Neutropenia					x		
Cardiac disorders	Cardiac arrhythmias	Tachycardia				x			
		Torsade de pointes						x	
		Ventricular arrhythmia						x	
Ear and labyrinth disorders	Hearing disorders	Hypoacusis				x			
	Inner ear and VIIIth cranial nerve disorders	Tinnitus				x			
		Vertigo					x		
Eye disorders	Vision disorders	Visual impairment				x			
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Dyspepsia			x				
		Flatulence			x				
		Vomiting			x				

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
General disorders and administration site conditions	General system disorders NEC	Asthenia			x			
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatic necrosis					x	
		Hepatitis				x		
		Jaundice cholestatic				x		
		Liver disorder				x		
Immune system disorders	Allergic conditions	Allergic oedema				x		
		Anaphylactic reaction					x	
		Anaphylactic shock						x
		Hypersensitivity				x		
Infections and infestations	Infections - pathogen unspecified	Superinfection			x			
Injury, poisoning and procedural complications	Injuries NEC	Tendon rupture					x	
	Procedural related injuries and complications NEC	Serum sickness					x	
Investigations	Cardiac and vascular investigations (excl enzyme tests)	Electrocardiogram QT prolonged						x
	Enzyme investigations NEC	Blood alkaline phosphatase increased			x			
	Gastrointestinal investigations	Amylase increased				x		
	Haematology investigations (incl blood groups)	International normalised ratio increased						x
	Hepatobiliary investigations	Blood bilirubin increased			x			

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Transaminases increased			x			
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite			x			
	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemia				x		
		Hypoglycaemia					x	
Musculoskeletal and connective tissue disorders	Joint disorders	Arthritis				x		
	Muscle disorders	Hypertonia				x		
		Muscle spasms					x	
		Muscular weakness						x
		Myasthenia gravis						x
	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal pain			x			
	Tendon, ligament and cartilage disorders	Tendonitis					x	
Nervous system disorders	Cranial nerve disorders (excl neoplasms)	Olfactory nerve disorder					x	
	Headaches	Migraine					x	
	Increased intracranial pressure and hydrocephalus	Intracranial pressure increased						x
		Benign intracranial hypertension						x
	Movement disorders (incl parkinsonism)	Tremor				x		
	Neurological disorders NEC	Coordination abnormal						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Dysaesthesia				x		
		Dysgeusia			x			
		Gait disturbance					x	
		Hypoaesthesia				x		
		Paraesthesia				x		
	Seizures (incl subtypes)	Seizure				x		
Psychiatric disorders	Anxiety disorders and symptoms	Agitation			x			
		Anxiety				x		
	Changes in physical activity	Psychomotor hyperactivity			x			
	Deliria (incl confusion)	Confusional state				x		
	Depressed mood disorders and disturbances	Depression				x		
	Disturbances in thinking and perception	Hallucination				x		
	Schizophrenia and other psychotic disorders	Psychotic disorder					x	
	Sleep disorders and disturbances	Abnormal dreams					x	
Sleep disorder				x				
Renal and urinary disorders	Nephropathies	Tubulointerstitial nephritis				x		
	Renal disorders (excl nephropathies)	Renal failure				x		
		Renal impairment			x			
		Crystalluria					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Urinary tract signs and symptoms	Haematuria				x		
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Dyspnoea				x		
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Urticaria			x			
	Epidermal and dermal conditions	Acute generalised exanthematous pustulosis						x
		Erythema multiforme					x	
		Pruritus			x			
		Stevens-Johnson syndrome					x	
		Toxic epidermal necrolysis					x	
	Skin and subcutaneous tissue disorders NEC	Erythema nodosum					x	
	Skin appendage conditions	Hyperhidrosis				x		
Skin vascular abnormalities	Petechiae					x		
Surgical and medical procedures	Vascular therapeutic procedures	Vasodilation procedure				x		
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Hypotension				x		
		Syncope				x		
	Vascular inflammations	Vasculitis					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
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Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Appendix table 39: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - biologics: anti-TNF α

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia		x					
		Pancytopenia					x		
	Haemolyses and related conditions	Haemolytic anaemia					x		
		Platelet disorders	Immune thrombocytopenic purpura			x		x	
			Thrombocytopenia		x	x			
			Thrombotic thrombocytopenic purpura					x	
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphadenopathy		x					
	White blood cell disorders		agranulocytosis						x
			Leukocytosis		x				
			Leukopenia	x	x				x
			Lymphocytosis				x		
			Lymphopenia				x		
			Neutropenia		x				
Cardiac disorders	Cardiac arrhythmias	Arrhythmia				x			
		Bradycardia				x			
		Cardiac arrest						x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
		Tachycardia		x					
	Cardiac disorders signs and symptoms	Cyanosis				x			
		Palpitations		x					
	Coronary artery disorders	Myocardial ischaemia						x	
	Heart failures	Cardiac failure			x				
	Pericardial disorders	Pericardial effusion				x			
Ear and labyrinth disorders	Hearing disorders	Deafness			x				
	Inner ear and VIIIth cranial nerve disorders	Tinnitus			x				
		Vertigo		x					
Eye disorders	Eye disorders NEC	Eye swelling		x					
		Periorbital oedema			x				
	Ocular infections, irritations and inflammations	Blepharitis		x					
		Conjunctivitis		x					
		Endophthalmitis					x		
		Hordeolum			x				
	Vision disorders	Keratitis			x				
		Blindness							x
			Diplopia			x			
		Visual impairment		x					
Gastrointestinal disorders	Gastrointestinal haemorrhages NEC	Gastrointestinal haemorrhage		x					
	Gastrointestinal motility and defaecation conditions	Gastrooesophageal reflux disease		x					

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Gastrointestinal signs and symptoms	Dysphagia			x			
	Gastrointestinal ulceration and perforation	Intestinal perforation			x	x		
	Oral soft tissue conditions	Cheilitis			x			
	Salivary gland conditions	Sjogren's syndrome		x				
General disorders and administration site conditions	General system disorders NEC	Chest pain		x				
		Chills		x				
		Face oedema				x		
		Granuloma					x	
		Inflammation				x		
		Infusion related reaction	x					
		Oedema			x			
		Impaired healing			x	x		
Hepatobiliary disorders	Gallbladder disorders	Cholecystitis			x			
		Hepatic and hepatobiliary disorders	Autoimmune hepatitis				x	
			Hepatic failure					
		Hepatic function abnormal			x			
		Hepatic steatosis				x		
		Hepatitis				x	x	
		Hepatitis B					x	
		Hepatocellular injury				x		
		Jaundice						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders	Allergic conditions	Allergic respiratory system		x				
		Anaphylactic reaction			x	x		
		Anaphylactic shock					x	
	Immune disorders NEC	Sarcoidosis			x	x		
Infections and infestations	Bacterial infectious disorders	Bacterial infection		x	x			
		Cellulitis		x				
		Furuncle					x	
	Fungal infectious disorders	Candida infection		x				
		Fungal infection		x	x			
	Infections - pathogen unspecified	Arthritis infective		x				
		Diverticulitis				x		
		Impetigo		x				
		Infection parasitic					x	
		Lower respiratory tract infection		x				
		Meningitis					x	
		Necrotising fasciitis		x				
		Neurological infection				x		
		Oral infection		x				
		Paronychia		x				
	Vaccine breakthrough infection							x
	Viral infectious disorders	Hepatitis B					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Herpes zoster		x				
		Viral infection	x					
Investigations	Enzyme investigations NEC	Blood lactate dehydrogenase increased		x				
	Haematology investigations (incl blood groups)	Activated partial thromboplastin time prolonged		x				
	Hepatobiliary investigations	Blood bilirubin increased			x			
	Immunology and allergy investigations	Autoantibody positive		x	x			
		Complement factor abnormal				x		
	Lipid analyses	Lipids increased	x					
	Metabolic, nutritional and blood gas investigations	Blood uric acid increased		x				
	Water, electrolyte and mineral investigations	Blood sodium abnormal		x				
Metabolism and nutrition disorders	Bone, calcium, magnesium and phosphorus metabolism disorders	Hypocalcaemia		x				
		Hypophosphataemia		x				
	Electrolyte and fluid balance conditions	Hypokalaemia		x				
	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemia		x				
Musculoskeletal and connective tissue disorders	Connective tissue disorders (excl congenital)	Systemic lupus erythematosus			x			
	Muscle disorders	Rhabdomyolysis			x			

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Musculoskeletal and connective tissue disorders NEC	Musculoskeletal pain	x					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukaemias	Leukaemia				x		
	Lymphomas Hodgkin's disease	Hodgkin's disease				x		
	Lymphomas non-Hodgkin's T-cell	Hepatosplenic T-cell lymphoma						x
	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphoma				x		
	Miscellaneous and site unspecified neoplasms benign	Benign neoplasm		x				
	Reproductive neoplasms female malignant and unspecified	Cervix carcinoma					x	
	Skin neoplasms malignant and unspecified	Malignant melanoma Neuroendocrine carcinoma of the skin Skin cancer				x	x	
								x
				x				
Nervous system disorders	Central nervous system infections and inflammations	Myelitis transverse					x	
	Central nervous system vascular disorders	Cerebrovascular accidents				x		
	Headaches	Migraine		x				
	Mental impairment disorders	Amnesia				x		
	Movement disorders (incl parkinsonism)	Tremor				x		

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Neurological disorders NEC	Agitation			x			
		Hypoaesthesia		x				
		Paraesthesia		x				
		Somnolence				x		
		Peripheral neuropathies	Neuropathy peripheral			x		
		Seizures (incl subtypes)	Seizure			x		
	Spinal cord and nerve root disorders	Nerve root compression		x				
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety		x				
		Nervousness			x			
	Deliria (incl confusion)	Confusional state			x			
	Mood disorders and disturbances NEC	Apathy					x	
Mood altered				x				
Renal and urinary disorders	Renal disorders (excl nephropathies)	Pyelonephritis			x			
		Renal impairment		x				
	Urinary tract signs and symptoms	Haematuria		x				
	Urinary tract signs and symptoms	Nocturia				x		
Reproductive system and breast disorders	Sexual function and fertility disorders	Erectile dysfunction			x			
	Bronchial disorders (excl neoplasms)	Asthma		x				
		Bronchospasm					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Respiratory, thoracic and mediastinal disorders		Chronic obstructive pulmonary disease			x				
	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease			x		x		
		Pulmonary fibrosis					x		
		Pulmonary oedema					x		
	Pleural disorders	Pleural effusion			x		x		
		Pleurisy					x		
	Upper respiratory tract disorders (excl infections)	Epistaxis		x					
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema					x		
	Cornification and dystrophic skin disorders	Hyperkeratosis			x				
	Cutaneous neoplasms benign	Skin papilloma			x				
	Epidermal and dermal conditions	Dermatitis		x					
		Dermatomyositis						x	x
		Dry skin			x				
		Psoriasis			x				
		Scar				x			
	Skin and subcutaneous tissue infections and infestations	Stevens-Johnson syndrome						x	
		Toxic epidermal necrolysis						x	
		Fungal skin infection			x				
Onychomycosis					x				

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Skin appendage conditions	Hyperhidrosis		x				
		Night sweats				x		
		Onychoclasia		x				
		Rosacea				x		
		Seborrhoea				x		
	Skin vascular abnormalities	Ecchymosis		x				
		Petechiae					x	
	Epidermal and dermal conditions	Contusion		x				
		Dermatitis bullous				x		
		Erythema multiforme					x	
	Pigmentation disorders	Pigmentation disorder			x			
	Skin vascular abnormalities	Cutaneous vasculitis					x	
		Flushing		x				
Vascular disorders	Aneurysms and artery dissections	aortic aneurysm				x		
	Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Arterial occlusive disease				x		
		Peripheral ischaemia				x		
		Vasospasm					x	
	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse					x	
		Hypotension		x				
		Syncope				x		
	Embolism and thrombosis	Thrombophlebitis				x		
Vascular disorders NEC	Hot flush		x					

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Vascular haemorrhagic disorders	Haematoma		x	x			
	Vascular hypertensive disorders	Hypertension		x				
	Vascular inflammations	Vasculitis			x	x		

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Appendix table 40: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category – corticosteroids

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Blood and lymphatic system disorders	White blood cell disorders	Granulocytosis				x			
		Lymphopenia				x			
		Monocytopenia				x			
Cardiac disorders	Coronary artery disorders	Myocardial infarction						x	
	Heart failures	Cardiac failure congestive						x	
	Myocardial disorders	Myocardial rupture						x	
Endocrine disorders	Adrenal gland disorders	Adrenal insufficiency						x	
		Steroid withdrawal syndrome						x	
	Hypothalamus and pituitary gland disorders	Hypopituitarism						x	
Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract				x	x	x	
		Cataract subcapsular		x					
		Corneal thinning							x
	Glaucoma and ocular hypertension	Glaucoma				x	x	x	
	Ocular structural change, deposit and degeneration NEC	Chorioretinopathy							x
		Exophthalmos							x
Scleral thinning								x	
Gastrointestinal disorders	Gastrointestinal conditions NEC	Gastric disorder						x	
	Gastrointestinal haemorrhages NEC	Gastric haemorrhage						x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Gastrointestinal inflammatory conditions	Oesophagitis						x
	Gastrointestinal ulceration and perforation	Gastroduodenal ulcer					x	x
		Peptic ulcer		x				
General system disorders and administration conditions	General system disorders NEC	Asthenia					x	
		Fatigue					x	x
		Influenza like illness			x			
		Malaise					x	x
		Oedema peripheral					x	
	Tissue disorders NEC	Impaired healing		x				x
Immune system disorders	Allergic conditions	Anaphylactic reaction					x	
		Drug hypersensitivity						x
Infections		Oropharyngeal candidiasis				x		
	Infections - pathogen unspecified	Infection susceptibility increased		x				x
		Opportunistic infection						x
	Mycobacterial infectious disorders	Tuberculosis						x
Injury, poisoning and procedural complications	Bone and joint injuries	Spinal compression fracture						x
	Injuries NEC	Tendon rupture						x
Investigations	Hepatobiliary investigations	Hepatic enzyme increased						x
	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance decreased						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
	Neurological, special senses and psychiatric investigations	Intraocular pressure increased						x	
	Water, electrolyte and mineral investigations	Urine calcium increased						x	
Metabolism and nutrition disorders	Acid-base disorders	Alkalosis hypokalaemic						x	
		Metabolic acidosis						x	
	Electrolyte and fluid balance conditions	Sodium retention		x					
	Glucose metabolism disorders (incl diabetes mellitus)	Glucose tolerance impaired							x
		Increased insulin requirement							x
	Lipid metabolism disorders	Epidural lipomatosis							x
Musculoskeletal and connective tissue disorders	Bone disorders (excl congenital and fractures)	Osteonecrosis					x	x	
		Osteoporosis		x		x	x	x	
	Fractures	Pathological fracture						x	
	Muscle disorders	Muscle twitching		x					
		Myalgia		x			x		x
		Myopathy							x
	Musculoskeletal and connective tissue disorders NEC	Growth retardation							
	Joint disorders	Arthralgia		x				x	
Neoplasms benign, malignant and	Soft tissue neoplasms malignant and unspecified	Kaposi's sarcoma						x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
unspecified (incl cysts and polyps)									
Nervous system disorders	Increased intracranial pressure and hydrocephalus	Benign intracranial hypertension				x	x		
		Intracranial pressure increased						x	
	Mental impairment disorders	Amnesia						x	
	Neurological disorders NEC	Somnolence			x				
	Seizures (incl subtypes)	Seizure						x	
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety						x	
		Nervousness		x					
	Cognitive and attention disorders and disturbances	Cognitive disorder						x	
	Deliria (incl confusion)	Confusional state						x	
	Mood disorders and disturbances NEC	Affective disorder		x					
		Euphoric mood		x					x
		Irritability		x					x
	Personality disorders and disturbances in behaviour	Personality change						x	
	Psychiatric and behavioural symptoms NEC	Abnormal behaviour						x	
	Psychiatric disorders NEC	Mental disorder						x	
Schizophrenia and other psychotic disorders	Psychotic behaviour							x	
	Psychotic disorder							x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Reproductive system and breast disorders		Menstruation irregular						x	
Respiratory, thoracic and mediastinal disorders	Pulmonary vascular disorders	Pulmonary embolism						x	
	Respiratory disorders NEC	Hiccups						x	
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Angioedema						x	
	Cornification and dystrophic skin disorders	Skin atrophy		x					
		Epidermal and dermal conditions	Allergic exanthema		x				x
			Dermatitis contact		x				x
			Erythema						x
		Pruritus						x	
	Skin reaction			x					
	Skin and subcutaneous tissue disorders NEC	Lipodystrophies					x		
	Skin vascular abnormalities	Ecchymosis			x				x
		Petechiae			x				x
Telangiectasia								x	
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Hypotension						x	
	Embolism and thrombosis	Embolism arterial						x	
		Thrombosis						x	
Vascular inflammations	Vasculitis					x	X		

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
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Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Appendix table 41: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - immunosuppressives: antimetabolites

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia megaloblastic				x			
		Aplastic anaemia				x			
		Bone marrow failure				x			
		Pancytopenia				x			
	White blood cell disorders	agranulocytosis					x		
		Granulocytopenia					x		
Gastrointestinal disorders	Gastrointestinal ulceration and perforation	Gastrointestinal ulcer					x		
	Malabsorption conditions	Steatorrhoea			x				
	Oral soft tissue conditions	Mouth ulceration				x			
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Cholestasis		x	x				
		Hepatic necrosis				x			
		Liver disorder		x					
		Liver injury					x		
		Venoocclusive liver disease					x		
Infections and infestations	Bacterial infectious disorders	Bacterial infection			x				
	Fungal infectious disorders	Fungal infection			x				
Metabolism and nutrition disorders	Appetite and general nutrition disorders	Decreased appetite	x		x				
Neoplasms benign, malignant and	Leukaemias	Acute myeloid leukaemia				x	x		
	Lymphomas non-Hodgkin's T-cell	Hepatosplenic T-cell lymphoma					x		

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
unspecified (incl cysts and polyps)	Lymphomas non-Hodgkin's unspecified histology	Non-Hodgkin's lymphoma		x		x			
	Metastases	Metastasis					x		
	Miscellaneous and site unspecified neoplasms malignant and unspecified	Squamous cell carcinoma		x					
	Reproductive neoplasms female malignant and unspecified	Cervix carcinoma			x		x		
		Vulval cancer			x				
	Skin neoplasms malignant and unspecified	Skin cancer					x		
	Soft tissue neoplasms malignant and unspecified	Kaposi's sarcoma			x				
Sarcoma						x			
Reproductive system and breast disorders	Sexual function and fertility disorders	Oligospermia					x		
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease				x			
		Pneumonitis					x		
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Acute febrile neutrophilic dermatosis						x	
		Photosensitivity reaction				x			
		Stevens-Johnson syndrome				x	x		
		Toxic epidermal necrolysis				x	x		
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; NEC – not elsewhere classified									

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
<p>Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.</p>								

Appendix table 42: All adverse reactions recorded in summary of product characteristics (SPCs), but not in Crohn's disease trials, by frequency category - immunosuppressives: methotrexate

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia		x				
		Anaemia megaloblastic				x		
		Aplastic anaemia					x	
		Bone marrow failure					x	
		Pancytopenia				x		
	Haematopoietic neoplasms (excl leukaemias and lymphomas)	Lymphoproliferative disorder					x	
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphadenopathy					x	
	White blood cell disorders	agranulocytosis				x		
Eosinophilia							x	
Cardiac disorders	Pericardial disorders	Cardiac tamponade				x		
		Pericardial effusion				x		
		Pericarditis				x		
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Vertigo			x			
Eye disorders	Eye disorders NEC	Lacrimation increased					x	
		Periorbital oedema					x	
	Ocular infections, irritations and inflammations	Blepharitis					x	
		Conjunctivitis					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Ocular sensory symptoms NEC	Photophobia					x	
	Retina, choroid and vitreous haemorrhages and vascular disorders	Retinopathy					x	
	Vision disorders	Blindness					x	
		Visual impairment				x		
Gastrointestinal disorders	Dental and gingival conditions	Gingivitis				x		
	Gastrointestinal haemorrhages NEC	Gastrointestinal haemorrhage			x			
		Haematemesis					x	
		Melaena				x		
	Gastrointestinal inflammatory conditions	Enteritis				x		
	Gastrointestinal motility and defaecation conditions	Megacolon					x	
	Gastrointestinal ulceration and perforation	Gastrointestinal ulcer			x			
	Malabsorption conditions	Malabsorption			x			
	Oral soft tissue conditions	Stomatitis	x					
General disorders and administration site conditions	Tissue disorders NEC	Impaired healing					x	
Hepatobiliary disorders		Acute hepatic failure					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
	Hepatic and hepatobiliary disorders	Chronic hepatitis					x		
		Hepatic cirrhosis			x				
		Hepatic failure					x		
		Hepatic fibrosis			x				
		Hepatic steatosis			x				
		Hepatotoxicity					x		
		Herpes simplex hepatitis						x	
Immune system disorders	Allergic conditions	Anaphylactic shock			x				
		Anaphylactoid reaction			x				
		Hypersensitivity			x				
	Immune disorders NEC	Hypersensitivity vasculitis			x				
	Immunodeficiency syndromes	Hypogammaglobulinaemia						x	
Immunosuppression							x		
Infections and infestations	Bacterial infectious disorders	Furuncle					x		
		Nocardiosis					x		
	Fungal infectious disorders	Pneumocystis jirovecii pneumonia					x	x	
	Infections - pathogen unspecified	Opportunistic infection						x	
		Pharyngitis					x		
		Sepsis						x	
	Viral infectious disorders	Herpes zoster		x	x				
Injury, poisoning and procedural complications	Exposures, chemical injuries and poisoning	Toxicity to various agents			x				

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Investigations	Protein and chemistry analyses NEC	Blood albumin decreased			x			
	Renal and urinary tract investigations and urinalyses	Blood creatinine increased				x		
		Blood urea increased				x		
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite	x					
	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus				x		
	Metabolism disorders NEC	Metabolic disorder						x
	Purine and pyrimidine metabolism disorders	Hyperuricaemia				x		
Musculoskeletal and connective tissue disorders	Bone disorders (excl congenital and fractures)	Osteoporosis			x			
	Fractures	Stress fracture				x		
	Muscle disorders	Muscular weakness					x	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm related morbidities	Tumour lysis syndrome					x	
Nervous system disorders	Encephalopathies	Encephalopathy			x			
	Increased intracranial pressure and hydrocephalus	Brain oedema						x

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Movement disorders (incl parkinsonism)	Paresis				x		
	Neurological disorders NEC	Dysgeusia					x	
		Meningism					x	
		Paraesthesia					x	
		Somnolence		x				
	Seizures (incl subtypes)	Seizure			x			
	Central nervous system infections and inflammations	Meningitis aseptic					x	
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirths	Abortion						x
		Foetal death						x
	Foetal complications	Foetal damage						x
Psychiatric disorders	Cognitive and attention disorders and disturbances	Cognitive disorder					x	
	Deliria (incl confusion)	Confusional state			x			
	Depressed mood disorders and disturbances	Depression			x			
	Mood disorders and disturbances NEC	Mood altered				x		
	Schizophrenia and other psychotic disorders	Psychotic disorder						x
	Sexual dysfunctions, disturbances and gender identity disorders	Loss of libido					x	

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
Renal and urinary disorders	Bladder and bladder neck disorders (excl calculi)	Cystitis noninfective			x				
	Renal disorders (excl nephropathies)	Anuria				x			
		Azotaemia				x			
		Oliguria				x			
		Renal failure				x			
	Urinary tract signs and symptoms	Dysuria			x				
		Proteinuria					x		
Reproductive system and breast disorders	Breast disorders	Gynaecomastia					x		
	Female reproductive tract infections and inflammations	Vaginal inflammation			x				
		Menstrual cycle and uterine bleeding disorders	Menstrual disorder					x	
		Sexual function and fertility disorders	Erectile dysfunction					x	
	Infertility						x		
	Oligospermia						x		
	Vulvovaginal disorders (excl infections and inflammations)	Vaginal discharge					x		
		Vaginal ulceration			x				
Respiratory, thoracic and mediastinal disorders	Bronchial disorders (excl neoplasms)	Asthma				x			
		Chronic obstructive pulmonary disease					x		
	Acute pulmonary oedema							x	
	Alveolitis		x						

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known	
	Lower respiratory tract disorders (excl obstruction and infection)	Interstitial lung disease		x					
		Pulmonary fibrosis			x				
		Pleural disorders	Pleural effusion					x	
		Respiratory disorders NEC	Apnoea				x		
	Dyspnoea						x		
Skin and subcutaneous tissue disorders	Angioedema and urticaria	Urticaria			x				
	Epidermal and dermal conditions	Dermatitis exfoliative							x
		Dermatitis herpetiformis				x			
		Erythema		x					
		Erythema multiforme					x		
		Photosensitivity reaction				x			
		Pruritus		x					
		Psoriasis				x			
		Rash		x					
		Rash erythematous						x	
		Skin necrosis							x
	Stevens-Johnson syndrome				x				
	Toxic epidermal necrolysis				x				
	Pigmentation disorders	Pigmentation disorder						x	
		Skin hyperpigmentation				x			
Skin and subcutaneous tissue disorders NEC	Rheumatoid nodule			x					

SOC	HLGT	PT	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
	Skin and subcutaneous tissue infections and infestations	Paronychia					x	
	Skin vascular abnormalities	Ecchymosis				x		
		Petechiae				x		x
		Telangiectasia					x	
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Hypotension				x		
	Embolism and thrombosis	Embolism				x		
	Vascular haemorrhagic disorders	Haemorrhage						x
	Vascular inflammations	Vasculitis			x			

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term NEC – not elsewhere classified

Frequency: VERY COMMON, $\geq 1/10$; COMMON, $\geq 1/100$ to $< 1/10$; UNCOMMON $\geq 1/1,000$ to $< 1/100$; RARE, $1/10,000$ to $< 1/1,000$; VERY RARE, $< 1/10,000$; and frequency not known, cannot be estimated from the available data.

Appendix table 43: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - 5-ASAs

SOC	HLGT	PT	Recorded as potential ADR
Blood and lymphatic system disorders	Platelet disorders	Thrombocytosis	X
Eye disorders	Eye disorders NEC	Dry eye	
Gastrointestinal disorders	Anal and rectal conditions NEC	Proctalgia	
	Gastrointestinal inflammatory conditions	Crohn's disease Enteritis	
	Gastrointestinal motility and defaecation conditions	Diarrhoea haemorrhagic	X
	Gastrointestinal signs and symptoms	Abdominal distension	
		Abnormal faeces	X
	Gastrointestinal stenosis and obstruction	Ileus	
		Intestinal obstruction	
		Intestinal stenosis	
		Subileus	
	Oral soft tissue conditions	Oral pain	
Tongue conditions	Glossodynia		
General disorders and administration conditions	General system disorders NEC	Asthenia	X
		Chest discomfort	
		Chills	
		Feeling abnormal	
		Hernia	
		Malaise	
		Oedema	X
Stenosis			

SOC	HLGT	PT	Recorded as potential ADR
	Therapeutic and nontherapeutic effects (excl toxicity)	Drug intolerance	X
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatomegaly	
Infections and infestations	Infections - pathogen unspecified	Abscess	
		Peritonitis	
		Pyuria	X
		Sepsis	
Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Intestinal anastomosis complication	
Investigations	Physical examination and organ system status topics	Weight decreased	X
	Protein and chemistry analyses NEC	C-reactive protein increased	X
	Renal and urinary tract investigations and urinalyses	Blood creatinine increased	
Metabolism and nutrition disorders	Lipid metabolism disorders	Hyperlipidaemia	X
Musculoskeletal and connective tissue disorders	Muscle disorders	Muscle spasms	
	Musculoskeletal and connective tissue disorders NEC	Back pain	X
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Reproductive neoplasms female malignant and unspecified	Ovarian cancer	
	Reproductive neoplasms male malignant and unspecified	Benign neoplasm of epididymis	
Pregnancy, puerperium and perinatal conditions	Pregnancy, labour, delivery and postpartum conditions	Pregnancy	
Psychiatric disorders	Sexual dysfunctions, disturbances and gender identity disorders	Libido decreased	
	Suicidal and self-injurious behaviours NEC	Completed suicide	
Renal and urinary disorders	Urolithiases	Nephrolithiasis	

SOC	HLGT	PT	Recorded as potential ADR
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis	
	Skin appendage conditions	Night sweats	
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Surgery	
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified			

Appendix table 44: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - antibiotics: macrolides

SOC	HLGT	PT	Recorded as potential ADR
Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Crohn's disease	
Infections and infestations	Fungal infectious disorders	Vulvovaginal candidiasis	
Infections and infestations	Infections - pathogen unspecified	Anal abscess	
Musculoskeletal and connective tissue disorders	Joint disorders	Arthralgia	
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Hospitalisation Surgery	
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified			

Appendix table 45: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - antibiotics: nitroimidazole derivatives

SOC	HLGT	PT	Recorded as potential ADR
Cardiac disorders	Coronary artery disorders	Angina pectoris	
Endocrine disorders	Adrenal gland disorders	Cushingoid	X
		Cushing's syndrome	
Gastrointestinal disorders	Anal and rectal conditions NEC	Anorectal discomfort	
		Proctalgia	
	Gastrointestinal haemorrhages NEC	Rectal haemorrhage	
	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal signs and symptoms	Abdominal pain upper	
	Oral soft tissue conditions	Oral pain	
	Tongue conditions	Glossitis	
General disorders and administration conditions	General system disorders NEC	Fatigue	
		Oedema	X
		Pain	
Hepatobiliary disorders	Hepatic and hepatobiliary disorders	Hepatotoxicity	
Infections and infestations	Bacterial infectious disorders	Furuncle	
	Fungal infectious disorders	Oral candidiasis	
	Infections - pathogen unspecified	Abdominal abscess	
		Abscess	
		Anal abscess	
		Nasopharyngitis	
		Urinary tract infection	
		Vaginal infection	
	Viral infectious disorders	Hepatitis C	

SOC	HLGT	PT	Recorded as potential ADR
Investigations	Haematology investigations (incl blood groups)	White blood cell count decreased	
	Hepatobiliary investigations	Alanine aminotransferase increased	
		Liver function test increased	
	Physical examination and organ system status topics	Weight decreased	
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	Fistula	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Miscellaneous and site unspecified neoplasms malignant and unspecified	Adenocarcinoma	
Nervous system disorders	Movement disorders (incl parkinsonism)	Parkinson's disease	
	Neurological disorders NEC	Agitation	
		Burning sensation	
	Peripheral neuropathies	Neuropathy peripheral	
	Sleep disturbances (incl subtypes)	Insomnia	X
Skin and subcutaneous tissue disorders	Skin appendage conditions	Acne	X
		Alopecia	
	Skin vascular abnormalities	Purpura	X
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Abscess drainage	
Vascular disorders	Embolism and thrombosis	Deep vein thrombosis	
Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified			

Appendix table 46: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - antibiotics: quinolones

SOC	HLGT	PT	Reported as possible ADR
Endocrine disorders	Adrenal gland disorders	Cushingoid	X
		Cushing's syndrome	
Gastrointestinal disorders	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal signs and symptoms	Abdominal pain	
	Oral soft tissue conditions	Oral pain	
	Tongue conditions	Glossitis	
General disorders and administration conditions	General system disorders NEC	Fatigue	
		Pain	
Infections and infestations	Fungal infectious disorders	Fungal infection	
		Mucocutaneous candidiasis	
		Onychomycosis	
		Oral candidiasis	
		Vulvovaginal candidiasis	
		Infections - pathogen unspecified	Abscess
	Viral infectious disorders	Anal abscess	
		Infection	
		Nasopharyngitis	
		Opportunistic infection	
		Upper respiratory tract infection	
		Vaginal infection	
		Anogenital warts	
		Herpes simplex	
Oral herpes			

SOC	HLGT	PT	Reported as possible ADR
Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Anastomic leak	
		Infusion related reaction	X
		Stomal hernia	
Investigations	Physical examination and organ system status topics	Weight decreased	
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	Fistula	
	Tendon, ligament and cartilage disorders	Tendon pain	
Nervous system disorders	Central nervous system vascular disorders	Superior sagittal sinus thrombosis	
	Neurological disorders NEC	Agitation	
	Sleep disturbances (incl subtypes)	Insomnia	X
Skin and subcutaneous tissue disorders	Skin appendage conditions	Acne	
	Skin vascular abnormalities	Purpura	X
Surgical and medical procedures	Gastrointestinal therapeutic procedures	Colectomy	
	Therapeutic procedures and supportive care NEC	Hospitalisation	
		Surgery	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified

Appendix table 47: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - biologics: anti-TNF α

SOC	HLGT	PT	Reported as possible ADR
Endocrine disorders	Adrenal gland disorders	Cushingoid	X
Eye disorders	Vision disorders	Vision blurred	
Gastrointestinal disorders	Anal and rectal conditions NEC	Anal fissure	
	Gastrointestinal haemorrhages NEC	Haematochezia	
	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal signs and symptoms	Abdominal distension	
		Abdominal pain upper	
		Abdominal tenderness	
		Flatulence	
	Gastrointestinal stenosis and obstruction	Anal stenosis	
		Ileus	
		Intestinal obstruction	
Oral soft tissue conditions	Aphthous ulcer		
General disorders and administration conditions	Administration site reactions	Injection site bruising	X
		Injection site erythema	X
		Injection site haemorrhage	X
		Injection site irritation	X
		Injection site pain	X
		Injection site pruritus	X
	Fatal outcomes	Death	
	General system disorders NEC	Chest discomfort	X

SOC	HLGT	PT	Reported as possible ADR
		Chest pain	X
		Flushing	X
		Multiple organ dysfunction syndrome	
		Oedema peripheral	
	Therapeutic and nontherapeutic effects (excl toxicity)	Drug intolerance	
Hepatobiliary disorders	Gallbladder disorders	Cholelithiasis	
Immune system disorders	Allergic conditions	Type IV hypersensitivity reaction	X
Infections and infestations	Bacterial infectious disorders	Legionella infection	
		Listeriosis	
		Nocardiosis	
		Staphylococcal sepsis	
	Fungal infectious disorders	Aspergillus infection	
		Blastomycosis	
		Coccidioidomycosis	
		Histoplasmosis	
		Mucocutaneous candidiasis	
		Onychomycosis	
		Pneumocystis jirovecii pneumonia	
		Vulvovaginal candidiasis	
	Infections - pathogen unspecified	Abdominal abscess	
		Abdominal wall abscess	
		Abscess	
		Anal abscess	

SOC	HLGT	PT	Reported as possible ADR
		Appendicitis	
		Bronchitis	
		Gastroenteritis	
		Gastrointestinal infection	
		Infection	
		Infectious colitis	
		Liver abscess	
		Nasopharyngitis	
		Pelvic abscess	
		Pelvic inflammatory disease	
		Peritonitis	
		Pharyngitis	X
		Pneumonia	X
		Pyelonephritis	
		Rhinitis	
		Skin infection	
	Mycobacterial infectious disorders	Pulmonary tuberculosis	
	Viral infectious disorders	Anogenital warts	
		Cytomegalovirus infection	
		Hepatitis C	
		Herpes simplex	
		Herpes virus infection	
		Oral herpes	

SOC	HLGT	PT	Reported as possible ADR
Injury, poisoning and procedural complications	Injuries NEC	Contusion	
	Procedural related injuries and complications NEC	Infusion related reaction	
		Post procedural complication	
		Procedural pain	
	Stomal hernia		
Investigations	Gastrointestinal investigations	Pancreatic enzymes increased	
	Hepatobiliary investigations	Alanine aminotransferase abnormal	
		Liver function test abnormal	X
		Liver function test increased	
	Immunology and allergy investigations	Antinuclear antibody positive	
		Double stranded DNA antibody	
	Musculoskeletal and soft tissue investigations (excl enzyme tests)	Bone density decreased	
Physical examination and organ system status topics	Weight decreased		
Toxicology and therapeutic drug monitoring	Drug specific antibody present		
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Hyperphagia	X
		Malnutrition	
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	Anal fistula	
		Fistula	
		Pain in extremity	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasms malignant and unspecified (incl nipple)	Breast cancer	
	Gastrointestinal neoplasms malignant and unspecified	Rectal adenocarcinoma	

SOC	HLGT	PT	Reported as possible ADR
		Rectal cancer	
	Haematopoietic neoplasms (excl leukaemias and lymphomas)	Haematological malignancy	
	Lymphomas non-Hodgkin's T-cell	Natural killer-cell lymphoblastic lymphoma	
	Miscellaneous and site unspecified neoplasms malignant and unspecified	Carcinoma in situ	
		Neoplasm	
		Neoplasm malignant	X
		Squamous cell carcinoma	
	Renal and urinary tract neoplasms malignant and unspecified	Bladder cancer	
		Renal cell carcinoma	
	Skin neoplasms malignant and unspecified	Basal cell carcinoma	
		Neoplasm skin	
Nervous system disorders	Central nervous system vascular disorders	Superior sagittal sinus thrombosis	
	Neurological disorders NEC	Dysgeusia	
		Sensory loss	
		Syncope	
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirths	Abortion spontaneous	
	Pregnancy, labour, delivery and postpartum conditions	Pregnancy	
Psychiatric disorders	Mood disorders and disturbances NEC	Mood swings	X
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Laryngeal pain	
		Pulmonary mass	

SOC	HLGT	PT	Reported as possible ADR
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Dermatitis atopic Skin lesion	
	Skin and subcutaneous tissue disorders NEC	Skin ulcer	
	Skin appendage conditions	Acne	
	Skin vascular abnormalities	Hypersensitivity vasculitis	
Surgical and medical procedures	Gastrointestinal therapeutic procedures	Appendicectomy	
		Intestinal resection	
	Therapeutic procedures and supportive care NEC	Antibiotic therapy	
		Fistula repair Hospitalisation Surgery	
Vascular disorders	Embolism and thrombosis	Venous thrombosis	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified

Appendix table 48: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) – corticosteroids

SOC	HLGT	PT	Reported as a possible ADR
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia	X
	Coagulopathies and bleeding diatheses (excl thrombocytopenic)	Increased tendency to bruise	X
Endocrine disorders	Adrenal gland disorders	Adrenal disorder	
	Thyroid gland disorders	Hyperthyroidism	
Eye disorders	Vision disorders	Visual impairment	
Gastrointestinal disorders	Abdominal hernias and other abdominal wall conditions	Inguinal hernia	
	Dental and gingival conditions	Tooth disorder	
	Gastrointestinal conditions NEC	Anal fistula	
	Gastrointestinal haemorrhages NEC	Melaena	X
	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal motility and defaecation conditions	Diarrhoea haemorrhagic	
	Gastrointestinal signs and symptoms	Abdominal mass	
		Abdominal pain upper	
		Flatulence	
		Vomiting	X
	Gastrointestinal stenosis and obstruction	Ileus	
		Intestinal obstruction	
	Gastrointestinal ulceration and perforation	Duodenal ulcer	
Salivary gland conditions	Dry mouth	X	
General disorders and administration site conditions	General system disorders NEC	Chills	
		Flushing	X

SOC	HLGT	PT	Reported as a possible ADR
		Influenza like illness	
		Oedema	X
		Oedema peripheral	X
Infections and infestations	Fungal infectious disorders	Oral candidiasis	
		Vulvovaginal candidiasis	X
	Infections - pathogen unspecified	Anal abscess	X
		Conjunctivitis	X
		Mesenteric abscess	
		Nasopharyngitis	
		Psoas abscess	
		Respiratory tract infection	
		Sinusitis	
	Viral infectious disorders	Respiratory tract infection viral	
		Viral infection	
Injury, poisoning and procedural complications	Bone and joint injuries	Hand fracture	X
Investigations	Endocrine investigations (incl sex hormones)	Blood cortisol abnormal	
		Blood cortisol decreased	X
	Haematology investigations (incl blood groups)	Haemoglobin decreased	
		White blood cell count increased	X
	Hepatobiliary investigations	Alanine aminotransferase increased	X

SOC	HLGT	PT	Reported as a possible ADR
		Aspartate aminotransferase increased	X
	Physical examination and organ system status topics	Weight increased	
	Protein and chemistry analyses NEC	Blood albumin decreased	X
		C-reactive protein increased	
		Protein total decreased	X
	Renal and urinary tract investigations and urinalyses	Blood creatinine increased	X
	Water, electrolyte and mineral investigations	Blood calcium decreased	X
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Decreased appetite	X
	Bone, calcium, magnesium and phosphorus metabolism disorders	Hypocalcaemia	X
	Lipid metabolism disorders	Lipohypertrophy	X
Musculoskeletal and connective tissue disorders	Joint disorders	Arthritis	
		Joint swelling	X
	Musculoskeletal and connective tissue disorders NEC	Back pain	X
		Fistula	
Nervous system disorders	Demyelinating disorders	Multiple sclerosis	
Pregnancy, puerperium and perinatal conditions	Maternal complications of pregnancy	Ectopic pregnancy	
	Pregnancy, labour, delivery and postpartum conditions	Pregnancy	
		Unintended pregnancy	
Psychiatric disorders	Mood disorders and disturbances NEC	Affect lability	X
		Mood altered	X
	Menstrual cycle and uterine bleeding disorders	Metrorrhagia	

SOC	HLGT	PT	Reported as a possible ADR
Reproductive system and breast disorders	Vulvovaginal disorders (excl infections and inflammations)	Bartholin's cyst	
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Laryngeal pain	
		Oropharyngeal pain	
Skin and subcutaneous tissue disorders	Upper respiratory tract disorders (excl infections)	Nasal mucosal ulcer	X
	Angioedema and urticaria	Swelling face	
	Epidermal and dermal conditions	Eczema	X
	Skin appendage conditions	Alopecia	X
		Hair growth abnormal	X
Surgical and medical procedures	Head and neck therapeutic procedures Therapeutic procedures and supportive care NEC	Hypertrichosis	X
		Dental operation	
		Hospitalisation	
Vascular disorders	Vascular disorders NEC	Flushing	
		Hot flush	X
	Vascular hypertensive disorders	Hypertensive crisis	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified

Appendix table 49: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - immunosuppressives: antimetabolites

SOC	HLGT	PT	Reported as a possible ADR
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemia macrocytic	
	White blood cell disorders	Lymphopenia Neutropenia	
Cardiac disorders	Coronary artery disorders	Angina pectoris	
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Vertigo	
Endocrine disorders	Adrenal gland disorders	Cushingoid	x
Eye disorders	Anterior eye structural change, deposit and degeneration	Cataract	x
Gastrointestinal disorders	Anal and rectal conditions NEC	Anal fissure	
		Proctalgia	
	Exocrine pancreas conditions	Pancreatitis acute	
	Gastrointestinal haemorrhages NEC	Gastrointestinal haemorrhage	
	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal motility and defaecation conditions	Constipation	
	Gastrointestinal signs and symptoms	Abdominal pain	
		Abdominal pain upper	
		Abdominal symptom	
		Dyspepsia	
Flatulence			
Gastrointestinal stenosis and obstruction	Intestinal obstruction		
	Subileus		
Administration site reactions	Injection site reaction	x	

SOC	HLGT	PT	Reported as a possible ADR
General disorders and administration conditions	Body temperature conditions	Pyrexia	
	General system disorders NEC	Asthenia	
		Facial pain	
		Fatigue	
		Influenza like illness	
		Malaise	
		Swelling	
	Therapeutic and nontherapeutic effects (excl toxicity)	Drug intolerance	
Hepatobiliary disorders	Bile duct disorders	Biliary colic	
	Hepatic and hepatobiliary disorders	Hepatitis acute	
Immune system disorders	Allergic conditions	Seasonal allergy	
Infections and infestations	Bacterial infectious disorders	Clostridium difficile infection	
	Infections - pathogen unspecified	Abdominal abscess	
		Anal abscess	
		Appendicitis	
		Conjunctivitis	
		Eye infection	
		Gastroenteritis	
		Gastrointestinal infection	
		Hordeolum	
		Infection	
		Pneumonia	
		Respiratory tract infection	
		Rhinitis	

SOC	HLGT	PT	Reported as a possible ADR
		Skin infection	
		Upper respiratory tract infection	
		Urinary tract infection	
		Vaginal infection	
	Viral infectious disorders	Hepatitis C	
		Herpes virus infection	
		Herpes zoster	
		Influenza	
		Lower respiratory tract infection viral	
Injury, poisoning and procedural complications	Bone and joint injuries	Fracture	
	Injuries NEC	Arthropod sting	
	Procedural related injuries and complications NEC	Post procedural complication	x
Investigations	Endocrine investigations (incl sex hormones)	Blood cortisol decreased	
	Enzyme investigations NEC	Blood alkaline phosphatase increased	
	Gastrointestinal investigations	Amylase increased	
		Lipase increased	
	Haematology investigations (incl blood groups)	Platelet count decreased	
		White blood cell count decreased	x
	Hepatobiliary investigations	Alanine aminotransferase increased	
		Aspartate aminotransferase increased	
		Gamma-glutamyltransferase increased	
		Hepatic enzyme increased	
Liver function test increased			
		Transaminases increased	x

SOC	HLGT	PT	Reported as a possible ADR
	Metabolic, nutritional and blood gas investigations	Blood glucose abnormal	
	Musculoskeletal and soft tissue investigations (excl enzyme tests)	Bone density decreased	x
	Physical examination and organ system status topics	Weight increased	
	Protein and chemistry analyses NEC	C-reactive protein increased	
Metabolism and nutrition disorders	Appetite and general nutritional disorders	Hyperphagia	x
	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemia	
	Iron and trace metal metabolism	Iron deficiency	
	Metabolism disorders NEC	Hyperamylasemia	
Musculoskeletal and connective tissue disorders	Bone disorders (excl congenital and fractures)	Osteoporosis	
	Joint disorders	Arthralgia	
		Joint stiffness	
	Muscle disorders	Muscle spasms	
		Myalgia	
	Musculoskeletal and connective tissue disorders NEC	Anal fistula	
		Back pain	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Reproductive neoplasms male malignant and unspecified	Prostate cancer	
Nervous system disorders	Demyelinating disorders	Demyelination	
	Headaches	Headache	
	Movement disorders (incl parkinsonism)	Parkinson's disease	
	Neurological disorders NEC	Dysgeusia	
		Paraesthesia	x

SOC	HLGT	PT	Reported as a possible ADR
		Post herpetic neuralgia	
		Sensory loss	
	Sleep disturbances (incl subtypes)	Insomnia	
	Spinal cord and nerve root disorders	Sciatica	
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirths	Abortion spontaneous	
	Pregnancy, labour, delivery and postpartum conditions	Pregnancy	
Psychiatric disorders	Anxiety disorders and symptoms	Nervousness	
	Deliria (incl confusion)	Confusional state	
	Depressed mood disorders and disturbances	Depression	
	Mood disorders and disturbances NEC	Mood swings	x
	Sleep disorders and disturbances	Sleep disorder	
Renal and urinary disorders	Nephropathies	Glomerulonephritis	
Reproductive system and breast disorders	Menstrual cycle and uterine bleeding disorders	Dysmenorrhoea	
	Sexual function and fertility disorders	Sexual dysfunction	
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Cough	
		Laryngeal pain	
	Upper respiratory tract disorders (excl infections)	Rhinitis allergic	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Eczema	
		Pruritus	
		Rash	
	Skin appendage conditions	Acne	x
Surgical and medical procedures	Gastrointestinal therapeutic procedures	Hernia repair	

SOC	HLGT	PT	Reported as a possible ADR
		Intestinal resection	
	Head and neck therapeutic procedures	Tooth extraction	
		Toothache	
	Therapeutic procedures and supportive care	Fistula repair	
	NEC	Hospitalisation	
		Surgery	x
Vascular disorders	Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Peripheral coldness	
	Decreased and nonspecific blood pressure disorders and shock	Hypotension	
	Vascular inflammations	Phlebitis	

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Appendix table 50: All adverse events recorded in Crohn's disease trials, but not in summary of product characteristics (SPCs) - immunosuppressives: methotrexate

SOC	HLGT	PT	Reported as a possible ADR
Cardiac disorders	Coronary artery disorders	Myocardial infarction	
Gastrointestinal disorders	Exocrine pancreas conditions	Pancreatitis acute	
	Gastrointestinal haemorrhages NEC	Haematochezia	
	Gastrointestinal inflammatory conditions	Crohn's disease	
	Gastrointestinal motility and defaecation conditions	Constipation	
	Gastrointestinal signs and symptoms	Abdominal distension	
General disorders and administration conditions	General system disorders NEC	Asthenia	
		Influenza like illness	
		Oedema peripheral	
Infections and infestations	Infections - pathogen unspecified	Anal abscess	
		Infection	
		Nasopharyngitis	
		Respiratory tract infection	
	Viral infectious disorders	Influenza	
Injury, poisoning and procedural complications	Injuries NEC	Contusion	
	Procedural related injuries and complications NEC	Infusion related reaction	x
		Procedural pain	
Investigations	Enzyme investigations NEC	Blood alkaline phosphatase increased	
	Hepatobiliary investigations	Alanine aminotransferase abnormal	
		Alanine aminotransferase increased	

SOC	HLGT	PT	Reported as a possible ADR
		Aspartate aminotransferase increased	
		Gamma-glutamyltransferase increased	
		Liver function test abnormal	
		Transaminases increased	
	Musculoskeletal and soft tissue investigations (excl enzyme tests)	Bone density decreased	
	Toxicology and therapeutic drug monitoring	Drug specific antibody present	
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders NEC	Back pain	
		Pain in extremity	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Miscellaneous and site unspecified neoplasms malignant and unspecified	Carcinoma in situ	
		Neoplasm malignant	
Nervous system disorders	Cranial nerve disorders (excl neoplasms)	Optic neuritis	
	Neurological disorders NEC	Dizziness	
		Syncope	
	Peripheral neuropathies	Polyneuropathy	
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract disorders (excl obstruction and infection)	Pneumonitis	
	Pulmonary vascular disorders	Pulmonary embolism	
	Respiratory disorders NEC	Cough	
		Laryngeal pain	
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	Rash	
		Skin lesion	

SOC	HLGT	PT	Reported as a possible ADR
Surgical and medical procedures	Gastrointestinal therapeutic procedures	Intestinal resection	
	Therapeutic procedures and supportive care NEC	Surgery	
Vascular disorders	Embolism and thrombosis	Venous thrombosis	

Note: SOC – System Organ Classification; HLGT – Higher Level Group Term (clinical grouping of multiple preferred terms); PT – preferred term; ADR – adverse drug reaction; NEC – not elsewhere classified