**Reporting of harms outcomes: A comparison of journal publications with unpublished clinical study reports of orlistat trials**

**Alex Hodkinson1\*, Carrol Gamble1, Catrin Tudur Smith1**

1MRC North West Hub for Trials Methodology Research, Department of Biostatistics, University of Liverpool, Liverpool.

\*Corresponding author

E-mail address: [ahoddy@liverpool.ac.uk](mailto:ahoddy@liverpool.ac.uk) (A.Hodkinson).

# Abstract

**Background:** The quality of harms reporting in journal publications is often poor which can impede upon the risk-benefit interpretation of a clinical trial. Clinical study reports (CSRs) can provide more reliable, complete, and informative data on harms compared to the corresponding journal publication. This case study has compared the quality and quantity of harms data reported in journal publications and CSRs of orlistat trials.

**Methods:** Publications related to clinical trials of orlistat were identified through comprehensive literature searches. A request was made to Roche (Genentech; South San Francisco, CA) for CSRs related to the orlistat trials identified from our search.We compared adverse events (AEs), serious adverse events (SAEs), the reporting of 15 harms criteria in both document types, and compared meta-analytic results using data from CSR against journal publications.

**Results:** Five journal publications with matching CSR were available for five independent clinical trials. Journal publications did not always report the complete list of identified AEs and SAEs. We found some differences in magnitude of the pooled risk difference between both document types with a statistically significant risk difference for 3 AEs and 2 SAEs using data reported in the CSR, they were of mild intensity and unrelated to orlistat. The CONSORT harms reporting criteria were often satisfied within the methods section of CSRs (70-90% of methods section criteria satisfied in CSRs compared to 10-50% in journal publications) but both document types satisfied 80-100% of results section criteria albeit with greater detail provided in the CSR.

**Conclusions:** In this case study, journal publications provided insufficient information on harms outcomes of clinical trials and did not specify that a subset of harms data were being presented. CSRs often present data on harms, including SAEs which are not reported or mentioned in journal publications. Therefore CSRs could support a more complete, accurate and reliable investigation, and researchers undertaking evidence synthesis of harm outcomes should not rely only on incomplete published data presented in journal publications.

**Keywords:** Harms, orlistat, clinical study report, adverse event, adverse effect, randomised controlled trial, systematic review, evidence-based healthcare, obesity.

# Background

There are two driving concerns that continue to grow when relying on published medical research to reflect the truth [[1](#_ENREF_1)]. Firstly, trials often remain unpublished years after completion and the results are therefore invisible to the public. Secondly, trials often display a distorted representation, where publications present a biased or misleading description of the design, conduct, or results of a trial [[2](#_ENREF_2)] [[3](#_ENREF_3)].

Journal publications and registry reports currently represent the main information source for obtaining summaries of clinical trial data for the purposes of clinical and health policy decision making [[4](#_ENREF_4)]. Results in the past have found reporting in journal publications to be inadequate and inconsistent [[5](#_ENREF_5)], and although clinical trial registries have been responsible for making major strides in improving the transparency of trial data, a recent study suggested that the results from trial registries often remain invisible [[6](#_ENREF_6)].

The Clinical Study Report (CSR) is a structured document which summarises the analysis methods and results of a clinical trial submitted for marketing authorization of an investigational medicinal product in the European Union, Japan, or the United States. CSRs are an “integrated” full report which can be up to a thousand pages in length, and include extensive detailed information on the efficacy and harms of interventions. Information in these documents relating to harms are usually separated individually by adverse event (AE) and serious adverse event (SAE) terms in summary tables and listings.

In the past researchers have made major efforts to gain access to CSRs, with the intention to inform regulatory decision-making [[7](#_ENREF_7)]. The information contained within CSRs has proved vital when evaluating both the efficacy [[8](#_ENREF_8)] and safety [[9](#_ENREF_9)] of clinical interventions. Evidence from journal publications has previously been questioned, and even overturned by findings from unpublished information reported in the CSR [[10](#_ENREF_10)]. On December 2009 Roche was the first global health-care company to release ‘Clinical Study Reports’ after growing concerns over their product Tamiflu [[8](#_ENREF_8)]. Their policy now allows researcher’s access to CSRs and summary reports that have been used for regulatory purposes since 1st January 1999. In 2010 the European medicine agency (EMA) [[11](#_ENREF_11)] became the first major regulatory agency to agree to an open access policy to confidential documents, including CSRs. However, in 2013 the EMA was forced to take a backwards step, when the general court of the European Union (EU) ordered them to limit the access to their reports due to legal cases from two drug companies [[12](#_ENREF_12)]. The EMA has since published their final policy on access to documents and CSRs in October 2014 [[13](#_ENREF_13)].

Orlistat (Trade name: Xenical) is marketed by Roche in most countries. It is used in the treatment of obesity, as a selective inhibitor of gastric and pancreatic lipase [[14](#_ENREF_14)]. Mild but unpleasant Gastrointestinal (GI) side effects are commonly reported with orlistat use. A recent review [[15](#_ENREF_15)] including 16 randomized placebo controlled trials of orlistat estimated an increased risk of discontinuations due to AEs of 3% (95% CI 1-4%) with orlistat. The most common AEs leading to withdrawal were GI (40%); only eight (50%) trials specified the number of AEs due to GI problems. Another study [[16](#_ENREF_16)] including 29 trials of orlistat indicated an increase in risk for diarrhoea, flatulence, abdominal pain and dyspepsia in orlistat treated patients compared with placebo. No SAEs were reported in these reviews. There is concern that there may also be an associated increased risk of serious hepatic events as indicated in a case series study using primary care data from the Clinical Practice Research Datalink (CPRD) [[17](#_ENREF_17)].

We aim to carry out an exploratory review consisting of two main analyses: (i) to compare the number(s) of reported harms (AEs and SAEs) and (ii) the structured reporting of harms. Both analyses will be assessed between CSRs and journal publications using a case study of Roche sponsored orlistat trials to provide a summary of the added value, if any, from CSRs. To our knowledge an in-depth exploration including a detailed meta-analysis of this type has not been published in previous CSR related research.

# Methods

We planned to identify independent trials each of which were reported within two different trial summary reports: Clinical Study Reports (CSRs) and publically available journal publications. The aim was to compare these document types and determine whether there were inconsistencies in quality and quantity of reporting of harms. CSRs were released by Roche (Genentech; South San Francisco, CA).

## Identifying the studies

A search was implemented by one researcher (AH) in the Cochrane Central register (final search 6 July 2013) and Ovid MEDLINE (final search 2 July 2013) to obtain all relevant published randomised controlled trials comparing-orlistat against placebo for obesity treatment. The search strategies are provided in Additional file 1. Each full article was assessed independently by one reviewer (AH) to determine eligibility. We included published and unpublished RCTs investigating the use of orlistat. No restriction was placed on the clinical area. Excluded studies were observational studies and those that did not specify orlistat as their primary intervention.

## Data collection and Extraction

Roche was contacted and asked to provide the corresponding CSRs for each of the publications identified. A Roche CSR consists of the five modules of information:

Module I: The ‘Core report’ – Background and rationale, objectives, materials and methods, efficacy results, safety results, discussion, conclusion and appendices.

Module II: ‘Study documents’ – Protocol and amendment history, blank case report forms (CRFs), subject information sheet and consent form, glossaries of original and preferred terms, randomization list, reporting analysis plan (RAP), certificates of analysis, list of investigators and list of ethics committee.

Module III: ‘Listings of demographic and efficacy data’.

Module IV: ‘Listing of safety data’.

Module V: ‘Statistical report and appendices’ – Statistical analysis and efficacy results.

For each matching document pair (CSR and journal publication) the following data were extracted:

* Content and characteristics of both document types: whether a clear primary objective of safety was defined, word count of information relating to harms in both the journal publication (including any online supplementary material) and in the CSR documents of text only (word count performed using the software AnyCount version 7.0 [[18](#_ENREF_18)]). Missing pages relating to safety due to redactions were noted in the results, we managed to obtain these upon further requests.
* Name of each reported adverse event (AE) and serious adverse event (SAE) term recorded for both placebo and orlistat, with the overall number of patients in the safety population, as defined in the respective document. The intensity grading (i.e., mild, moderate or severe), relationship to orlistat and definition of SAEs was also observed where possible. SAEs were defined as any event being fatal or life-threatening, requiring hospitalization or prolongation of hospitalization or an overdose. The AE coding system was also detailed.
* Reporting structure of harms (CONSORT-harms [[19](#_ENREF_19)] used as a benchmark). The CONSORT extension for reporting harm outcomes extends 10 checklist items of the CONSORT (2001) checklist to help support the reporting of harms-related data from RCTs. This includes guidance on how to report harms in the title and abstract, introduction, methods (definitions, collection, and analysis), results (withdrawals, denominators and type) and the discussion.

One researcher (AH) extracted, and a second reviewer (CTS) checked the data extraction. Discrepancies in rates of agreement were resolved through consensus or recourse to a third reviewer (CG) where necessary. As there were no disagreements in the data extraction for the first three trials (NM16189, M37013, M37002), extraction for the final two trials was only carried out by one reviewer (AH).

## AEs and SAEs

For a particular trial, all harms (AEs and SAEs) reported in either journal publication or CSR were extracted and compared across the two document types. The clinically validated medical terminology dictionary MedDRA is commonly used during the regulatory process by all stakeholders in healthcare; it is used for coding harm outcomes. These reported outcomes are then organized into each of the five hierarchy levels of the MedDRA dictionary: system organ class, high level group term, high level term, preferred term and lowest level term. Outcomes are usually reported in journal publications and CSRs as MedDRA preferred term level events. Therefore we compare the total number of reported MedDRA preferred terms and if a preferred term was reported in both the CSR and journal publication the numerical data were compared and any discrepancies noted.

For each MedDRA preferred term (AE and SAE) the data extracted from CSRs were used to estimate risk differences which were pooled across trials using fixed effect meta-analysis. A corresponding meta-analysis was performed using the data extracted from journal publications wherever relevant. The pooled Risk Difference (RD) with 95% confidence interval[[20](#_ENREF_20)] and the I2 statistic[[21](#_ENREF_21)] were compared between CSR and journal publication based analyses. As the SAE data were sparse a sensitivity analysis was undertaken to pool the relative risk (RR). We stress that these meta-analysis results are based on a subset of the eligible trials of orlistat and are presented for the purpose of methodological comparison rather than definitive clinical results.

## Structured reporting of harms

Using the CONSORT-harms extension [[19](#_ENREF_19)] as a benchmark for reporting harms data from a randomised controlled trial, documents were assessed across fifteen adapted criteria (see Table 1) that focus on the methods and results. Each trial was classified as follows for each individual criteria:

BOTH both documents report the criteria

CSR only reported criteria in clinical study report

Pub only reported criteria in trial publication

NR criteria not reported in either document

The total number of criteria satisfied in each CSR and journal publication for a particular trial was calculated and expressed as a percentage of 15 criteria.

When both document types reported on any particular individual criteria (i.e. BOTH), the reported information was compared and classified as follows:

CSR (+) The CSR provides more information than the journal

publication

Similar (O) Both document types provide equal and similar information

CSR (-) The journal publication provides more information than the CSR

# Results

Thirty-one journal publications related to 31 randomised controlled trials of orlistat were identified from our search (Figure 1). We requested access to full CSRs from Roche corresponding to each of these trials. The CSRs could not be provided for 26 of these trials: 17 trials were not Roche-sponsored, and CSRs were not held by Roche and 9 trials pre-dated Roche’s policy extension, which only allows access to trials dating back to the 1st January 1999.

CSRs were obtained and matched with the corresponding journal publication for five trials (NM16189 [[17](#_ENREF_17)], M37013 [[18](#_ENREF_18)], M37002 [[19](#_ENREF_19)], M37047 [[20](#_ENREF_20)], BM15421 [[21](#_ENREF_21)]). Module I of the CSR was provided for all trials. Module II was not provided for one trial (BM15421) and module V was not provided for one trial (NM16189). We contacted Roche to provide reasons for these missing modules and for four missing pages, and they informed us that these sections contained confidential information and had to be removed. Modules III and IV were not provided for any of the trial CSRs since they contained individual patient data listings.

Table 2 shows the content and characteristics for each trial document pair. Safety was not the primary objective for any of the five trial journal publications, but was defined as a secondary objective in three journal publications [[22](#_ENREF_22), [23](#_ENREF_23)] [[24](#_ENREF_24)], and not specified in two journal publications [[25](#_ENREF_25), [26](#_ENREF_26)]. Two trials [[23](#_ENREF_23)] [[25](#_ENREF_25)] were published in the Journal of Diabetes, Obesity and Metabolism, two trials [[24](#_ENREF_24), [26](#_ENREF_26)] in the Journal of Diabetes Care, and one trial [[22](#_ENREF_22)] in the Journal of the American Medical Association (JAMA).

The mean word count across the five trial journal publications was 7265 (Standard deviation (sd) 1894) with an average of 10% of words (mean (sd) 757 (287)) dedicated to safety. The CSRs had a mean (sd) of 163411 (96872) words across all trials, with approximately 3% (mean (sd) 4663 (1446)) related to safety. The mean difference between the CSR and journal publication was 3906 (95% CI (1756, 6056)) words.

## Comparison of reported adverse event and serious adverse event data

MedDRA version 2.3 had been used to code AEs and SAEs in all five trials.

## Adverse Events

The total number of MedDRA preferred terms for AEs varied across trials (Figure 2 (Forest plots are provided in Additional file 1). Journal publications did not always report the complete list of terms identified in the corresponding CSR but all of these ‘missing’ AEs were of mild to moderate intensity and were unrelated to the intervention. For instance, in one trial (M37013) there was very good consistency in reporting between the CSR and journal publication with 18 AEs in total, 18 (100%) of which were listed in the CSR and 17 (94%) within the journal publication. However there was very poor consistency for the three trials (M37002, M37047, BM15421) with 5% or fewer of the total AEs being reported in the journal publication (M37002 1 (5%); M37047 1 (4%); BM15421 0 (0%)). When a MedDRA preferred term was listed in both the CSR and journal publication, there was complete agreement in the numerical results (Additional file 2) except for one trial (M37013) where 3 additional patients with ‘abdominal pain’ on orlistat were identified within the journal publication.

In the meta-analysis (MA) for the AEs (Table 3), 61 individual MedDRA preferred terms were reported in either the CSR or journal publication across the five trials (Additional file 1). 30 (49%) of these terms were reported in the CSR and corresponding journal publication for at least one trial allowing a comparison of pooled results. In 6 (20%) of the 30 MA comparisons the magnitude of effect differed (the 95% CI for the pooled risk difference (RD) did not overlap between the CSR and journal publication results). These include the AE terms: ‘increased defecation’, ‘oily spotting’, ‘oily evacuation’, ‘faecal incontinence’, ‘soft stools’ and ‘faecal urgency’. For the 31 AE terms that had only been reported in a CSR, 23 (74%) analyses suggested an increased risk of an AE on orlistat, 2 (6%) of which were statistically significant (faeces discolouration and dry skin); these AEs were mild and were unrelated to treatment. For 4 (13%) terms there was an increased risk of an event with placebo, 1 (3%) of which was statistically significant (haemorrhoids) and of mild grading.

**Serious Adverse Events**

The total number of MedDRA preferred terms for SAEs were generally poorly reported in journal publications (Figure 3; Additional file 3). For the four trials (M37013, M37002, M37047, BM15421) only 11% or fewer of the total SAE terms were reported in the journal publication with 11%, 0%, 0% and 0% respectively. All SAEs that were reported only in the CSR were of mild intensity grading and were unrelated to the treatment.

In trial NM16189 there were 19 SAEs terms reported across the CSR and journal publication. 13 of these were reported in both documents, either with full numerical agreement (12 SAE terms), or with disagreement in numerical results (1 depression SAE on orlistat reported in the CSR and 2 depression SAEs reported in the journal publication) (Additional file 3). Five SAE terms were only reported within the CSR (demyelination (1) and bronchospasm aggravated (1) on placebo, and convulsions (1), suicidal ideation (1) and liquid stools (1) on orlistat). Encephalomyelitis SAE was reported for placebo within the publication but not the CSR. Trial M37013 reports 9 SAEs with only “diarrhoea and dehydration” on orlistat reported in both documents. The remaining 8 SAEs were only reported in the CSR; death (1), diabetes mellitus (1), hysterectomy and perineoplasty (1), mitral lesion (1) on placebo and cholaeistiny due to chronic cholelithiasis (1), nephrectomy due to previous renal carcinoma (1), nephrectomy and lithotripsy due to previous nephrolithiasis (1), ovary carcinoma and ascites (1) on orlistat. The three remaining trials (M37002, M37047 and BM15421) report a high number of SAEs (40, 53 and 255) within the CSR that have not been reported in the corresponding journal publication.

In the MA for the SAEs (Table 4), 326 individual terms were reported in either the CSR or journal publication across the five trials (Additional file 4). 14 (4%) of these terms were reported in the CSR and corresponding journal publication for at least one trial allowing a comparison of the pooled results. For the 311 (95%) terms that had only been reported in a CSR, 16 (5%) analyses suggested an increased risk of an SAE on orlistat, 2 (13%) of which were statistically significant (carotid artery stenosis, varicose veins) but all of these were mild and unrelated. In the sensitivity analysis, pooling Relative Risk rather than Risk Differences, no SAEs were found to be statistically significant. However we were unable to estimate the pooled relative risk for 10 AEs (including carotid artery stenosis, varicose veins) since they include multiple studies reporting no events in the placebo group.

## Structured reporting of harms

The quality of reporting harms related information, as assessed against the 15 criteria adapted from the CONSORT-harms checklist, are displayed in Table 5.

The CSRs satisfied 70-90% the methods related criteria across the 5 trials compared to the journal publications that satisfied between 10-50%. CSRs consistently provided much greater detail regarding planned analyses than the journal publication and on only one occasion did the journal publication provide greater detail than the CSR (trial M37013; item 3 timing and time frame of surveillance for AEs). Both CSRs and journal publications satisfied 80-100% of criteria within their results sections, but greater detail was generally provided in the CSR. This included full summary tables of AEs and SAEs data, including withdrawals due to harm, severity grading and denominators for the numbers included in the safety population.

# Discussion

This case study has shown differences in the completeness and quality of reporting harms related information between journal publications and CSRs for 5 orlistat trials. Information on patient-relevant harm outcomes, including SAEs, required for unbiased trial evaluation was missing from the publicly available journal article. Including these missing data from CSRs altered the magnitude of the pooled risk difference estimates in a few cases, and even resulted in 5 statistically significant differences (including 3 AEs and 2 SAEs). The statistically significant risk differences for AEs were faeces discolouration, dry skin and haemorrhoids; and for SAEs were carotid artery stenosis and varicose veins. However, the statistical significance of these SAEs could not be confirmed in a sensitivity analysis pooling relative risks [[27](#_ENREF_27), [28](#_ENREF_28)] due to zero events. The events were graded mild and were classified as unrelated to treatment. Overall the results from the journal publications in this study follow findings from past studies [[15](#_ENREF_15)] [[16](#_ENREF_16)] with a more detailed meta-analysis showing predominantly mild gastrointestinal harm outcomes.

The quality of reporting between journal publications and CSRs showed inconsistencies when assessed by the CONSORT-harms reporting criteria. 70-90% of the methods section criteria were more often satisfied within the CSRs, compared to only 10-50% of the criteria in the journal publications. But, both document types satisfied 80-100% of results section criteria albeit with greater detail provided in the CSR. The journal publication was often incomplete when reporting planned analyses and summary tables of AEs and SAEs which were missing information on withdrawals, severity grading and numbers in the safety population. Journal publications are often impeded by word count restrictions. However, inadequate reporting of harms is still noticeable even after the release of the CONSORT-harms extension [[19](#_ENREF_19)], as the findings from our recent review [[29](#_ENREF_29)] suggest. In contrast, CSRs have no such word restrictions imposed and theoretically all relevant information should be included. An alternative more viable solution appears to be that journals should require more thorough reporting of harms via online supplements (e.g., de-identified CSRs, study protocols and complete tables of AE related information) [[30](#_ENREF_30)].

In a recent study [[4](#_ENREF_4)] findings on harms information obtained from CSRs were found to be more complete and robust compared with the corresponding publically available sources (journal publications and registry reports). Over 86% of all harm outcomes (AEs and SAEs) were available from the CSRs, compared to only 26% from the journal publications. Combining harms data from registry reports and journal publications increased the proportion of outcomes to 43%. Furthermore, withdrawals due to AEs were detailed completely in 91% of CSRs, with only 51% of journal publications providing complete information. In another study [[31](#_ENREF_31)] inadequate reporting of harms was shown in the Medtronic manufactured product, recombinant human bone morphogenetic protein 2 (rhBMP-2) used in spinal fusion surgery. As in our investigation, harms data were found to be missing from the publications, with considerably more data found in the corresponding trial CSRs. Further evidence of poor reporting of benefits and harms were found in a recent investigation of the product duloxetine in patients with major depressive disorder [[32](#_ENREF_32)]. The CSRs contained extensive data on major harms that were unavailable in journal publications and in trial registry reports. Restricting evidence synthesis to journal publications would effectively miss these important harms. Further empirical comparisons such as ours, in different clinical areas, would be valuable.

The drive to make clinical trial data more accessible has garnered widespread international support, with funders, academics, pharmaceutical industry, publishers and regulators supporting the move towards greater transparency. For example the BMJ recently stated that it will no longer publish trials of drugs or devices where the authors do not commit to making the relevant anonymised patient level data available, this is due to be extended to all submitted clinical trials from the 1st of July 2015. In addition the EMA have now adopted their new policy making clinical trials data more accessible [[13](#_ENREF_13)], including access to full CSRs. Roche should also be commended for voluntarily submitting their data and allowing further access to their CSRs. The new EU clinical trial regulation [[33](#_ENREF_33)] published on 27th May 2014, also states under section (67) that: “trial data should be publically accessible and presented in an easily searchable format, with related data and documents (including trial protocol and CSR) linked together by the EU trial number”.

Our study has a number of limitations. First of all, the meta-analysis results do not provide comprehensive unbiased clinical results as they are based only on a subset of the 5 eligible orlistat trials due to being unable to obtain CSRs for the remaining 26 identified trials which were not Roche sponsored or pre-dated Roche’s policy (dating back to 1 January 1999). The meta-analyses were conducted without any adjustment for multiplicity, meaning that there is an increased chance of a false positive result and the results should be interpreted with caution. In addition, for the five CSRs obtained from Roche in this study, some of the reports failed to include any information from modules II, III, IV and V, and some had missing pages. Individual participant level data and potentially other important information on harms are often presented in Roche’s CSR modules III-V. Access to these modules and confidential patient listings may have been restricted due to privacy violations, and t In a recent study [[34](#_ENREF_34)] reviewers re-analysed one of SmithKline Beecham’s studies by requesting and accessing the full individual participant level data sets to compare the efficacy and safety of paroxetine. The findings from this study support the necessity of making trial individual participant level data and protocols available to help evidence based decisions. In module I of the CSRs they also detailed that only commonly observed AEs (defined as those events with incidence rate in orlistat group of ≥ 5%) were summarized, indicating that there are potentially more unreported AEs missing from the primary trial data. Therefore the results in this study were based only on the information available.

# Conclusions

This case study confirms that CSRs can provide more complete and robust information on harms data collected in clinical trials, compared to publically available journal publications. CSRs often provide extensive information about the study methods including design, conduct and analysis of the trial. On the other hand these reports are able to supplement journal publications to help facilitate the assessment of risk of bias in evidence synthesis of harm outcomes. Consequently, restricting an evidence synthesis to journal publications could have implications to systematic reviewers and other stakeholders involved in healthcare research when reaching reliable conclusions about the harmful effects of medical interventions.

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**Additional files**

**Additional file 1: ‘Additional file 1 - Forest plots for AEs and Search Criteria.pdf’, Figure S1: Forest plots for all adverse event MedDRA preferred terms reported in CSR and journal publications and Table S1: Search criteria used in both Cochrane central and MEDLINE.**

**Additional file 2: ‘Additional file 2 - Reporting of AEs.xls’, Table S2 Reporting of adverse events in Clinical Study Reports (CSRs) and journal articles for Olistat trials.**

**Additional file 3: ‘Additional file 3 - Reporting of SAEs.xls’, Table S3 Reporting of serious adverse events (SAEs) in Clinical study reports (CSRs) and journal articles for Olistat trials.**

**Additional file 4: ‘Additional file 4 - SAEs Meta-Analysis results.xls’, Table S4 SAEs Meta-Analysis results.**

**Competing interests**

All authors have completed the ICMJE uniform disclosure form at

[www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for submitted work; no financial conflicts of interest.

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SinceCSRs were redacted and prepared by Roche (Genetach; South San Francisco, CA) patient consent was already obtained from the published trials.

Data extraction form and protocol available on request from [ahoddy@liverpool.ac.uk](mailto:ahoddy@liverpool.ac.uk)

**Authors’ Contributions**

AH carried out all screening of literature; AH extracted data and CTS and CG checked for consistency; AH, CTS and CG interpreted results and drafted the manuscript.

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**Figures:**

Figure 1: Title:Flow diagram for obtaining trial reports.

Figure 2: Title: The total number of MedDRA preferred term (Adverse Events) reported in CSRs and Journal publications across all five trials. Footnote: Total: Total number of individual MedDRA preferred terms related to AEs reported across the CSR and journal publication for a trial.

Figure 3: Title: The total number of serious adverse events reported in CSRs and Journal publications across all five trials.

Footnote: Total: Total number of individual MedDRA preferred terms related to SAEs reported across the CSR and journal publication for a trial.

**Tables:**

Table 1: Fifteen criteria (adapted from the CONSORT-harms extension) assessed to evaluate the completeness of reporting methods and results of harms.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Criteria** | **Criteria description** | **Description of complete reporting for criteria** |
| **Methods** | 1 | List addressed adverse events with definitions. | Listed AEs with definitions (with attention, when relevant, to grading). |
| 2 | Mode for collecting data. | Full description of questionnaires, interviews, or tests used to collect information on harms. Detailed information on questions asked. |
| 3 | Timing and time frame of surveillance. | Description of time frame of surveillance for AEs, with stopping period detailed. |
| 4 | Attribution methods. | Person responsible for making attribution disclosed and whether blinding was used. |
| 5 | Intensity of ascertainment. | Specify clearly how withdrawals are handled in the analyses. |
| 6 | Harms related monitoring. | Plans for monitoring and rules for stopping for benefits and harms separately. |
| 7 | Coding of AEs. | Reference to any coding system used and person responsible for the coding. |
| 8 | Handling of recurrent events. | Specify how recurrent events are handled, detailed as separate events or as one. |
| 9 | Timing issues. | Timing of events if recurrent explained. |
| 10 | Plans to perform any statistical analyses and inferences. | Described how pre-specified statistical analyses are separated from post hoc analyses, and any common problems addresses. |
| **Results** | 11 | Withdrawals and discontinuations. | Reasons for discontinuations and separated by arm. Flow diagrams used to display withdrawals. |
| 12 | Denominators for analyses on harms. | Analyses and definitions used and clearly stated (i.e. Intention To Treat (ITT)), and all denominators for safety population are clearly detailed. |
| 13 | Specifying AE type. | Results presented separately by System Organ Classification type. |
| 14 | Grading or scaling used. | Each AE type should offer appropriate metrics of absolute risk. |
| 15 | Seriousness per arm. | Reported separately for each type of event. |

Table 2: Content and characteristics of trial documents.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial ID** | **NM16189** | | **M37013** | | **M37002** | | **M37047** | | **BM15421** | |
| Safety primary objective of trial? | No† | | No† | | No¥ | | No¥ | | No† | |
| Journal publication: Author, journal and year | **Chanoine [**[**22**](#_ENREF_22)**]**, Journal of the American Medical Association (JAMA (2005) | | **Halpern [**[**23**](#_ENREF_23)**]**, Diabetes, Obesity and Metabolism (2003) | | **Hanefeld [**[**25**](#_ENREF_25)**]**, Diabetes, Obesity and Metabolism (2002) | | **Kelley [**[**26**](#_ENREF_26)**]**, Diabetes Care (2002) | | **Torgerson [**[**24**](#_ENREF_24)**]**, Diabetes Care (2004) | |
| CSR Research report no. (date of CSR) | 1011426 (2003) | | 1002688 (2000) | | 1003882 (2001) | | 1002743 (2001) | | 1008213 (2002) | |
| **Word count (including text and numbers, but not tables)** | | | | | | | | | | |
| Trial document | Pub | CSR | Pub | CSR | Pub | CSR | Pub | CSR | Pub | CSR |
| Total number of words in documentϵ | 10568 | 146801 | 6371 | 45464 | 6382 | 140166 | 7090 | 170347 | 5915 | 314277 |
| Total number of words relating to safety (% of total) | 1147 (10.9) | 4883 (3.3) | 908 (14.3) | 2664 (5.9) | 638  (10) | 4964 (3.5) | 707  (10) | 4150 (2.4) | 387  (6.5) | 6653 (2.1) |
| **CSR Moduleᶲ supplied by Roche** |  | | | | | | | | | |
| I | 🗸Π | | 🗸 Π | | 🗸 | | 🗸 Π | | 🗸 Π | |
| II | 🗸 | | 🗸 | | 🗸 | | 🗸 | | \* | |
| III | \* | | \* | | \* | | \* | | \* | |
| IV | \* | | \* | | \* | | \* | | \* | |
| V | \* | | 🗸 | | 🗸 | | 🗸 | | 🗸 | |

Footnote:

CSR; Clinical Study Report, Pub; Journal publication; †Safety secondary objective in both CSR and Journal publication; ¥Objective to assess improvements in glycaemic control, and cardiovascular disease risk, in both CSR and Journal publication; **ᶲModule:** **I** = Core report (background and rationale, objectives, materials and methods, efficacy results, safety results, Discussion, conclusion and appendices); **II** = Study documents (protocol and amendments history, black case report form (CRF), subject information sheet and consent form, glossaries of original and preferred terms, randomization list, reporting analysis plan (RAP), certificates of analysis, list of investigators, list of ethics committee); **III** = Listing of demographic and efficacy data; **IV** = Listing of safety data; **V** = Statistical reports and appendices (Statistical analysis, efficacy results). 🗸Module provided in CSR; \*Roche did not provide these modules, since it contained individual patient data listings and therefore was deleted.”; ϵ We could only count words for modules that were made available by Roche, so the actual number would be greater than this. The percentage of words relating to harms would therefore differ; Π CSRs each had one missing page in module I, of which Roche provided upon further requests. Any additional information from this was used in the results.

Table 3: Summary of meta-analysis results for the individual MedDRA preferred term adverse events pooled across all five trials.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Adverse Events (AEs)** |  |  | **Breakdown of adverse events reporting** | | |
| **Meta-analysis characteristic** | **Total** | **Once in CSR and journal publication** | **CSR** | **Journal publication** |
| Number of AE terms reported (% of total) | 61 | 30 (49%) | 31 (51%) | 0 (0) |
| Direction of pooled risk effect in meta-analysis |  | For all 30 AEs there is agreement in direction of the pooled risk effect between the pairing of documents | * 23 (74%) showed increased pooled risk of AE on orlistat * 4 (13%) showed no difference * 4 (13%) showed increased pooled risk of AE on placebo |  |
| AE listings for when there is a change in effect including statistical significance |  | * Pooled risk effect was greater in journal publication for 4 AEs; *increased defecation, oily spotting, oily evacuation, faecal incontinence* * Pooled risk effect was greater in CSR for 2 AEs; *soft stools, faecal urgency* | * 2 (6%) of the 23 AEs were statistically significant; *faeces discolouration, dry skin\** * 1 (3%) of the 4 AEs with increased risk on placebo was statistically significant; *haemorrhoids\** |  |

Footnote:

\*these adverse events were mild and unrelated to treatment.

Table 4: Summary of meta-analysis results for the individual MedDRA preferred term serious adverse events pooled across all five trials.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Serious Adverse Events (SAEs)** |  |  | **Breakdown of serious adverse events reporting** | | |
| **Meta-analysis characteristic** | **Total** | **Once in CSR and journal publication** | **CSR** | **Journal publication** |
| Number of SAE terms reported (% of total) | 326 | 14 (4%) | 311 (95%) | 1 (<1%) |
| Direction of pooled risk effect in meta-analysis |  | For all 14 SAEs there is agreement in direction of the pooled risk effect between the pairing of documents | * 16 (5%) showed increased pooled risk of SAE on orlistat * 281 (90%) showed no difference * 14 (5%) showed a increased pooled risk of SAE on placebo | The 1 SAE showed increased pooled risk on placebo |
| SAE listings for when there is a change in effect including statistical significance |  |  | 2 (13%) of the 16 SAEs were statistically significant; *carotid artery stenosis, varicose veins\** | 1 SAE; *encephalomyelitis* was statistically non-significant |

Footnote:

\*these serious adverse events were mild and unrelated to treatment.

Table 5: Comparison of 15 harms criteria (CONSORT-harms extension used as a benchmark).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | **Trial ID** | | | | |
| **Criteria** | **Description of item** | **NM16189** | **M37013** | **M37002** | **M37047** | **BM15421** |
| **Methods Criteria** | **1** | List addressed adverse events with definitions. | CSR | CSR | CSR | CSR | CSR |
| **2** | Mode of collecting harms data. | BOTH O | BOTH O | BOTH O | CSR | BOTH + |
| **3** | Timing and time frame of surveillance for adverse events. | BOTH O | Pub | CSR | NR | BOTH + |
| **4** | Attribution methods. | CSR | NR | CSR | NR | NR |
| **5** | Intensity of ascertainment. | CSR | BOTH O | CSR | CSR | CSR |
| **6** | Harms related monitoring. | CSR | BOTH O | CSR | CSR | CSR |
| **7** | Coding of AEs. | CSR | CSR | BOTH + | CSR | CSR |
| **8** | Handling of recurrent events. | NR | CSR | NR | CSR | NR |
| **9** | Timing issues. | CSR | CSR | CSR | NR | CSR |
| **10** | Plans to perform any statistical analyses and inferences. | CSR | BOTH + | BOTH + | BOTH + | BOTH + |
| Total items satisfied for methods criteria in CSR (% of total 10 items assessed) | | 9 (90) | 8 (80) | 9 (90) | 7 (70) | 8 (80) |
| Total items satisfied for methods criteria in publication (% of total 10 items assessed) | | 2 (20) | 5 (50) | 3 (30) | 1 (10) | 3 (30) |
| **Results criteria** | **11** | Withdrawals and discontinuations. | BOTH + | BOTH + | BOTH + | BOTH + | CSR |
| **12** | Denominators for analyses on harms. | BOTH O | BOTH O | BOTH + | CSR | BOTH O |
| **13** | Specifying AE type. | BOTH + | BOTH + | BOTH + | BOTH + | BOTH + |
| **14** | Grading or scaling used. | NR | BOTH + | BOTH + | BOTH + | BOTH + |
| **15** | Seriousness per arm. | BOTH + | BOTH + | BOTH + | BOTH + | BOTH + |
| Total items satisfied for results criteria in CSR (% of total 5 items assessed) | | 4 (80) | 5 (100) | 5 (100) | 5 (100) | 5 (100) |
| Total items satisfied for results criteria in publication (% of total 5 items assessed) | | 4 (80) | 5 (100) | 5 (100) | 4 (80) | 4 (80) |
| Total items satisfied in CSR (% of total 15 items assessed) | | | 13 (87) | 13 (87) | 14 (93) | 12 (80) | 13 (87) |
| Total items satisfied in publication (% of total 15 items assessed) | | | 6 (40) | 10 (67) | 8 (53) | 5 (33) | 7 (47) |

Footnote:

BOTH = ‘reported in CSR and the corresponding journal publication’; CSR = ‘only reported within the CSR’; Pub = ‘only reported in journal publication’; NR = ‘neither reported in the CSR or journals publication’. Completeness of data where agreement (BOTH) is made coded as: + ‘More complete in CSR’; O ‘Similar quality for both documents’; - ‘less complete in the CSR’.