Improving the planning and monitoring of recruitment to clinical trials

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

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Abstract

Title: Improving the planning and monitoring of recruitment to clinical trials
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Background: Successfully recruiting the pre-specified number of participants in a clinical trial remains a difficult challenge that negatively impacts all stakeholders. The approaches used to predict and monitor recruitment, including sources of information utilised, remains frequently hidden and unreported. There is an increasing number of publications describing statistical models for recruitment prediction, however there is not enough evidence about how this is done in practice.

Methods: We conducted three systematic reviews to identify (1) statistical models used for recruitment prediction at the design stage of a trial, (2) methods to monitor patient recruitment and (3) statistical models used for prediction during trial conduct. To determine methods used in practice, a cohort of 125 RCTs was investigated regarding the reporting of predicted and observed recruitment. In addition, two surveys were conducted, one to statisticians working in clinical trials and the other to the chief investigators of newly funded trials. To facilitate the implementation of selected models identified, we developed an interactive web application with Shiny. Using feedback from the statisticians' survey, a new approach building on the Poisson model is provided to address concerns around flexibility and complexity of recruitment process.

Results: Existing models to predict recruitment at the design stage of the trial were either deterministic or stochastic, including Poisson, Poisson-Gamma, Bayesian and simulation models. Models were increasingly complex when used for ongoing recruitment prediction where accrual data were available. Conversely, for monitoring of patient recruitment against initial targets, the methods identified were simplistic and included tables and graphs to present the expected versus the actual number of patients recruited per month.
Recruitment prediction reporting in main trial publications was often limited to stating the sample size target. The survey of chief investigators indicated that the data source most commonly used to predict trial recruitment was audit data from across multiple centres with the impact of specific eligibility criteria being the most frequently adjusted factor. The survey of statisticians indicated that statisticians are not always involved in recruitment prediction, and simple approaches are mainly used for both recruitment prediction and monitoring. The Shiny application developed bridges the gap between development and implementation of some models. The new web-based tool based on the Poisson model, which focuses greater attention on allowance factors whilst maintaining stochasticity but minimising complexity, may help investigators to better plan, monitor patient recruitment, and in decision making about the corrective actions required.

Conclusion: This thesis contributes to knowledge enhancement of the methods used for recruitment prediction and monitoring of patients in clinical trials and in providing an interface to facilitate implementation. In addition, a simple model is provided, which places the emphasis on allowing for factors that reduce recruitment capacity. This work will assist investigators with choosing the right model/approach for their trial leading to improvements in the accuracy of recruitment prediction and reducing waste in research.

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Abbreviations

Abbreviation	Expansion
AI	Accrual Index
AP	Accelerated Prior
BM	Brownian Motion
BMJ	British Medical Journal
CI	Chief Investigator
CONSORT	The Consolidated Standard for Reporting of Trials
CTU	Clinical Trial Unit
EcLiPSE	Emergency treatment with Levetiracetam or Phenytoin in Status Epilepticus
ECRIN	European Clinical Research Infrastructure Network
EuCos	European Correspondents
FBM	Fractional Brownian Motion
HP	Hedging Prior
HPP	Homogenous Poisson Process
HTA	Health Technology Assessment
IDSMC	Independent Data and Safety Monitoring Committee
IP	Informative Prior
JAMA	The Journal of the American Medical Association
LCTC	Liverpool Clinical Trials Centre
MRC	Medical Research Council
NEJM	The New England Journal of Medicine
NHPP	Non Homogenous Poisson Process
NIHR	The National Institute for Health Research
ORRCA	Online Resource for Recruitment research in Clinical triAls
P-G model	Poisson-Gamma model
PRCT	Patient Recruitment in Clinical Trials
RCT	Randomised Clinical Trial
RI	Recruitment Index
ROAM	Radiation versus Observation following surgical resection of Atypical Meningioma
SORM	Second Order Recruitment Model
SPRM	Sequential Patient Recruitment Monitoring
SR	Systematic Review
TOPS	Timing Of Primary Surgery for Cleft Palate
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration

Chapter 1: Introduction

1.1. Clinical trials

A clinical trial is a prospectively organised research study performed in study participants, which aims to evaluate a medical, surgical, or behavioural intervention. A clinical trial allows researchers to explore whether a new treatment is safe and effective in people. Often a clinical trial is used to determine whether a new treatment is more effective and/or has less harmful side effects than the standard treatment.

The definition for Clinical Trials or Interventional Studies as given by ClinicalTrials.gov (https://clinicaltrials.gov/) is: "A clinical trial is a research study in which human volunteers are assigned to interventions (for example, a medical product, behaviour, or procedure) based on a protocol (or plan) and are then evaluated for effects on biomedical or health outcomes."

Clinical trials advance through four main phases to test a treatment, find the appropriate dosage, and look for side effects. If, after the first three phases, researchers find a drug or other intervention to be safe and effective, it is approved by the relevant authority for clinical use and its effects continue to be monitored.

A well-known type of clinical study is the randomised clinical trial (RCT), where two or more groups of participants are compared to investigate a new treatment/therapy. The experimental groups that receive a new treatment are compared against a control group that receive the current standard treatment, which might be the best existing treatment, no treatment or a placebo. The groups compared should be as similar as possible so that the researchers can conclude that the comparison results are based only on the treatment received. Randomisation of participants in each group is implemented and it is one essential factor to ensure that the study will produce unbiased results.

Systematic reviews (SR) of RCTs, followed by individual RCTs, are the top two tiers in the hierarchy of evidence, which is used to inform research practice. A systematic review can demonstrate that further RCTs are not required, or point to a gap of the evidence. When further RCTs are required, information to support the proposed design is required and this may come from a systematic review or other sources including individual trials, pilot studies, observational research or audits. See Jones *et al* for a review of how systematic reviews are being used to inform future RCTs [1].

The design of an RCT can be complex or simple in its nature; however successful delivery depends on many factors and here we focus on the challenge of predicting and monitoring patient recruitment in clinical trials.

1.2. Patient recruitment in clinical trials

Patient recruitment is widely recognised as a key determinant of success for clinical trials. Thus, the leading reason for trials' discontinuation is poor recruitment [2]. However, recruiting the required number of patients in clinical trials remains a challenging issue [3, 4]. In the UK, 45% of publicly-funded trials struggled to recruit to their target sample size, and time and financial extensions were requested [5], while 26% of the RCTs funded by the Swiss National Science Foundation were prematurely discontinued due to slow recruitment [6].

Failing to recruit the required number of participants can extend the trial duration and result in an increase in recruitment and trial costs. Another result of inadequate recruitment can be the compromise of the statistical power of the study, which adversely affects its ability to answer the clinical question posed. In addition, all the resources used for these studies are wasted if whatever results and lessons learned remain unpublished, since discontinued trials are more likely to remain unpublished than completed trials [2]. Thirdly, patients' trust and willingness to participate in clinical trials may be compromised.

It is important to improve prediction of recruitment and get it right more often. Using the right information and methodology is essential. If this information was always available, then we would be able to investigate the limitations of the different methods and sources used in practice. This however is not the case, because patient recruitment issues and challenges are seldom reported in publications.

If investigators were able to accurately predict patient recruitment, then the research team could possibly provide more realistic timelines, and in combination with the funders, they would be able to evaluate the resources required to complete the study and publish the results. This would be an important reduction of waste in research.

Despite the extensive investigation in identifying recruitment issues [7-9] and exploring different strategies to enhance patient recruitment [10, 11], sufficient recruitment remains a formidable challenge.

1.2.1. Design stage

At the design stage of the clinical trial, recruitment prediction is a very important task, since this is the first step to assure that the scientific question can feasibly be considered, as it will be answered only if there are enough participants to support the hypothesis. The available information from the published literature is combined with the investigators' expertise to inform the recruitment plan. The target sample size is determined by a power calculation that is parameterised by both statistical and clinical variables.

Patient recruitment during the trial conduct is compared to the initial expectations of the research team. The researchers set the recruitment targets themselves using available sources of information. If they are overly optimistic in their expectations, then this can be detrimental to the study success and their experience later. However, trials need to be attractive to funders and costs increase with prolonged recruitment periods. Therefore, there is a tension between realistic expectations and acceptability from the funders' perspective.

A cohort examination of trials that were discontinued early, identified that overestimation of prevalence of eligible participants and biased views of recruiters were amongst the most frequently reported reasons [12].

A systematic review of statistical models for recruitment prediction identified an absence of user-friendly software to implement the models and a need for models to be validated against both retrospective and prospective data [13].

1.2.2. Monitoring stage

Monitoring patient recruitment allows for the identification of delays and problems with recruitment. Investigating the reasons behind inadequate recruitment is the step that follows the identification, and corrective actions should be taken to improve recruitment and help enrolment to get back on track. Monitoring can be done by comparing the monthly figures expected with the actual monthly patient accrual. Tabular or graphical measures can be used for this comparison, but there is a lack of understanding of what is done in practice and to the best of our knowledge, there is no available information in the literature covering this area.

There is a growing trend for the incorporation of an internal pilot into a clinical trial, such that the feasibility of recruitment is reviewed at an early stage. These internal

pilots specify stop-go-amend criteria to evaluate recruitment adequacy and decide whether or not to proceed to the main trial phase [14, 15]. This is a step forward in traditional monitoring as it specifies cut points at which actions should be taken.

When patient recruitment is not going as expected, determining the best time for the corrective actions to be taken is another important time point that needs to be investigated and discussed further. Once again, there is a lack of guidance in the literature about these important time points during the recruitment monitoring, which need to be defined in advance based on the predefined thresholds related to the desirable recruitment targets. The timing of corrective actions has an impact on the trial's successful completion, which at a first stage depends on adequate recruitment.

1.2.3. Re-profiling stage

There are two basic stages in predicting patient recruitment; (1) prediction at design stage, before trials starts when there are no real data available, which was described above and (2) interim prediction where it is possible to use observed accrual data and update the trial recruitment plan for the remaining period. At both stages, similar models can be used, however the input parameters will be determined differently, with those used during trial conduct able to incorporate observed recruitment performance.

When recruitment is defined as inadequate at the monitoring stage, then corrective actions, such as staff training to improve recruitment within centres, adding more centres [16], revising the monthly centres' expectations and more, are usually considered. A decision needs to be made as to whether recruitment can be brought back on track or whether the recruitment plan needs to be revised and the recruitment curve re-profiled accordingly. This needs to be done in discussion with the funders; however how this is done in practice remains unreported.

1.3. Rationale for the thesis

As described above, recruitment problems have practical and financial impacts, delaying completion of research or reducing its timely impact on patient health and well-being and wasting resources in research.

Patient recruitment in most trials is inadequate in comparison to what was expected. The main reason for this discrepancy is the initial prediction, which is frequently based on wrong assumptions, unreliable data sources and overly simplistic methods. The ability to learn from experiences across trials is prevented as the assumptions, data

sources, and methods used are not reported. Thus, little is known about how applicants requesting funding for clinical trials estimate the recruitment period for the proposed trial, or about methods used to adapt recruitment curves when revising recruitment periods or including additional centres.

Whilst statistical methods targeting advances in this area have been developed, the application of these methods is limited. Tools based on these methods to predict and monitor patient recruitment are needed as they could facilitate in the implementation of statistical methodology [13]. There is a need to identify current practice and bridge the gap between the development of methodology and its implementation.

The focus of this thesis is to explore and compare published statistical methodology on recruitment, investigate the statistical methods currently used by the research teams to predict and monitor recruitment in clinical trials and subsequently to develop user-friendly statistical tools with a web-based interface that can be used to predict, monitor and re-profile patient recruitment.

1.4. Aims and objectives of the thesis

The central aim of this thesis is to explore all the available statistical models that can be used for recruitment prediction and monitoring of patients in clinical trials and develop user-friendly applications that will support models' implementation. The research is guided by three main objectives, which are to:

1. Map the statistical methods described in the literature about recruitment prediction and monitoring. This was achieved by conducting systematic reviews about the statistical models used to predict recruitment at the design stage of the trial and during the trial conduct (ongoing recruitment prediction) and approaches used to monitor recruitment.
2. Investigate the level of information provided in the publications about predicted and observed patient recruitment, and identify the current practice for recruitment prediction and monitoring used by the research team within clinical trials. The 25 latest publications from five high impact factor journals were explored to evaluate recruitment reporting, while the current practice was determined by surveying the statisticians and the chief investigators from the National Institute for Health Research, the UK Clinical Research Collaboration registered Clinical Trial Units network and the European Clinical Research Infrastructure Network.

3. Develop guidance supported by software with a web-based interface in order to bridge the gap between the development of methodology and its implementation. This was achieved by developing a Shiny application for the implementation of already known models and by developing a new web-based tool based on the Poisson model to support recruitment prediction, monitoring and re-profiling in a clinical trial.

The research conducted within the different projects was then brought together to make recommendations for practice, indicate the availability of statistical tools and discuss necessary future research.

1.5. Thesis structure

The remainder of this thesis is structured as follows:

Chapter 2: presents a systematic review describing models for recruitment prediction at the design stage of a clinical trial.

Chapter 3: presents a systematic review describing methods for monitoring patient recruitment in clinical trials.

Chapter 4: presents a systematic review describing statistical models that can be used for ongoing recruitment prediction based on observed patient recruitment.

Chapter 5: presents the results from a cohort examination of RCTs, which we conducted to evaluate the level of information reported in RCT publications about predicted and observed patient recruitment.

Chapter 6: presents the results from the two surveys where we asked the Chief Investigators and the Statisticians about the approaches they use for recruitment prediction and monitoring at the design stage of the trial when they apply for funding and during trial conduct.

Chapter 7: presents the Shiny application and how selected statistical models described in the literature can be implemented within an interactive framework without requiring a statistical background for the user.

Chapter 8: presents a new web-based tool based on the Poisson model, which was developed to give the users the opportunity to include all the factors they believe will have an impact on patient recruitment, and incorporate the required uncertainty by using the Poisson stochastic model.

Chapter 9: presents the overall discussion, future work and conclusion.

Chapter 2: A systematic review describes models for recruitment prediction at the design stage of a clinical trial

Preface

Many clinical trials fail to accurately predict participant accrual. This means that trial completion may take longer and/or cost more than originally thought. While participant recruitment is complex, one approach to improving the situation may lie in improvements to the methods used to predict recruitment.

Chapter 2 describes the results of a systematic review we conducted to identify the statistical methods that can be used for recruitment prediction of patients at the design stage of a clinical trial. Thirteen eligible articles were included and the models varied considerably in the factors included and in their complexity. They were assessed and categorised according to their nature and ability to incorporate information for recruitment prediction. Work arising from this chapter has been published in Journal of Clinical Epidemiology (JCE, 2019, open access) (Appendix A: Publications). Sections of this chapter include direct excerpts of the published manuscript. This systematic review and comparison of available methods will help researchers to identify models meeting the requirements of their study and to determine the information required for their implementation. I wrote the original draft of the published manuscript, which was edited by senior authors and has been subject to peer review.

2.1. Introduction

Successfully recruiting the pre-specified number of clinical trial participants remains a difficult challenge negatively impacting all stakeholders [3]. Twenty-six percent of trials funded by the Swiss National Science Foundation (SNSF) were prematurely discontinued due to slow recruitment [6]. Despite investment targeting recruitment difficulties [17, 18], there has been no improvement over time and 45% of trials supported by two prestigious UK funding bodies, Health Technology Assessment and Medical Research Council (HTA & MRC), fail to meet their original recruitment targets [5].

There are several factors that may contribute to lower than expected participation rates [19]. Delays with contracting, centre initiation delays, inadequate planning, insufficient staff and overoptimistic expectations are some common reasons leading to failure to recruit within the pre-specified time frame. A cohort examination of trials that were

discontinued early found that overestimation of the prevalence of eligible participants was amongst the most frequently reported reasons [12]. A key problem is therefore within recruitment prediction at the design stage.

Many interventions targeting recruitment and retention difficulties have been suggested and implemented, despite the absence of evidence to support their use [11]. In addition, recruitment prediction was also highlighted in an identification and prioritisation study, which was undertaken with the aim to identify and prioritise unanswered questions around recruitment in clinical trials. As a result, the question "What are the best ways to predict recruitment rates to a randomised trial and what impact do such predictions have on recruitment?" was identified as one of the ten highest priority questions to be investigated and answered [20].

The purpose of our study is to systematically review methods to predict recruitment in the design stage of clinical trials.

2.2. Methods

2.2.1. Identification of potentially eligible studies

The search strategy was split by articles published pre or post July 2008. The Barnard *et al* systematic review [13] was used to identify eligible articles published up to July 2008 (see Figure 1). This review included statistical models for recruitment prediction at the design stage of a clinical trial or during ongoing recruitment. Articles published up to December 2016 were identified by searching the "Recruitment prediction" domain in the Online Resource for Recruitment research in Clinical triAls (ORRCA) (www.orrca.org.uk) [21]. ORRCA is a searchable database of research related to clinical trial recruitment, where the relevant articles are assigned to one or more of 42 predefined recruitment domains grouped under six categories [22]. The ORRCA database was created to facilitate the conduct of research relating to recruitment in clinical trials by identifying all relevant literature in a single searchable database. ORRCA searches five databases: MEDLINE (Ovid), Scopus, Cochrane Database of Systematic Reviews and Cochrane Methodology Register, Science Citation Index Expanded and Social Sciences Citation Index within the ISI Web of Science and Education Resources Information Center. All research relevant to recruitment in clinical trials is identified from those searches, and classified according to a number of domains.

ORRCA was initially searched in May 2018 with the search rerun in June 2018 following completion of the ORRCA update to include publications for the period 2015-2016. Articles included in the "Recruitment prediction" domain were handsearched.

In addition, references of eligible papers were reviewed to identify any additional articles not identified within the search strategy.

A search was also conducted using Google (June 2018) to identify potentially eligible papers in the grey literature. This used the advanced search tool specifying the period 2008 to 2016 including all of the words "trial", "recruitment", "prediction" and "model" in combination with the exact phrase "recruitment model". The search also included at least one of the words "predict", "estimate", "forecast", "enrol", and "statistical" occurring anywhere in the article.

2.2.2. Eligibility criteria/Study selection

Research articles describing statistical methods for recruitment prediction at the design stage of a clinical trial were eligible for inclusion.

Exclusion criteria were:

- Articles discussing recruitment that did not include statistical methods for recruitment prediction.
- Review articles that did not also propose a new model, although the reference list of these papers were searched for potentially relevant articles.
- Articles describing statistical models that could not be implemented prior to the start of participant enrolment.

I reviewed the titles and abstracts of all retrieved papers. The full texts of these papers were obtained and the final inclusion was determined following discussion by EG, SD and CG. Disagreements between reviewers were resolved by consensus.

2.2.3. Data extraction

The data to be extracted from each method were determined following discussion by all authors. The information extracted from each article included: the statistical model, model parameters required for its implementation, consideration of seasonal effects, factors relating to multicentre trials such as recruitment rates variation, centres initiation rates, and whether the models had been implemented and evaluated using real

data from clinical trials and/or simulated data. Google Form was used for data extraction. I completed the data extraction, which was then checked and discussed with CG.

2.3. Results

2.3.1. Search results

The search results are presented in Figure 1. A total of thirteen papers were eligible for inclusion. Four out of 13 eligible articles were identified both from the review of Barnard *et al* [13] and in the ORRCA database and five of the publications identified from the Google search were also included in the ORRCA database. One paper focused only on deterministic models [23], another paper described both deterministic and stochastic approaches [24] and eleven papers described only stochastic methods. The definition of a deterministic and a stochastic method is provided in the following section.

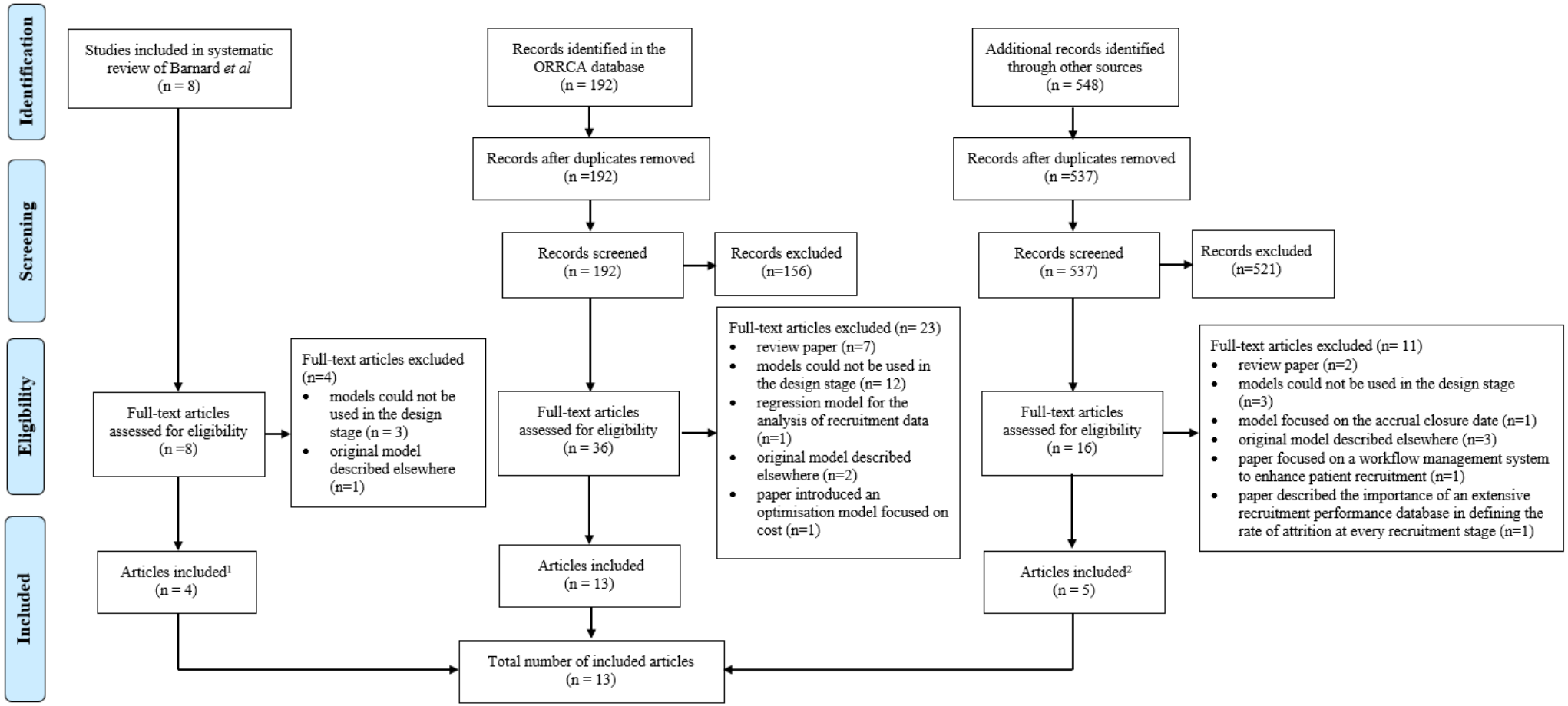

Identification
Screening
Eligibility
Included
Studies included in systematic review of Barnard et al (n = 8)
Records identified in the ORRCA database (n = 192)
Additional records identified through other sources (n = 548)
Records after duplicates removed (n =192)
Records after duplicates removed (n =537)
Records screened (n = 192)
Records excluded (n=156)
Records screened (n = 537)
Records excluded (n=521)
Full-text articles assessed for eligibility (n =8)
Full-text articles excluded (n=4)
models could not be used in the design stage (n = 3)
original model described elsewhere (n=1)
Full-text articles assessed for eligibility (n = 36)
Full-text articles excluded (n= 23)
review paper (n=7)
models could not be used in the design stage (n= 12)
regression model for the analysis of recruitment data (n=1)
original model described elsewhere (n=2)
paper introduced an optimisation model focused on cost (n=1)
Full-text articles assessed for eligibility (n = 16)
Full-text articles excluded (n= 11)
review paper (n=2)
models could not be used in the design stage (n=3)
model focused on the accrual closure date (n=1)
original model described elsewhere (n=3)
paper focused on a workflow management system to enhance patient recruitment (n=1)
paper described the importance of an extensive recruitment performance database in defining the rate of attrition at every recruitment stage (n=1)
Articles included[1] (n = 4)
Articles included (n = 13)
Articles included[2] (n = 5)
Total number of included articles (n = 13)

Figure 1: PRISMA flow diagram

[1] 4 eligible articles identified from the review of Barnard et al, were also identified in the ORRCA database
[2] 5 eligible publications identified from the additional Google search for the period 2008-2016, were also identified in the ORRCA database; one of the publications resulting from the Google search was a master thesis, the relevant paper of which was found in the ORRCA database

2.3.2. Classification of models

Key features of the models were identified and used to group them accordingly. Models are either deterministic in that they assume a fixed recruitment rate or stochastic in that there is random variation around an average recruitment rate. In an unconditional model the specified recruitment rate stays the same, in a conditional model the rate varies according to time.

Recruitment rates may be homogenous within a time period or nonhomogeneous incorporating variation in the expected recruitment rate.

The model classifications and data extracted are summarised in Table 1 and Table 2.

2.3.2.1. Deterministic models

Unconditional model

The unconditional model assumes a constant linear recruitment rate. The trial's recruitment period is simply calculated as the sample size target divided by the total number of recruited patients expected each month.

$$expected\ recruitment\ period = \frac{sample\ size\ target}{expected\ number\ of\ patients\ to\ be\ recruited\ per\ month}$$

The method can incorporate variability in centre recruitment rates by averaging the recruitment rate across all centres, providing the overall rate is then constant over time. However, this is a strong assumption and would require all centres to be open to recruitment at day zero, recruiting at capacity, without seasonal variation. Application of this approach may substantially overestimate recruitment in the initial months. Carter *et al* [24] and Comfort [23] described the limitations of this approach with Comfort providing a simple equation to support implementation for multicentre trials, as shown below.

$$N_m = (S_m R t_e) + N_0 \quad (2.1)$$

where

S_m: total number of centres expected to be open to recruitment

R: expected recruitment rate (number of patients/centre/month)

t_e: recruitment duration (months from the first patient recruited to the last patient recruited)

N_m: Required sample size

N_0: Number of patients already recruited, which is equals to zero when considering recruitment prediction at the design stage of the study

When recruitment duration is the question of interest, then the above formula can be rearranged to

$$t_e = (N_m - N_0)/(S_m R)$$

and calculate the expected recruitment duration in months, when the required sample size, the number of centres expected to be open and the expected recruitment rate per centre per month are known.

Conditional model

The conditional model allows for time dependent changes in the overall recruitment rate [24]. It splits the overall recruitment period into successive intervals, with each interval having its own recruitment rate. This allows variation in recruitment rate caused by staggered centre initiation times and factors such as seasonal effects to be incorporated. The conditional model can incorporate variation in recruitment rates between centres and allow for reduced capacity in recruitment, for example during the first months of centre opening. There is no closed form for this flexible but deterministic approach, which is easiest to implement within a spreadsheet package [24].

As an alternative to requiring a spreadsheet implementation but at a cost of reduced flexibility, Comfort described a conditional deterministic model termed a second order recruitment model (SORM) [23]. In this piecewise model the recruitment rate is initially conditional on the cumulative number of centres open to recruitment, with centres starting with an average initiation rate until all centres are open to recruitment. At this point enrolment becomes linear and unconditional. Comfort provided closed form equations (mathematical processes that can be completed in a finite number of operations) to implement the model and the model takes its name from the “quadratic” term in the equation for the conditional piece of the model.

The centre initiation rate (I_r) is defined with the formula below

$$I_r = \frac{(S_m - S_0)}{t_s} \quad (2.2)$$

where

S_m: total number of centres

S_0: initial centres open

t_s: centre start up time

In this piecewise model, during the first period when centres are expected to open to recruitment gradually, the recruitment rate is conditional on the cumulative number of centres, and an average initiation rate is assumed for the centres. Once the average initiation rate has been defined, the expected number of patients to be recruited during this period is calculated as follows:

$$N_q(t \leq t_s) = (\frac{1}{2} I_r t^2 + S_0 t)R + N_0 \quad (2.3)$$

If $N_q < N_m$ the remaining number of patients will be recruited during the linear recruitment phase as shown below:

$$N_l(t > t_s) = S_m R t + N_q \quad (2.4)$$

This method assumes that recruitment rate is constant once all centres are open and that each centre recruits at the same average rate. Although the piecewise approach to this model could be extended, its use is best restricted to scenarios where recruitment rates across centres are similar and the recruitment rate can be expected to be stable once all centres are open.

When the total recruitment period is the question of interest, then the SORM formula is transformed as follows:

$$t_e = \frac{(N_m - N_q)}{S_m R} + t_s$$

Model Class		Description	Parameters required to implement the model at the design stage	Model Output
<u>Deterministic</u> **Unconditional models** Comfort [23], Carter [24]		The model assumes a constant rate of recruitment throughout the study.	• sample size target • expected number of patients to be enrolled per month	**Comfort** • time required to recruit to target sample size or • number of participants that can be achieved within a set recruitment period **Carter** • time required to recruit to target sample size
<u>Deterministic</u> **Conditional models**	Second order recruitment model (SORM) Comfort [23]	Piecewise model: equations are provided for recruitment, conditional on centres opening rates followed by a constant unconditional rate of recruitment once all centres are open.	• number of centres • average centre initiation rate • total recruitment time • recruitment rate (patient/centre/month) • sample size target	• time required to recruit to target sample size
	Carter [24]	The model allows for time dependent variation in recruitment rates because of different centre openings and seasonal effects. This approach does not use statistical distributions or equations and is best implemented within a spreadsheet.	• sample size target • number of centres • expected number of patients per centre • the length of time in which the centre is open to recruitment • seasonality and other time dependent factors impacting recruitment	• time required to recruit the target sample size, adjusting for time dependent changes in the overall accrual rate

Stochastic **Poisson models** Senn [25], Carter [26], Carter [24], Lee [27]	Unconditional Poisson: the average rate at which patients arrive is constant over time [24-27] or Conditional Poisson: the recruitment rate of the Poisson process is uniformly distributed on [0-y] where y is the expected number of patients per month/per centre [24, 26]	• sample size target • the rate at which events occur in the Poisson process • start and end time or • all the above and • use a uniformly distributed number (0,1) to multiply the expected accrual rate	**Unconditional Poisson** • probability of achieving the target within time specified (Senn, Carter [24, 25]) • number of patients to be recruited by each interim time point, given the expected rate of recruitment (Lee) **Conditional Poisson** • time needed to obtain the desired sample size with a high probability allowing for a time-dependent variation in the rate.
Stochastic **Poisson-Gamma models** Anisimov [28], Anisimov [29], Anisimov [30], Anisimov [31]	Patients arrive at clinical centres independently, based on the Poisson process and the rates among centres vary as samples from a gamma distribution.	• sample size target • total recruitment time • number of centres • the time when each centre is open to recruitment; or with centres initiation delays described as random variables in specified intervals	• time required to recruit the predefined sample size accounting for the planned dates of centres initiation and the different recruitment rate per centre or • the minimal number of centres needed to complete recruitment by a certain date with a given confidence at any stage of the study

<u>Bayesian</u> models Gajewski [32], Zhang [33], Bakhshi [34]	NB. Focus restricted to prior specifications. Gajewski models average waiting time between successive participants while Zhang models the average recruitment rate using the normal distribution to specify the distribution for the average. Both models assume homogeneity. Bakhshi requires the existence of a set of previous trials utilising a meta-analysis approach, which incorporates variability between trials. The approach is described as not being fully Bayesian.	**Gajewski** • sample size target • recruitment duration • investigators confidence of finishing the trial on time as a single value between 0 and 1. **Zhang** • sample size target • the average recruitment rate • the variance for the average recruitment rate considered based on the certainty of investigators around the average. **Bakhshi** • requires a set of previous trials with data available on the number of patients recruited per centre per month.	**Gajewski** • patient accrual across a fixed time period and • accrual time to a target sample size **Zhang** • time to completion of patient recruitment under the assumption of the constant accrual **Bakhshi** • the time it will take to recruit the total number of subjects required
<u>Simulation</u> models Abbas [35]	Investigate several recruitment patterns in order to quantify the patient arrivals and calculate the length of time required to recruit the prespecified number of participants. Markov models have been used to explore the maximization of patient recruitment in a specific amount of time.	• number of patients • recruitment duration • intervals of time T • duration of each interval • probability that determines the number of patients that arrive within the proposed duration (fixed or random probability)	• length of time required to recruit the number of patients necessary for the trial

Table 1: Model categorisation and description of parameters required for their implementation

2.3.2.2. Stochastic Models

The use of a stochastic process allows for fluctuations observed around an average recruitment rate and importantly the associated uncertainty and variation to be expressed.

2.3.2.2.1. The Poisson Process

Unconditional Poisson Model

The Poisson distribution can be used to simulate the number of participants recruited each month. The unconditional Poisson model is the simplest of the stochastic approaches and only requires specification of the average recruitment rate across centres in the trial, as described by Senn [25]. Carter *et al* [24] described how the probability density function can be obtained for the time needed to recruit the target sample size by simulating data from the Poisson distribution.

Let λ represent the expected number of patients recruited per month across all centres and let T denote the time in months to enrol N patients, where N represents the required sample size. Denote N_t as the total number of patients recruited before time t, $t<T$ and let X_t the number of new patients recruited on month t such that $N_{t+1} = N_t + X_t$. Denote P $(N_t = n)$ as the probability that there have been exactly n patients recruited before time t. Then,

$$P(X_t = n) = \frac{e^{-\lambda t}(\lambda t)^n}{n} \tag{2.5}$$

is a Poisson distribution with mean λt. The randomness of λ can be incorporated if denoting λ_{kt} as the expected number of patients recruited on month t for centre k, k=1,2,……,K, and let the rate $\lambda_t^* = \sum_K \lambda_{kt}$ represent the mean number of patients recruited on month t across all centres.

Therefore, the total number of new patients, x, recruited on month t with rate λ_t^* under the Poisson distribution is expected to follow the following distribution:

$$P(X_t = x) = \frac{e^{-\lambda_t^*}(\lambda_t^*)^x}{x} \tag{2.6}$$

Thus, by utilising the Poisson distribution specified above, we can simulate random values for x, and empirically estimate the distribution of the recruitment period T.

Both Carter [26] and Lee [27] used a Normal approximation to the Poisson distribution.

Carter [26] showed how, if the average recruitment rate is constant over the recruitment period of the trial, the Normal approximation to the Poisson distribution can be used to formulate the recruitment period required to achieve the sample size target with a specified level of confidence. Alternatively, the formula can be rearranged to determine the required recruitment rate when the recruitment period is fixed.

Lee [27] also used a Normal approximation and proposed setting interim target recruitment points that need to be attained to achieve the sample size target at the end of recruitment with a specified probability. This probability is used to determine the minimum required recruitment goal at interim points. This again uses the Poisson distribution with a constant average recruitment rate and a Normal approximation with closed-form formulae provided. Moussa provides the code to implement Lee's method and extends this method to consider cost implications [36].

The advantage of the Normal approximation is the use of the closed formulae for implementing the methods along with the ability to set the probability of achieving the sample size target within the required time. However, this means that the average rate of recruitment must be sufficiently large for the normal approximation to hold and does not allow for variation in the given rate of recruitment.

Conditional Poisson Model

Given the often unrealistic assumption of a homogenous recruitment rate, by similarly conditioning on time as per the deterministic conditional model, Carter [26] allowed for a time-varying accrual rate. The average recruitment rate needs to be specified for each time interval of the recruitment period and the number of observations then simulated from the Poisson distribution according to the number of units of time contained in that interval. This can allow for staggered centre opening and seasonal effects. Carter *et al* [24] later adapted this approach further to allow the average recruitment rate itself from each interval to be simulated from a uniform distribution. A link was provided within the paper to SAS code to support implementation.

2.3.2.2.2. Poisson-gamma Model (P-G)

The analytic statistical technique of the Poisson-gamma model for the recruitment prediction was introduced by Anisimov and Fedorov [37, 38] and further described by Anisimov [28-30]. The model uses the Poisson process to describe variation in

recruitment over time, and models variation in the recruitment rates between centres using the gamma distribution.

In a multicentre clinical trial, the aim is to recruit *n* patients by *N* clinical centres in a specific time. Denote by λ_i the recruitment rate in centre *i*, which rates are viewed as a sample from a gamma-distributed population.

Denote by *T (n, N)* the time required to recruit *n* patients by *N* centres. Let $n_i(t)$ be the number of patients recruited by centre *i* up to time *t* and

$n(t) = \sum_{i=1}^{N} n_i(t)$ be the total number of patients recruited up to time *t* by all *N* centres. Suppose that centre i is initiated at some random time u_i, i=1,2,….,N. Then for any centre i, $n_i(t) = 0, t < u_i$, and $n_i(t) = \prod_{\lambda_i}(t - u_i)$ for t≥ u_i, where we denote by $\prod_{\lambda}(.)$ an ordinary Poisson process with rate λ. The overall rate is given by

$$\Lambda(t) = \sum_{i=1}^{N} \lambda_i \chi(u_i \leq t) \qquad (2.7)$$

where χ(A)=1 if A is true and χ(A)=0 otherwise. The process $n(t)$ is a non-homogeneous Poisson process with instantaneous Λ(t), and each newly initiated centre j will add an additional rate λ_j.

- If the rates λ_i are constants, then $n_i(t)$ is a Poisson process with rate λ_i and n(t) is a Poisson process with rate $\Lambda = \sum_{i=1}^{N} \lambda_i$ and T(n, N) as the time of the n^{th} event of the process n(t) is gamma distributed with parameters (n, Λ).
- If the rates λ_i are considered as a sample from the gamma distribution with parameters (α, β), Λ as their sum, is also gamma distributed with parameters (αN, β). Thus for any fixed t the variable $n(t)$ has a negative binomial distribution with parameters (αN, t/β). Time T (n, N) is a superposition of two independent gamma random variables Ga (n, Ga(αN, β)).

The model allows for variation in centre opening with each centres initiation time being uniformly distributed within a given interval since this is not known in advance [29]. This model was applied to real recruitment data of completed clinical trials and found to fit well when there is sufficient number of centres (>10 [29] or >20 [28, 38]), with all observed data being within two standard deviation near the theoretical mean and in addition, the empirical and theoretical curves representing the proportion of patients recruited by highly performing centres coincide. When fewer centres were involved, it was advised to estimate the rates individually.

When applied to recruitment prediction of an ongoing study, observed recruitment data are used to update the parameters of the initial recruitment model. The recruitment model can be also viewed in the empirical Bayesian setting where the recruitment rates are considered as random variables with some prior distribution, and by using current recruitment information a posterior distribution is calculated for the rates and then used for the prediction of patient recruitment. In this chapter we are focused on prediction at the design stage and therefore the usefulness of a Bayesian model is restricted at the specification of the prior. Implementation of the model is non-trivial and code to support doing so is not available. In his later papers Anisimov also considered the impact of randomisation schemes and prediction of drug supply [29, 31].

2.3.2.2.3. Bayesian methodology

The benefit of a Bayesian approach is in monitoring and prediction of ongoing recruitment. In a Bayesian method, investigators' prior beliefs of recruitment rates at the design stage are combined with observed recruitment rates during trial conduct to predict participant accrual for the remaining recruitment period. However, the prior specification can be viewed as the predicted or expected recruitment at the design stage and therefore we restrict our consideration to the formulations of the priors. As stated by Gajewski *et al*, careful and thoughtful elicitation of a prior distribution for accrual rates will force issues for future expectations about patient accrual patterns to be faced [32]. In this publication, the authors provided a model to estimate the average waiting time between participants, defined as the difference in dates when patients join the study. The waiting times are assumed to be exponentially distributed with mean θ. The prior distribution for θ is specified by the Inverse gamma $\sim$IG (nP,TP), where T is how long the investigator believes it will take to accrue the sample size target, n is the sample size target, and P, a value between 0 and 1, is how confident the investigator is that n will be achieved by time T. If the investigator is fully confident that n can be achieved by time T, such that P=1, then the prior sample size is the target sample size, and is otherwise reduced. TP, scales the response such that the expected waiting time is approximately T/n. This model assumes a constant accrual rate averaged across all centres. R code to implement the model is available on request from the authors of the original paper [32].

Zhang *et al* also used a Bayesian framework with a non-homogenous Poisson process that allows recruitment rates to vary over time [33]. Although they described how their approach could be amended to predict accrual in the planning stage of a clinical trial utilising prior information only, they do so by assuming a constant accrual rate. In doing so, the model loses its advantage over that of Gajewski *et al* which is also a homogenous Poisson process although expressed in waiting times rather than accrual rates. The prior specification of Zhang *et al* requires the anticipated average accrual rate after it stabilises to be specified (e.g. when all the centres expected to be open to recruitment have overcome the learning curve and can recruit at full capacity and no seasonality issues are expected, the average recruitment rate could be defined), along with the level of confidence in that prior belief. Therefore, the key difference between Gajewski *et al* and Zhang *et al* is in the questions asked to elicit the priors. Jiang *et al* [39] provided a user-friendly interface programme developed in R, based on the method of Gajewski *et al* [32] for the total number of patients that can be recruited within a fixed time in a clinical trial, with an updated version of the R package available [40]. A detailed description of the parameters of the Bayesian model is presented in chapter 7, where recruitment data from two clinical trials, one completed and one ongoing, have been used to present how the Poisson and Bayesian models included in the Shiny application perform.

Bakhshi *et al* used data from a meta-analysis of previous trials to estimate the parameters in the Poisson-gamma model [34]. This method is described as not being fully Bayesian as there are no hyper-distributions set on the parameters and the modelling of parameters has been conducted independently. They provided guidance on how to produce initial estimates at the trial design stage, with one parameter accounting for the trial-specific rate of recruitment and another one reflecting the different centre-specific recruitment rate. In addition, they described how such a prediction could be updated as the trial progresses. The results of the meta-analysis approach were suggested as an empirical way to set the prior parameters for the Poisson-gamma model, and they could be used to guide prediction.

2.3.2.2.4. Simulation models

Abbas *et al* used the Monte Carlo simulation Markov models to design different recruitment patterns using time as a discrete or continuous variable [35]. For each simulation, the time to achieve target sample size is recorded with mean and standard

deviation estimated across simulation. Models allow for discrete time with and without replacements and continuous time with a constant probability or a probability distribution applied to the conversion between states. In this method the states can be viewed as patient identification or approach to patient enrolment. The method is illustrated using an example where it is clear that reducing the conversion rate probability leads to extended recruitment times as would be expected.

			Site recruitment rates						Implementation		
Author	Model Class: Deterministic/Stochastic/ Bayesian/Simulation	Recruitment rate Deterministic (D) or Stochastic (S)	Constant recruitment rate required, Yes (Y) / No (N)	Site initiation rate: all open at T0 (T0), fixed average initiation rates (D) stochastic initiation rates (S)	Variation in site recruitment rates, Yes (Y)/ No (N)	No of sites >=10, Yes (Y)/ No (N)	Allows adjustments to recruitment rates e.g. seasonal variation, Yes (Y)/ No (N)	Average recruitment rate >10 required, Yes (Y)/ No (N)	Formulae, Yes (Y)/ No (N)	Programming Code provided, Yes (Y)/ No (N)	Model validation /implementation* using Real data (R)/ Simulated data (S)
Carter [24] Comfort [23]	Unconditional deterministic	D	Y	T0	Y[2]	N	N	N	Y	N	Carter (R) Comfort (S)
Carter [24]	Conditional deterministic	D	N	D	Y	N	Y	N	N	N	R
Carter [24] Comfort [23]	Conditional deterministic	D	Y[1]	D	N	N	N	N	Y	N	Carter (R) Comfort (S)
Senn [25] Carter [24]	Stochastic Poisson	S	Y	T0	Y[2]	N	N	N	N	N	Senn (theoretical example) Carter (R & S)
Carter [26]	Stochastic Poisson	S	Y	T0	Y[2]	N	N	Y	Y	N	
Lee [27]	Stochastic Poisson	S	Y	T0	Y[2]	N	N	Y	Y	Y[3]	Theoretical example

Carter [26]	Stochastic Poisson	S	N	D	Y[2]	N	Y	N	N	Y	
Anisimov[4] [28-31]	Stochastic Poisson-Gamma	S	N, rates assumed to follow a Gamma distribution	S	Y	Y	N	N	Y	N	R
Gajewski [32]	Bayesian	S	N, waiting time assumed to follow an Inverse gamma Distribution	D	N	N	N	N	Y	Y	R
Zhang [33]	Bayesian	S	Y	D	N	N	N	N	Y	N	R & S
Bakhshi [34]	Bayesian	S	N, rates assumed to follow a Gamma distribution	S	Y	N	N	N	Y	N	Real data from 18 trials used to define the prior information
Abbas [35]	Monte Carlo simulation Markov model	S	Recruitment probability constant or randomly distributed	T0	Y[2]	N	N	Y	Y	N	S

Table 2: Model classification and factors defining their flexibility and assumptions

**Model validation was done either by using actual recruitment data and comparing them to the accrual data resulting from the statistical model assumed, or by using simulated data resulting from the statistical model suggested to describe patient recruitment. Theoretical examples were used to further explain the model implementation.*

[1] Average recruitment rate is assumed to increase with site initiations

[2] Uses the recruitment rate across sites. Recruitment rates may vary by site so long as overall rate across sites is constant.

[3] Code available in Moussa [38].

[4] The model is Bayesian once accrual data are available. Here the focus is on the prior specification only.

2.4. Discussion

2.4.1. Main findings

The limited availability of resources for funding and conducting clinical trials means that the decisions on which research to fund must balance the importance of the clinical question against the time and cost required to answer it. This is increasingly important where the availability of potentially eligible participants to support recruitment across multiple ongoing trials is low. The accuracy of recruitment prediction at the design stage is therefore crucial; however, factors affecting recruitment may be complex and many.

This project aimed to systematically review models that may be implemented at the design stage of a clinical trial to predict patient recruitment. The models' spectrum extends from simple unconditional and conditional deterministic approaches [23, 24] to stochastic models that allow for variation around an average recruitment rate [26, 28, 31, 33] and Bayesian approaches where the expectations of the investigators are translated into prior information [32-34].

Whether the recruitment rates being specified represent an average number of participants or whether they are believed to be a guaranteed minimum number is an important consideration. If it is a guaranteed minimum specified, then a deterministic model is appropriate but to achieve this the average recruitment rate would have to be markedly higher. If it is an average rate, then the recruitment prediction should use a stochastic approach to allow for the variation and express the uncertainty accordingly. There may be divergence between funder and researcher perspectives and the interpretation of the figures presented and this potential should be explored further.

It is understandable that researchers may be reluctant to acknowledge the impact of considering their recruitment rates as an average. At best, an average recruitment rate will reach its target with a probability of 0.5 and this alone may explain existing observations around the percentage of trials recruiting to target as pre-specified at the design stage [5]. In addition, the use of these models will not prevent overoptimistic specification of parameters but may increase awareness of factors that should be considered and how they may be incorporated. Before greater accuracy in recruitment prediction is observed funders may also need to demonstrate willingness to fund longer recruitment periods than they may be currently perceived to do.

Although some of the authors provided the code of the method they introduced [24, 32, 36] (see Appendix B), it is unclear whether this is sufficient for potential users to be able to implement them. The complexity of some models may be a barrier to their implementation. However, the simplest stochastic models use the Poisson process, which is familiar to many statisticians and yet anecdotal experience would suggest they are not widely implemented. This may be because statisticians are not inherently involved in recruitment prediction.

The approaches used to predict recruitment, including sources of information utilised, remain frequently hidden and unreported. In chapter 5, where we investigate the level of information provided on final publications about expected and observed recruitment, the conclusion is that reporting of these figures is limited. On the other hand, even if reported as part of the trial results, it could be argued that this would represent a biased sample of experiences. According to Kasenda *et al* [2], clinical trials, which failed to reach the recruitment target and were discontinued are more likely to remain unpublished than completed trials and thus the knowledge and experience gained are not communicated to the research community.

Additional sources include national disease registries and databases, audit data from selected centres that may be extrapolated across centres or a 'best guess' approach based on clinician experience albeit without supporting data being readily available. Reliability of each needs to be assessed. However, not all causes of slow accrual may be known at the design stage, since many of these can be unexpected.

In multicentre clinical trials, variation in centre recruitment targets needs consideration. Combinations of factors, such as centre size, centre initiation dates and eligible patient population need to be considered alongside factors that may be less amenable to prediction from historic data, such as the size of existing centre research portfolios and resources to support new research, the extent of support for the clinical question itself, and patient willingness to participate. Approaches such as the Poisson-gamma recruitment model attempt to incorporate this level of complexity. However, this requires a distribution to be applied to centre recruitment rates and may be conceptually challenging for many in terms of specification of the parameters and how to obtain supporting data.

While it is clear that modelling recruitment represents a statistical challenge, until these models are implemented within the mainstream, the solutions proposed will be unattainable for many and any resulting improvements will not be observed. Yet, it needs to be considered whether there is a point at which continuing to expand on the complexity by the application of distributions will become unhelpful leading to an answer such that recruitment cannot be predicted to a pre-specified target time with a reasonable level of certainty. This requires consideration before developing further academic models that may never be implemented either due to their complexity or due to the wide variation depicted for the required recruitment period.

2.4.2. Strengths and Limitations

This review is the first to our knowledge that focuses on methods to predict recruitment at the design stage of a trial and outlines the parameters required for their implementation (Table 1) and any additional factors defining the models' assumptions and flexibility (Table 2). Thirteen articles were identified of which four were included in a previous related systematic review [13]. The previous related review did not differentiate models that could be used during the planning stage and this review adds to that systematic review by isolating these models and updating it.

One limitation of this study is that the search strategy for the review utilised two existing resources: the review of Barnard *et al* [13] and the ORRCA database [21], meaning that there are differences in the search strategies implemented to identify articles pre and post 2008. However, no additional eligible methods were identified via Google search or screening reference lists of eligible papers.

A further limitation is that any relevant article published after 2016 is not included in the synthesis of this review. The use of ORRCA meant that article inclusion was restricted to those published in 2016 at the latest. However, the statistical models described in the third review in chapter 4 can be used during the trial conduct to provide future prediction, and cover the period until September 2019. Some of these models have been included in both reviews since they could be used at both stages. When conducting the search for the 3rd review, which is very closely related to the 1st review, if there was a statistical model that could be used for recruitment prediction, then we would have chosen that and later classify it as a model to be used at the design stage or at a later stage. Thus, we are confident enough to say that we didn't miss any relevant model for the first review.

2.4.3. Summary

Factors affecting patient recruitment may be complex and many; thus, the accuracy of recruitment prediction and the follow up on patient monitoring to ensure that the trial will reach the recruitment target within the time expected, are crucial.

In addition, greater transparency is needed to support evaluation of methods used. Researchers should be clear about factors included in any model, data sources, and should clarify whether the monthly figures represent a guaranteed minimum number of participants per month or an "expected average". Modelling recruitment as a stochastic process at the design stage may lead to improvements in the prediction of recruitment and in understanding deviations from the "expected average". However, benefits may be limited if the approach taken leads to excessive variation.

Monitoring patient recruitment is the next essential step to ensure that the recruitment target will be achieved on time and if not, giving the research team the chance to make corrective actions at any stage of the trial conduct. The next chapter describes methods used to monitor patient recruitment, such as tables and graphs comparing expected against actual recruitment.

Statistical methodology continues to be developed to support prediction of recruitment in clinical trials. Until researchers implement these methods, they are limited in their potential to provide improved predictions.

Chapter 3: A picture paints a thousand words: A systematic review describes methods for monitoring of participant recruitment in clinical trials

Preface

In chapter 2 we discussed statistical models that could be used to predict recruitment of trial participants at the design stage of a clinical trial. In this chapter we systematically review methods that compare observed participant recruitment against that predicted at the design stage. Eligible methods include graphical and tabular approaches or simple metrics. The reliance on these methods is shown in chapter 6 where we present survey results from UK and European Networks demonstrating that such approaches form the main stay of those used to monitor trial recruitment progress against that expected at the design stage.

3.1. Introduction

Recruitment of clinical trial participants is challenging and when progress does not match prior expectations it risks compromising successful trial completion [41]. The primary reasons for recruitment failure include overly optimistic expectations, failure to start on time, inadequate planning, and insufficient effort [42].

Early detection of trials struggling to recruit optimises the ability of researchers to develop rescue strategies such as the alteration of trial eligibility criteria, or provision of additional resources. In the absence of potential solutions, recommendations may need to be made for the trial to close to support redistribution of resources to more promising clinical trials [43].

Frequent monitoring of clinical trial accrual performance should allow for earlier decisions to be made [27] with the need to compare observed accrual against that expected [42]. In oncology clinical trials, simple metrics such as the time-to-first-patient enrolment and the expected-time-to-accrual have been shown to be predictive of whether a trial will achieve its recruitment target [43]. More specifically, clinical trials that took more than two months to recruit the first patient were significantly less likely to reach the recruitment target on time than those trials, where the first patient was recruited within the first two months *(Odds Ratio: 0.637, 95% CI: 0.464–0.875, P = 0.005)*. Of the studies that were still recruiting beyond the expected recruitment period, those that did not reach at least 60% of the minimum expected accrual target

resulted in a statistically significant decrease in likelihood of achieving final recruitment numbers by the study closure *(Odds Ratio: 0.190, 95% CI: 0.055–0.652, P = 0.008)*.

In chapter 6, we present the results of a survey undertaken across UK and European Networks, which demonstrate that tables and graphs, which compare the expected and actual recruitment numbers, are the main stay approaches used to monitor trial recruitment progress against that predicted at the design stage. The purpose of this chapter is to systematically review tabular, graphical and other simple metrics for monitoring accrual in clinical trials.

3.2. Methods

3.2.1. Identification of potentially eligible studies

The search strategy used the ORRCA database [21]. The articles contained in ORRCA are categorised in recruitment domains; we handsearched the Trial Conduct domain "Monitoring and systems". At the time of the search, June 2019, ORRCA contained articles up to December 2016.

Citation tracking through Web of Science was used to identify articles published between January 2017 and September 2019. This involved citation tracking of all eligible articles identified from the search of ORRCA.

References of eligible papers were also reviewed for additional articles.

3.2.2. Eligibility criteria/Study selection

Research articles describing methods to compare predicted against actual recruitment were considered eligible and included:

- Any method directly comparing observed recruitment progress against that predicted at the design stage including tables, graphs, or simple metrics
- Any software tool, web platform, dashboard used for monitoring patient accrual

Exclusion criteria were as follows:

- Methods involving the use of statistical distributions (approaches using statistical methods for recruitment monitoring and subsequently for recruitment prediction during trial conduct will be explored in the next chapter)
- Articles describing clinical trial monitoring in areas other than recruitment
- Articles describing patient recruitment flow, with no comparison against predicted

- Review articles that did not propose a new method, although reference lists of such articles were searched for potentially relevant articles.

I reviewed the titles and abstracts of all retrieved papers. The full texts of these papers were obtained and the final inclusion was determined following discussion by EG, SD and CG. Disagreements between reviewers were resolved by consensus.

3.2.3. Data extraction

Data extraction was determined following discussion by all authors. Data were extracted on the specific monitoring approach used (graph, table, metric), whether it was done for the trial overall or by strata (e.g. centre level) and software/dashboard available for implementation. A word document was used for data extraction. I completed the data extraction, which was then checked and discussed with SD and CG.

3.3. Results

3.3.1. Search results

The search results are presented in Figure 2 below. A total of 12 articles met the eligibility criteria.

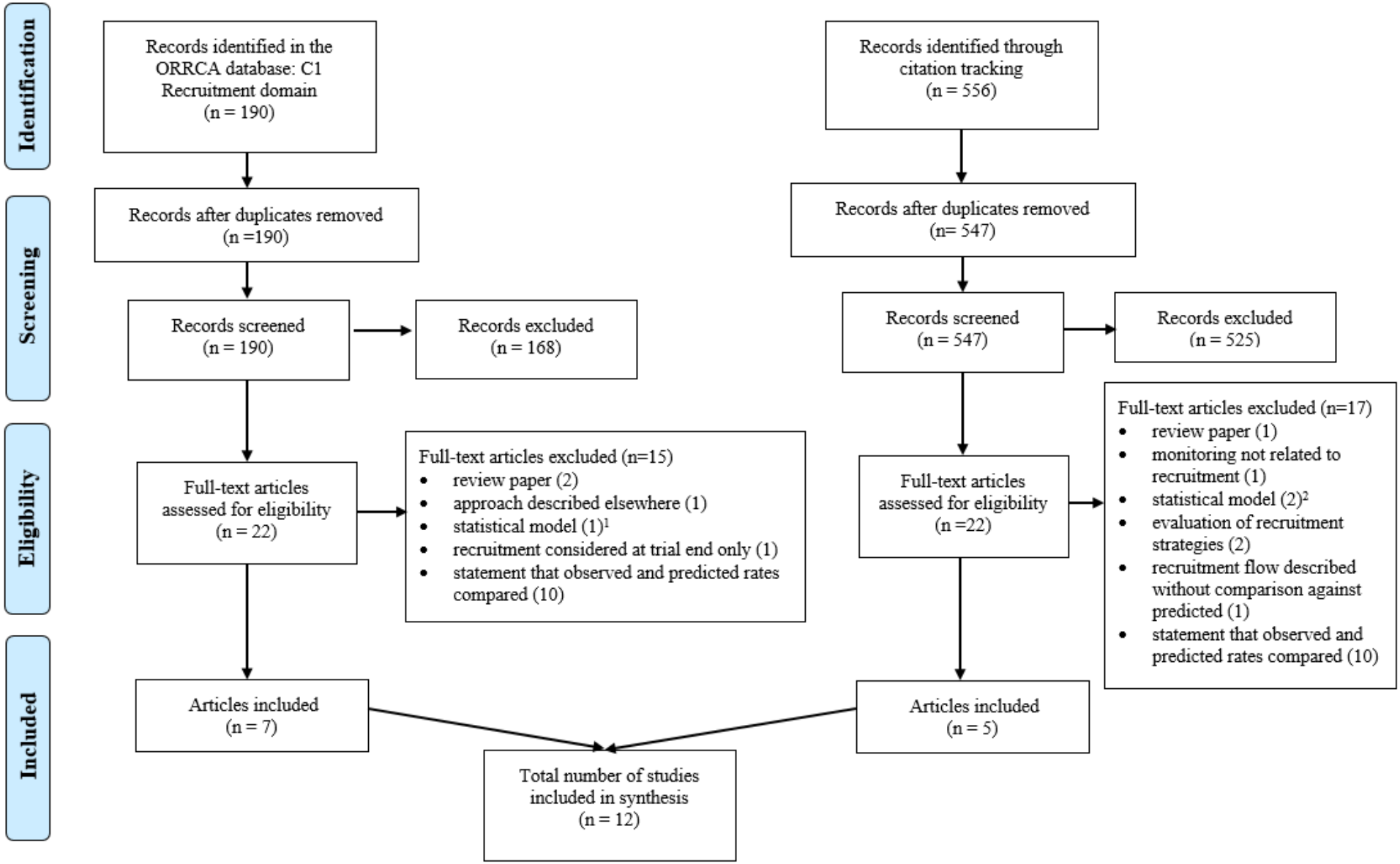

Identification
Screening
Eligibility
Included
Records identified in the ORRCA database: C1 Recruitment domain (n = 190)
Records identified through citation tracking (n = 556)
Records after duplicates removed (n =190)
Records after duplicates removed (n= 547)
Records screened (n = 190)
Records excluded (n = 168)
Records screened (n = 547)
Records excluded (n = 525)
Full-text articles assessed for eligibility (n = 22)
Full-text articles excluded (n=15)
review paper (2)
approach described elsewhere (1)
statistical model (1)[1]
recruitment considered at trial end only (1)
statement that observed and predicted rates compared (10)
Full-text articles assessed for eligibility (n =22)
Full-text articles excluded (n=17)
review paper (1)
monitoring not related to recruitment (1)
statistical model (2)[2]
evaluation of recruitment strategies (2)
recruitment flow described without comparison against predicted (1)
statement that observed and predicted rates compared (10)
Articles included (n = 7)
Articles included (n = 5)
Total number of studies included in synthesis (n = 12)

Figure 2: PRISMA flow diagram

[1] Lee 1983 (see Chapter 2)
[2] Kim *et al*, 2018 & Zhang and Lai, 2011 (see Chapter 4)

3.3.2. Classification of methods

The majority of eligible articles identified reported on the experience of recruitment in a particular trial (n=9/12). This recruitment experience of the trialists was the main focus of the paper rather than methods to monitor recruitment. These articles simply compared the number of patients recruited within a unit of time with the number predicted [44-52].

In addition, simple metrics for the evaluation of recruitment performance were developed and implemented within two articles [53, 54], one of which also presented a dashboard used to assess progress in real time for a large portfolio of trials. A further article introduced an electronic platform as a suitable web-based infrastructure to support monitoring of recruitment [55].

Description of each method and data extracted are summarised in

Table 3. The case reports utilising graphs of expected versus actual recruitment are not described further while the articles proposing metrics and tools to visualise recruitment progress are described in additional detail below.

Authors & Year	Method's Description	Summary report on recruitment figures	Further details
Treweek *et al* 2013 [44]	Centre-specific CONSORT diagrams for the recruitment figures and a CONSORT diagram for the trial as a whole during the monthly meetings were presented and discussed. Recruitment graph presenting the predicted versus actual monthly recruitment was provided.	The recruitment graph includes • planned total monthly recruitment • actual total monthly recruitment • recruitment duration	The authors suggested that estimating the number of potentially eligible participants who will provide consent and having an alternative plan, which includes opening more centres when the performance of some centres is not adequate, are two essential factors that should be taken into account.
Bjornson-Benson *et al* 1993 [45]	The progress of recruitment was monitored by tracking the cumulative rates of initial screening and randomisation in comparison to the expected rates over the projected 18 months of recruitment.	The recruitment graph includes • projected monthly screen rates • actual monthly screen rates • projected monthly randomisation rates • actual monthly randomisation rate • recruitment duration *Please see* Figure 3 *below*.	Reviewing recruitment activity every week allowed the investigators to make rapid decisions about moving resources from labor-intensive recruitment strategies that did not provide enough eligible participants to more effective recruitment strategies, helping them reach the randomisation target.
Zweben *et al* 2005 [46]	The coordinating centre tabulated weekly recruitment rates and provided feedback to the centres as a mean of identifying problems.	The recruitment graph includes • expected cumulative recruitment curve • actual cumulative recruitment curve • recruitment duration	Monitoring recruitment proved to be a useful tool in informing investigators about the number of months it would take for all centres to meet the recruitment goal. Historical recruitment rates were used to predict recruitment for future months. Study-wide and centre-specific retention methods developed were also discussed in this article.

Hays *et al* 2003 [47]	Overall recruitment progress and individual clinic performance was monitored with monthly reports illustrating the expected and actual cumulative enrolment.	The recruitment graph includes • projected recruitment • actual recruitment • recruitment duration	Weekly monitoring of clinic recruitment goals was necessary, including close review of reports distributed and they contributed to successful recruitment at the clinic level. A designated recruitment coordinator in each centre served as the contact person within the study on recruitment-related issues.
Childhood Asthma Management Program Research Group (CAMP) 2009 [48]	The recruitment process was monitored by the CAMP Coordinating Center. Clinic staff reported the number of visits initiated and randomisations completed, which were compared with the projected number of patients.	Two recruitment graphs include participant enrolment by calendar time with • projected versus observed patient recruitment for the trial overall (1st graph) and • projected overall recruitment curve versus observed recruitment curves per clinic (2nd graph)	A summary report of recruitment data was sent by the Coordinating Center to clinic directors and coordinators each month that recruitment was open. Clinics could monitor the study-wide performance, as well as their own performance in comparison to other clinics.
Powell *et al* 2016 [49]	Actual patient recruitment was monitored on a monthly basis and compared with the recruitment target.	The recruitment graph includes • the cumulative target number of patients • the cumulative number of participants recruited by referral pathway • recruitment duration	The accrual target per month was based on the average number of participants per month over 10 months, and then adjusted to account for season and time point in the study.
Mohebati *et al* 2012 [50]	The number of participants enrolled per month was monitored and compared to the target rates during the monthly meetings.	The recruitment graph includes • the anticipated number of enrolees • actual number of enrolees • recruitment duration	Outcomes, including the number of participants enrolled per month, were tracked. If recruitment were to lag by 20% or more of the target rate, modified strategies were implemented to enhance recruitment.

Gupta *et al* 2015 [51]	Using a Marketing and Information Technology (MARKIT) model for clinical trial management. Accrual rates were followed closely and reported monthly and compared with the expected projections.	The observed accrual rate was followed alongside the expected projections and the recruitment graph includes • expected rate of participant accrual • observed number of participants • recruitment duration *Please see* Figure 4 *below*.	Trial management is the main focus of this technology intervention, which was used to drive decisions for forecasting, resource planning, and iteration of recruitment strategies and tactics.
Kingry *et al* 2007 [52]	The cumulative number of randomised participants is compared with the goal over time in the recruitment graph. The R-factor related to the efficiency of recruitment has been calculated at the end of the feasibility phase and at the end of the main trial (see below Probstfield *et al*. 1987 [53]).	The recruitment graph for both the feasibility and the main trial includes • cumulative expected number of patients to be recruited • cumulative number of randomised patients • cumulative number of active clinical centres • recruitment duration	The recruitment results show the extreme sensitivity of recruitment to the number of active clinical centres. The authors suggest that for large clinical trials, the inclusion of a feasibility phase to facilitate recruitment planning should be considered.
Probstfield *et al* 1987 [53]	A single R statistic, which measures the degree to which accrual occurs as planned.	Parameters to be considered for the calculation of the R statistic • planned end of recruitment period, T • planned number of participants to be recruited, N • time after recruitment begins, W • t = W/T, the proportion of the recruitment period elapsed by time W • n(t) = cumulative number of participants recruited up to and including t • r(t) = n (t) / n , the proportion of the planned sample recruited by time t	The R statistic is used to measure the efficiency of the recruitment process at the end of recruitment period. However, it could be adapted and used to evaluate whether patient recruitment is adequate at different time periods.

Corregano *et al* 2015 [54]	An Accrual Index (AI) dashboard to assess recruitment progress in real time for a trial at the institutional level: the AI can be used to evaluate the study performance prospectively.	Factors to be considered for the AI evaluation metric are: • recruitment initiation date • accrual target • projected time to accrual completion (PTAC in months) • evaluable subjects enrolled (updated) • the recruitment time elapsed (the number of days elapsed from the Recruitment Initiation Date until the date of analysis, when recruitment is ongoing, divided by 30)	The dashboard incorporates accrual data captured routinely and provides the current AI, the most recent prior AI and the slope of change in the AI since last measured. Red, yellow, and green arrows are included to indicate whether the current patient accrual needs immediate remediation, merits cautious observation due to a downward trend or is consistently performing on time or ahead of schedule. Please see Figure 5 below.
Toddenroth *et al* 2016 [55]	Web-based reporting tool including a recruitment graph that contrasts the targeted and the observed cumulative progress of recruitment per month over time. An additional diagram displays the distribution of patients across study centres.	The dashboard displays two graphs. The first graph presents the following • patient recruitment goal per month • actual patient counts per month • recruitment duration The second graph displays patient state by recruiting centre with the following factors • cumulative patient counts for each centre and • patient status (active/dropout/completed study) per centre Please see Figure 7 below.	A study dashboard graphically summarises key progress indicators of patient accrual and trial documentation. The dashboard can be used to present the number and status of participants in multiple trials.

Table 3: Methods to monitor patient recruitment during the conduct of the trial

Recruitment Graph Examples

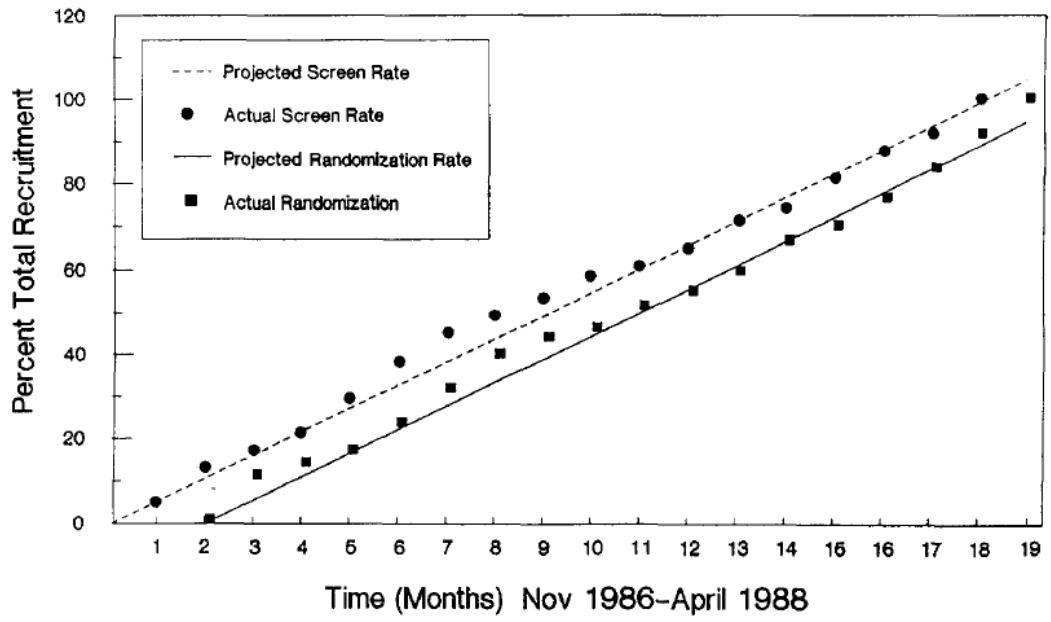


Figure 3: Monthly rates of screening and randomisation compared to target rates across the 18-month recruitment period (Bjornson-Benson et al 1993)

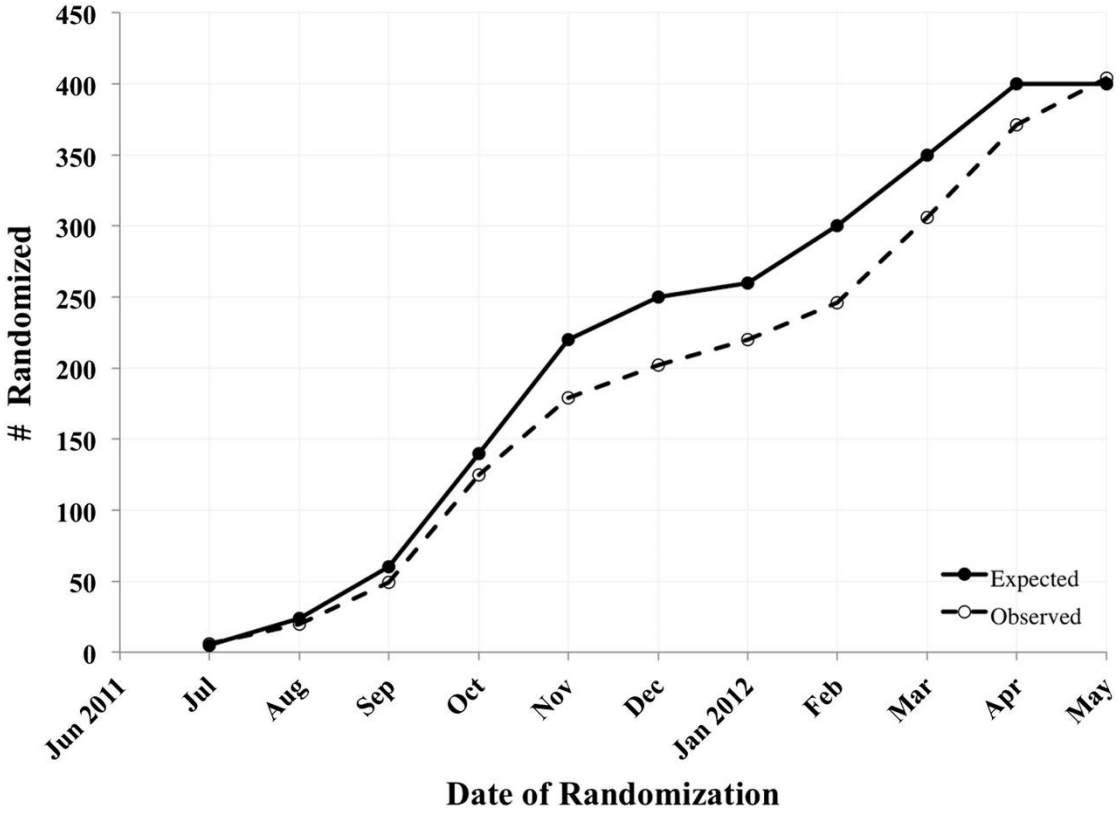


Figure 4: Expected (solid line) versus observed rate of participant accrual (dotted line) (Gupta et al 2015)

A metric to evaluate recruitment efficiency in a clinical trial

R statistic is a metric introduced by Probstfield *et al* in 1987 to measure the recruitment efficiency in a clinical trial retrospectively [53]. This metric measures the degree to which accrual occurs as planned at the end of the recruitment period, which may be either the stage when trial recruitment is completed or when the trial is stopped prematurely. R can be calculated based on the cumulative recruitment during the planned recruitment period as reported at times $0 < t_1 < t_2 < \cdots < t_k < \cdots < 1$. Where $r(t) = n(t)/n$, the proportion of the planned sample recruited by time t and $r(0) = 0$,

$$R = \sum(t_k - t_{k-1})[r(t_{k-1}) + r(t_k)].$$

R takes value equal to 1 when patient recruitment is completed within the predefined timeline, R<1 when recruitment lags and R>1 when patient recruitment is higher than anticipated. The authors pointed out the importance of R statistic for the planning of future trials. However, this metric could be adapted and used during the recruitment period to evaluate recruitment efficiency at different stages.

The Accrual Index (AI) described by Corregano *et al* [54] is another evaluation measure to describe how well recruitment performance is matching that predicted. It reflects the actual recruitment as a percentage of the expected at any given time, based on the investigators' anticipations about the timeline. AI expresses the fraction of the Accrual Target accrued over the fraction of the recruitment period elapsed. The parameters required for its implementation are listed in

Table 3.

$$\text{AI} = \frac{\frac{\text{Evaluable subjects enrolled}}{\text{Accrual Target}}}{\frac{\text{Days since recruitment start}/30}{\text{Projected time to accrual in months}}} \quad \text{or} \quad \text{AI} = \frac{\%\ \text{Accrual Target accrued}}{\%\ \text{PTAC elapsed}}$$

This metric was developed to evaluate recruitment progress towards the accrual goal and considering the allotted time for accrual. More specifically, a value of 1 means that it matches exactly with predicted rates with values below or above 1 meaning that patient recruitment is correspondingly below or above that expected.

Using Web-based infrastructure to support recruitment monitoring

The approach described above by Corregano *et al* [54] is visualised in a dashboard format as shown in Figure 5 below to evaluate the progress for a portfolio of ongoing studies with red (AI<0.9) equating to urgent remedial action, yellow (0.9-1) for caution and green (>=1.0) confirming that accrual is on time. There is a natural extension to an individual study with the AI calculated for each centre.

Study Name	Status	AI past month	AI current month	AI Trend (slope)	Percent PTAC elapsed
Protocol M	Open	↓0.33	↓0.22	↓-0.11	7%
Protocol X	Open		→0.94		8%
Protocol S	Open		↑1.22		8%
Protocol R	Open	↑2.40	↑2.00	↓-0.40	25%
Protocol N	Open	↑1.88	↑2.11	↑0.23	26%
Protocol T	Open	↑1.60	↑1.12	↓-0.48	42%
Protocol L	Open	↑1.07	↑1.04	↓-0.03	46%
Protocol Q	Open	↓0.50	↓0.70	↑0.19	46%
Protocol K	Open	↑1.89	↑1.57	↓-0.31	50%
Protocol G	Open	↓0.36	↓0.30	↓-0.06	75%
Protocol V	Open	↓0.80	↓0.86	→0.06	117%
Protocol W	Open	↓0.64	↓0.53	↓-0.12	133%
Protocol H	Open	↓0.70	↓0.70	→0.00	133%
Protocol Z	Open	↓0.64	↓0.64	→0.00	133%

Figure 5: The Protocol Accrual Index Dashboard is shown, configured with summary data for simplicity for the user. It is intended that users would look first at the Current AI and slope to assess whether accrual is on-time, then if needed, reference the Percent PTAC elapsed to understand the significance of the AI within the protocol life cycle (Corregano et al 2015)

In an attempt to improve the performance of a web-based reporting tool and avoid manual data entry, Toddenroth *et al* developed a study dashboard module for a continuous monitoring of trial recruitment and documentation [55]. The entry page of the dashboard displays key metrics for available studies as shown in Figure 6, which links to more detailed information such as study-specific enrolment per centre, as shown in Figure 7 below.

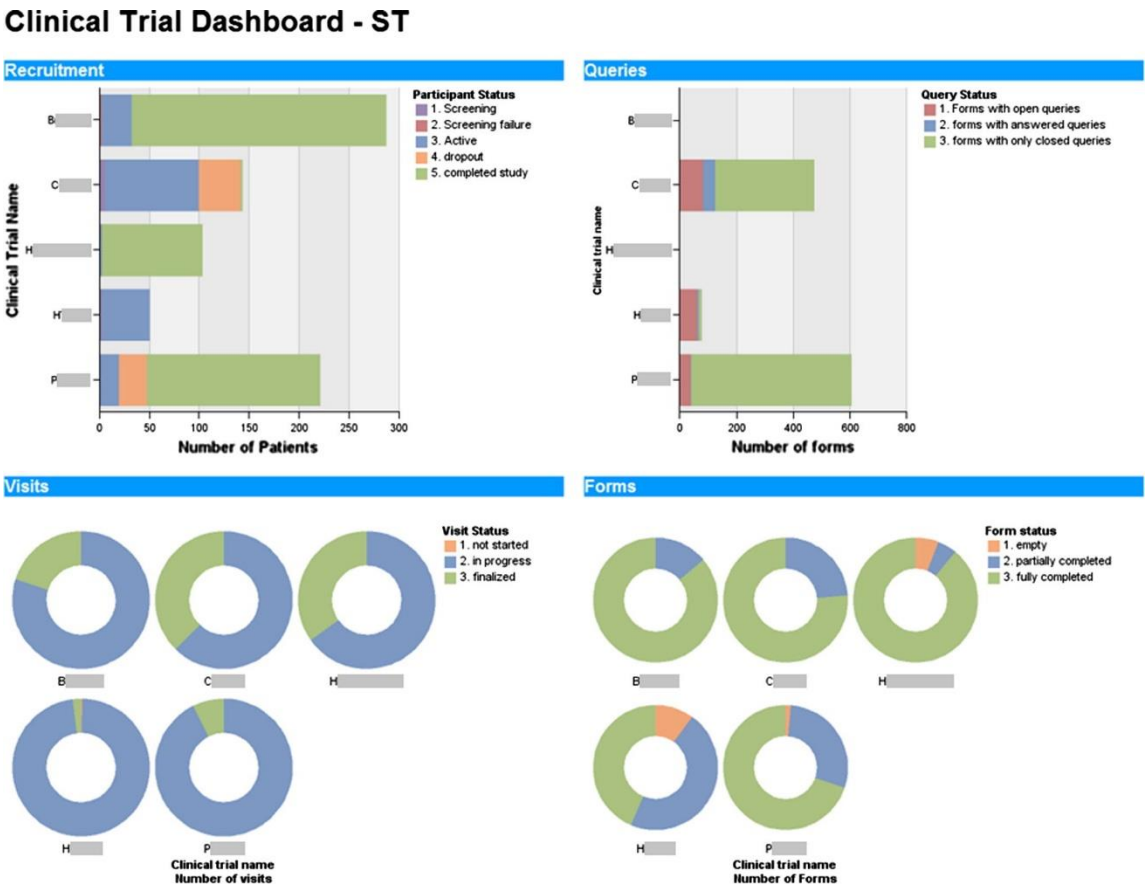


Figure 6: Screenshot of an exemplary entry page of the study dashboard. The displayed graphics provide an overview of the progress of patient recruitment, as well as of the frequency distribution of different types of data query, patient visit, and CRF completion (Toddenroth et al 2016)

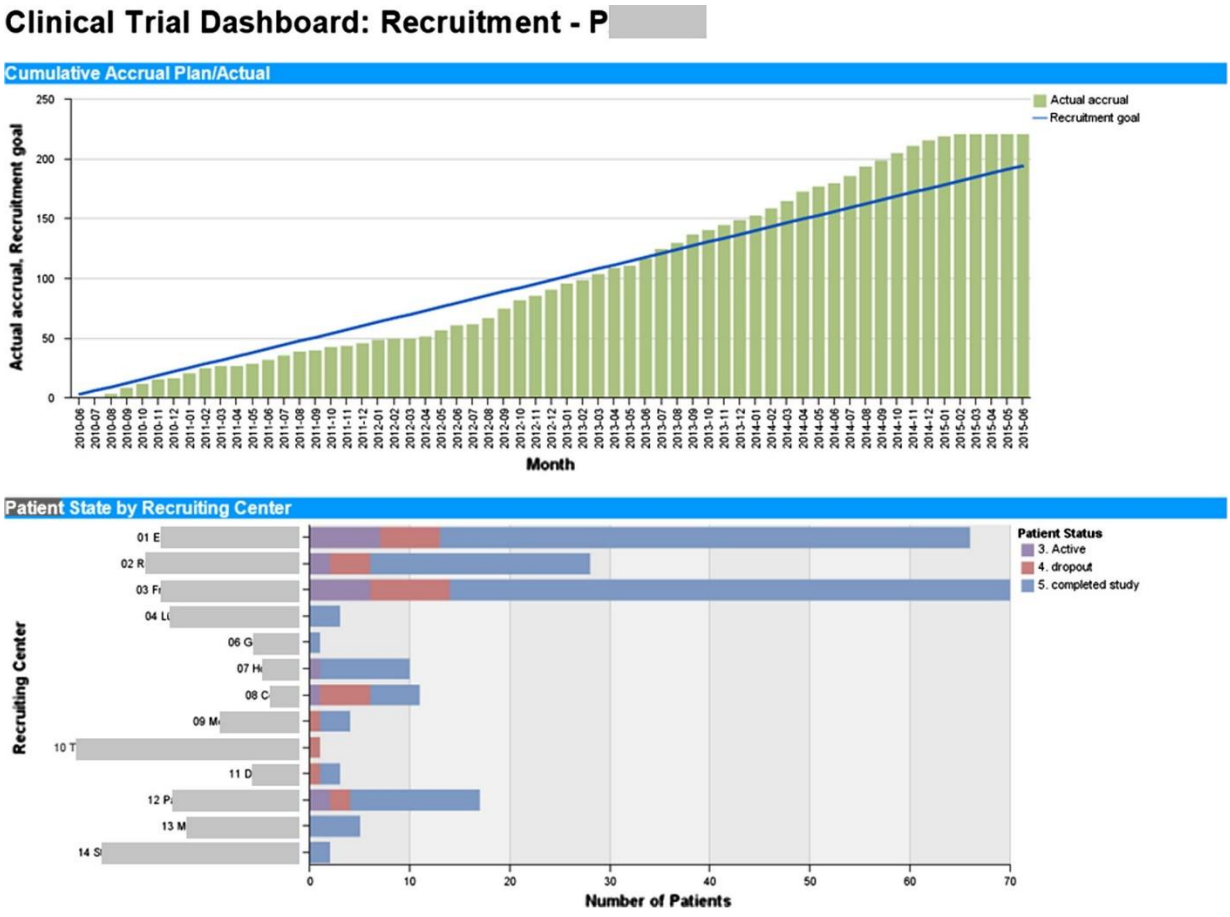


Figure 7: Screenshot of a dashboard view showing more detailed information for one of the studies that had been interactively selected. The upper part of the figure contrasts the targeted and the observed cumulative progress of recruitment over time; the lower diagram area displays the distribution of patients across study centres (Toddenroth et al 2016)

Graphical summaries provided are evaluated by the study coordinators as suitable for detecting recruitment inefficiencies and allow for practical remedies.

3.4. Discussion

3.4.1. Main findings

Patient accrual rate is often highly variable, requiring frequent monitoring of trial recruitment progress. However, there is a lack of simple metrics to measure the accrual success for a trial. Patients recruited per week or per month at a centre level or across all centres, are the measures most commonly used. As summarised in the article of Probstfield *et al*, recruitment efficiency is studied at different time points in the patient pathway, for example patients randomised as a percentage of patients screened, consenting to participate, or retained at the pre-enrolment visit; potential participants from the target population; the percentage of patients with the disease in the population screened; or the patient goal at an individual clinical centre [53].

This review identified that the majority of accrual monitoring articles describe recruitment experience within a specific trial, rather than developing informatics or methods to support monitoring activity [44, 46-52, 55]. This may reflect a gap in methods development or a practice of in-house development that is not being shared more widely.

The impact of centres in patient recruitment was captured by Kingry *et al* [52], Childhood Asthma Management Program Research Group [48] and Toddenroth *et al* [55]. In the first of these articles, the number of active centres was displayed alongside the expected and the actual patient overall recruitment curves [52]. In the second article, they monitored patient accrual per clinical centre against the overall projected and presented them in a recruitment graph [48], while the authors in the last article presented in a dashboard the distribution of patients across centres and included their status, which was recorded as active, dropout or completed the study [55]. This importantly links and monitors recruitment to retention. In 2005, the method introduced by Rojavin considered patient retention in the calculation of the recruitment index (RI) [56]. RI represents the number of days required for an average study centre in a multicentre clinical trial to recruit one analysable patient. The purpose of this specific study was to inform future studies and project the number of centres required and calculate the time needed to complete trial recruitment.

While all the included articles discuss whether patient recruitment is lacking in comparison to what was expected, the article by Mohebati *et al* is the only one defining a threshold as the lowest acceptable limit for the number of patients recruited [50]. Modified strategies to enhance recruitment were to be implemented if recruitment were to lag by 20% or more of the target rate. The value of monitoring recruitment is in identifying problems early enough to rectify the deliverables; knowing when to act in reference to the observations is key.

The importance of patient monitoring in clinical trials is directly related with decision making about the continuation of the trial. This decision has the potential to prevent waste in research by prioritising the clinical trials that seem promising. Availability of generalised methods that could be used for recruitment monitoring could facilitate this procedure. Recruitment metrics that can be used during trial conduct as described by Probstfield *et al* [53] and Corregano *et al* [54] may provide important measures for the

evaluation of recruitment performance. However, the uptake of these metrics may be low due to lack of knowledge of their existence or absence of evidence of the benefits.

Corregano *et al* also suggest presenting the percentage of the recruitment period elapsed as a useful metric to maintain awareness of time spent [54]. Yet, this would need to be compared with the percentage of patients successfully recruited. In trials with a strong seasonal factor you may expect greater divergence between these percentages depending on the time of year.

Traditionally, recruitment success in terms of reaching accrual target within the defined timeframe is evaluated at the end of the proposed enrolment period by calculating whether 100% of the expected accrual was achieved. This figure does not usually reflect time extensions that were required in addition to the time originally planned to achieve the targets. This may lack transparency as it does not indicate studies, which did not recruit on time.

Finally, web-based tools or dashboards to support patient monitoring and the communication of accrual data among centres in real time, could be proved effective for the trial team and allow them to make real-time decisions and corrective actions. This approach seems to be underutilised and research to understand whether the benefits would warrant the investment should be considered.

3.4.2. Strengths and Limitations

Monitoring approaches for patient recruitment are not frequently reported, with questions for best practice remaining unanswered. This review is the first to our knowledge that focuses on methods to directly compare recruitment progress with that predicted at the design stage.

One limitation of this review is that the search strategy utilised two different approaches for the period before and after 2016, namely the ORRCA database and citation tracking through Web of Science respectively. However, this is a reasonable approach, as it is highly likely that new papers proposing new approaches would reference previous relevant research. A further limitation is that groups of trialists may be developing approaches eligible for this review but not sharing these through published academic avenues.

3.4.3. Summary

Monitoring of patient accrual to ensure that the trial will reach the recruitment target within the predefined time is crucial and could help investigators to act on time. During the conduct of the trial, when the research team realise that patient recruitment falls below expectations, then corrective actions are needed. The use of new recruitment sources or strategies, addition of new clinics, or a change in protocol, should be developed and introduced as workable contingency plans and be followed up within the remaining period of patient recruitment.

In addition, greater transparency is needed to support recruitment monitoring, since approaches used by the researchers are rarely reported. Using graphical summaries, simple metrics and/or web-based infrastructure to support monitoring may lead to timely recognition of recruitment problems and therefore feasible solutions.

When corrective actions are not considered sufficient in bringing patient recruitment back on track, then an updated recruitment prediction followed by reprofiling of the trial is required. The next chapter describes statistical models that can be used for ongoing recruitment prediction. Predictions made during the trial recruitment period, using accrual data captured from the centres open to recruitment, may be considered more reliable than those made at the design stage of the study. Extension of recruitment period and/or funding are some of the recommendations proposed to reach the accrual target.

Chapter 4: Recruitment prediction during trial conduct: statistical models utilising available accrual data

Preface

In chapter 2 we discussed statistical methods that could be used to predict recruitment of trial participants at the design stage of a clinical trial. In chapter 3, graphical and tabular methods as well as simple metrics used to monitor recruitment were presented and their importance in decision making was highlighted. The data captured from centres that are open to recruitment may be used as the basis to inform or update prediction models. In this chapter, we present a systematic review of such models.

4.1. Introduction

Statistical models can be used to predict patient recruitment at the design stage of the trial [57]. It is then essential to follow the patient accrual to evaluate if the observed recruitment rate is comparable with the research team's initial expectations. If not, corrective actions need to be considered and/or the remaining recruitment period may need to be re-profiled.

Determining whether or not there is merit in continuing patient recruitment is important during the recruitment period [58]. A slow accrual decreases the likelihood that the research will provide results at the end of the trial with sufficient precision and make meaningful scientific inferences without risking the validity of results.

Predictions made part way through the recruitment period, informed by the observed recruitment rates, may be considered more reliable than those made at the design stage. Within the field of Human Immunodeficiency Virus (HIV), early enrolment records were shown to have a strong correlation with later accrual rates [59]. However, using the number of patients recruited by specific clinical centres to make predictions for future performance of the same centres or even of the performance of other centres is not without challenges. Reliance solely on the accrual data to date may lead to an underestimate or overestimate of the recruitment performance by the research team for the upcoming period. A careful combination of the initial expectations and the number of patients recruited to date, could be the answer to this challenge.

The application of statistical models could support ongoing recruitment prediction by allowing the user to consider stochastic fluctuations of recruitment rates over time and quantify associated uncertainty. The purpose of this stage of research is to systematically identify and review statistical models to predict recruitment during trial conduct using accrual data observed so far.

4.2. Methods

4.2.1. Identification of potentially eligible studies

The ORRCA database [21] was used to identify potentially eligible studies. The articles contained in ORRCA are categorised in recruitment domains; we handsearched the articles within the "Recruitment rate prediction" category. At the time of the search, June 2019, ORRCA included articles up to and including 2016.

To identify articles published between January 2017 to September 2019, citation tracking (October 2019) through Web of Science was used. This identified all articles that cited one or more of the studies identified from the ORRCA search.

References of eligible papers were also reviewed for additional articles.

4.2.2. Eligibility criteria/Study selection

Research articles describing statistical models to predict ongoing recruitment based on accrual to date were considered eligible.

- Statistical models requiring accrual data to predict one or more of the following
  - the time required to recruit the number of patients remaining
  - the number of patients to be recruited in the remaining time
  - the probability of reaching the target sample size on time

This approach includes revised predictions.

Exclusion criteria were as follows:

- Articles discussing recruitment problems and recruitment prediction that did not include a statistical model to predict ongoing recruitment.
- Review articles that did not propose a new model/approach, although the reference list of these articles was searched for potentially relevant articles.

I reviewed the titles and abstracts of all retrieved papers. The full texts of these papers were obtained and the final inclusion was determined following discussion by EG, SD and CG. Disagreements between reviewers were resolved by consensus.

4.2.3. Data extraction

I proposed the data to be extracted and this was reviewed by all authors. The areas of extraction were:

Input: data and parameters needed to implement the method e.g. sample size target, number of centres, duration of the recruitment period as a whole or remaining, and recruitment data to date.

Output: the results of model implementation e.g. time required to recruit to sample size target, the number of patients to be recruited in the remaining time, probability of reaching the sample size target within the remaining time.

Flexibility: whether recruitment rates were considered constant, time-dependent or centre-dependent, or any other factors used to support variation in rates.

Validation: whether the model has been implemented and evaluated using real data and/or simulated data.

In addition, any guidance provided about the amount of accrual data required for model implementation and guidance on thresholds to determine trial termination, were evaluated. A word document was used for data extraction. I completed the data extraction, which was then checked and discussed with SD and CG.

4.3. Results

4.3.1. Search results

The Prisma flow diagram is provided in Figure 8. A total of 11 articles were eligible for inclusion. One article describes the Poisson model with a time dependent recruitment rate [27], two articles present the Brownian [60] and Fractional Brownian Motion [61] methods to capture the enrolment process of long-term clinical trials, and another two articles introduce the Gamma-Poisson [38] and Pareto-Poisson [62] models. Bayesian approaches to model and predict patient recruitment are described by five articles [32, 33, 63-65] and finally another article introduces the Sequential Patient Recruitment monitoring (SPRM) [66], a new approach that combines monitoring and prediction for patient recruitment in clinical trials.

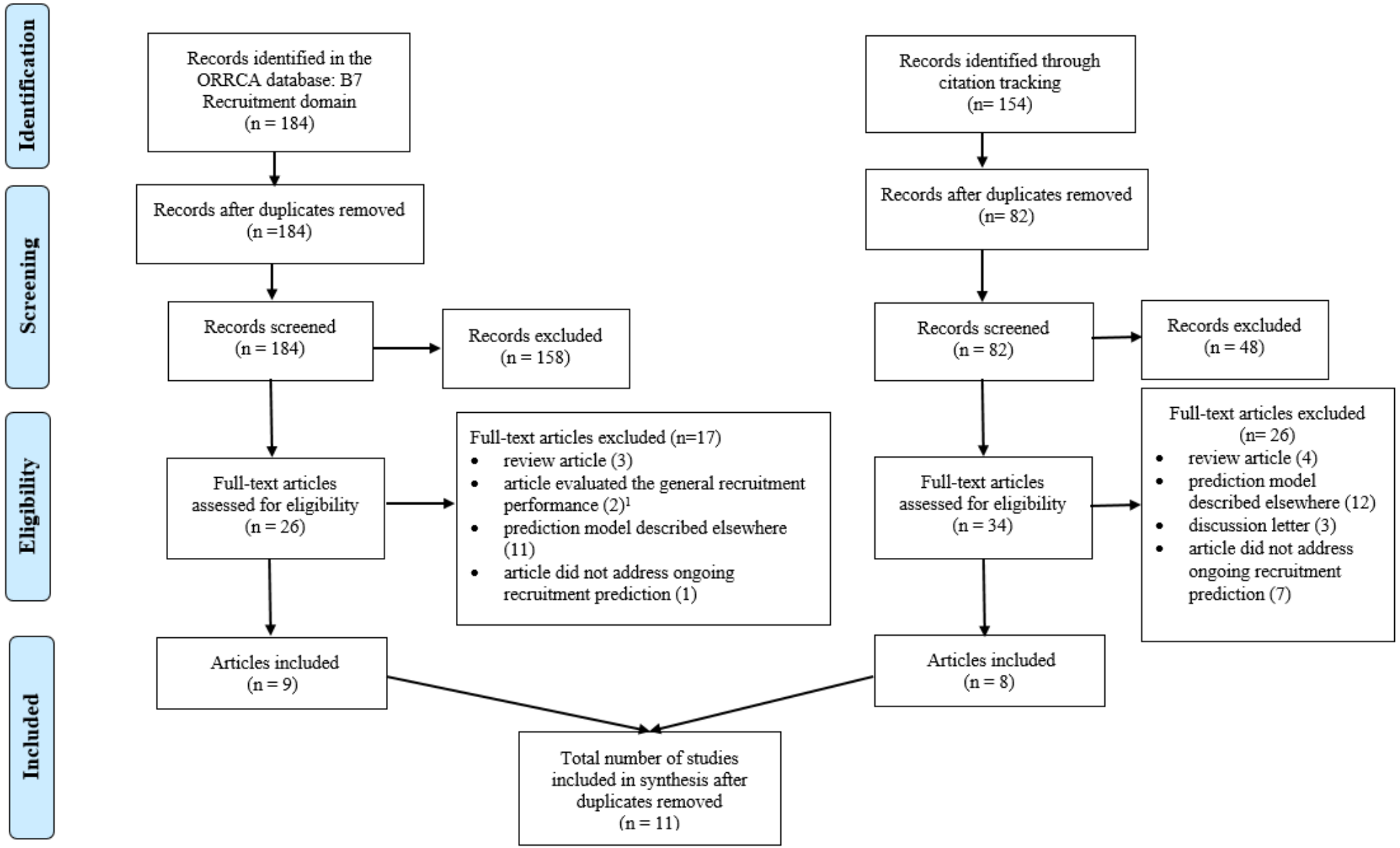

Identification
Screening
Eligibility
Included
Records identified in the ORRCA database: B7 Recruitment domain (n = 184)
Records after duplicates removed (n =184)
Records screened (n = 184)
Records excluded (n = 158)
Full-text articles assessed for eligibility (n = 26)
Full-text articles excluded (n=17)
review article (3)
article evaluated the general recruitment performance (2)[1]
prediction model described elsewhere (11)
article did not address ongoing recruitment prediction (1)
Articles included (n = 9)
Records identified through citation tracking (n= 154)
Records after duplicates removed (n= 82)
Records screened (n = 82)
Records excluded (n = 48)
Full-text articles assessed for eligibility (n = 34)
Full-text articles excluded (n= 26)
review article (4)
prediction model described elsewhere (12)
discussion letter (3)
article did not address ongoing recruitment prediction (7)
Articles included (n = 8)
Total number of studies included in synthesis after duplicates removed (n = 11)

Figure 8: PRISMA flow diagram

[1] Corregano *et al*, 2015 & Rojavin, 2005 (see Chapter 3)

4.3.2. Description of models

The models are summarised in Table 4 and Table 5.

4.3.2.1. Poisson model

The rationale for the approach proposed by Lee is that attainment of interim goals will ensure the sample size target is met [27]. As in chapter 2, the method uses the Poisson distribution with closed formula based on a normal approximation. However, it now builds on the method in chapter 2 by assuming a contagious Poisson distribution such that the expected recruitment rate of the current period depends on the observed rate. The method, utilising the observed recruitment data, can be used either to determine the required recruitment rate when the recruitment duration is fixed, or to project the final recruitment from an interim point.

In determining the required recruitment rate (described as Lee 1st model in the tables), Lee defines the minimum acceptable interim recruitment goal, n_i, at time t_i as the minimum number that will guarantee the user-defined probability, p, of recruiting the rest of participants in the time remaining. The required recruitment rate is then the λ that satisfies all interim periods i.e. the largest. Lee shows that the required recruitment rate rises with the increasing frequency of the interim monitoring, suggesting an associated "cost". It is therefore important to specify this at the start rather than at ad hoc timepoints, and the method may be of less value in early stages of recruitment when not all centres are open to recruitment or when seasonal factors are to be expected. Lee does discuss how adjustments can be made to the method to incorporate seasonal adjustment or weighting for slower recruitment during the start or final phases of patient recruitment.

In projecting final recruitment from an interim point (described as Lee 2nd model in the tables), the contagious Poisson is similarly used, and a variance is placed around the final projected numbers. From here, projected probabilities of achieving the final recruitment goal can be calculated either for the trial as a whole or for individual recruiting centres.

4.3.2.2. Brownian and Fractional Brownian Motion Models

Lai *et al* used a method to focus on a single interim point that utilises the accumulated accrual data to determine the remaining duration of trial recruitment [60]. However, they suggest that the recruitment data from the initial weeks of slow recruitment should be discarded, because it is not considered representative of the overall recruitment process.

The authors consider the number of patients recruited as a growth process and model it as a Brownian motion (BM), where the expected cumulative number of patients is a linear function of time. The cumulative number of patients expected to be randomised, f(t), is subtracted from the actual cumulative number of patients randomised, $X(t)$, and the deviation is modelled as a linear function of time forming a one-dimensional Brownian motion, $B(t)= X(t) – f(t)$. Linear regression is used to model the Brownian motion, defining the growth rate λ, and the intercept α of the expected growth function $f(t) = \alpha + \lambda(t)$. The confidence interval of the future path is also provided and it increases in width for predictions, which are further in the future.

The BM method proposed by Lai *et al* was restricted to a single interim point. This was due to an assumption of independence between recruitment periods, such that if multiple interim point were used then only the data accrued since the previous interim evaluation could be used to predict the next recruitment period [60].

In a follow-up work, Zhang and Lai proposed an extension using fractional Brownian motion (FBM) to address this assumption of independence within the recruitment period [61]. They used the least square as a method to fit the linear regression model and estimate the rate λ, and the intercept α of the expected growth function $f(t)$ as shown above, and method of moments was used to estimate the variance. The dependence between time periods is quantified by using the Hurst parameter with values between 0 and 1 ($0<H<1$). Larger values of the Hurst parameter lead to wider confidence intervals. While in the BM the value of H parameter is 0.5, in FBM a value of H parameter greater than 0.5 implies positive correlation while a value less than 0.5 implies negative correlation.

FBM does not consider the impact of centre performance, therefore the number of currently active clinical centres is not included in the model.

4.3.2.3. Gamma-Poisson and Pareto-Poisson models

In the model described by Anisimov & Fedorov [38], the authors investigate the properties of the Poisson-gamma (P-G) model. In chapter 2 this model was included for its use at the design stage. In this chapter the focus is on how this model can be used to predict recruitment in an ongoing trial.

In the P-G model, it is assumed that the patients arrive according to a Poisson process. The gamma distribution is used to incorporate centre variation in multi-centre trials. The method for the estimation of rates is determined by the number of centres. When the number of centres participating is more than twenty, then a Bayesian paradigm is used to predict the overall recruitment rate for the future, with a contribution from all centres. However, if fewer centres are initiated, then the rates are estimated individually for each centre.

During trial conduct, if patient recruitment is lagging, the impact of adding additional centres on the probability of completing trial recruitment on time can be estimated.

For an ongoing trial when the same duration of recruitment is assumed in all centres, the predicted time has a Pearson type VI distribution; however when the duration of recruitment is different for each centre, the Bayesian predicted time can't be calculated in the closed form, thus Monte Carlo simulations are used.

Jiang and Zink implemented the model described above in JMP Clinical 6.0, which is a clinical data analysis software (https://www.jmp.com/en_au/software/clinical-data-analysis-software.html) [67]. The platform to implement the model is not freely available.

The Gamma-Poisson predictive model described by Anisimov and Fedorov [38] has been extended to a Pareto-Poisson process by Mijoule *et al*, with a Pareto distribution of the rates instead of Gamma [62]. Gamma-Poisson and Pareto-Poisson models have been compared in relation to the expected recruitment duration, the quality of fitting the data and the sensitivity to parameter errors. The expected recruitment durations were not very different when comparing the models; however in relation to centres, the Pareto-Poisson model may work better for studies with a smaller number of "big" centres compared with the number of "small" ones. As a result, the authors recommended the use of the Poison-Gamma and also suggested using a uniform

distribution for the initiation of centres when centres' opening dates are not known precisely.

Model	Description	Parameters and data required to implement the model	Model's Output
Poisson model with time dependent recruitment rate	**Lee** 1983 [27] 1st model: determine the required recruitment rate and the minimum acceptable interim goals to achieve the interim and final goals with a predefined probability 2nd model: calculate the probability of reaching the target sample size at interim	• sample size target • recruitment period duration • observed recruitment data • number of interim monitorings • acceptable probability of achieving the interim and final sample size target	• the expected number of patients to be recruited during the remaining recruitment period (1st model) • projected probabilities of achieving the final recruitment goal estimated at interim (2nd model) • the length of extension that will make it possible to meet the requirement on patient recruitment (2nd model)

Brownian and Fractional Brownian Motion Models	**Lai** 2001 [60] Models the difference between cumulative expected and actual accrual as a Brownian motion (BM) by fitting a linear regression to the data. Accrual data can only be used to predict future recruitment once. Further predictions require use of "fresh" accrual data with previously used data discarded. Initial weeks of slow recruitment can be discarded and longer term projections are based on steady state recruitment. Confidence intervals are wider the further into the future the prediction is made. **Zhang and Lai** 2011 [61] Fractional Brownian motion (FBM) method can use previous accrual data more than once. It requires estimation of the Hurst parameter. Data up to one-third of the sample size target, after excluding the initial months of slow recruitment, have been used to model and predict the probability of reaching the recruitment goal.	• sample size target • recruitment period duration • recruitment period elapsed • observed recruitment data, X(t) • expected number of patients at time t, f(t)	• the probability of reaching recruitment goal given the cumulative recruitment at the time of modelling (BM & FBM)

Gamma-Poisson Model	**Anisimov and Fedorov** 2007 [38] The model predicts time required to achieve sample size target using observed recruitment data. it uses the Poisson process to describe variation in recruitment over time and it models variation in the recruitment rates between centres using the Gamma distribution	• sample size target • number of centres • recruitment period duration • recruitment period elapsed by centre • observed recruitment data by centre	• the remaining recruitment time & • the number of additional centres to open to reach the deadline with a pre-specified probability
Pareto-Poisson model	**Mijoule *et al*** 2012 [62] The model estimates the probability to complete the trial recruitment according to the planned recruitment deadline. the variation in patient recruitment over time is modelled by a Poisson process the variation in recruitment rates among different centres is modelled by the Pareto distribution	• sample size target • number of centres • recruitment period duration • recruitment period elapsed by centre • observed recruitment data by centre	• the probability of ending the trial on time & • the number of additional centres to open to reach the deadline with a pre-specified probability
Bayesian models	**Williford *et al*** 1987 [63] This Bayesian model assumes a nonconstant patient intake rate and can be used for monitoring patient accrual and predict future patient intake rate. Accuracy improves with increased accrual data.	• sample size target • recruitment period duration • observed recruitment data • recruitment period elapsed	• the future intake rate
	Gajewski *et al* 2008 [32] Develops a model based on waiting times using non-informative prior (P=0) with the observed data and informative prior with the observed data.	• sample size target • recruitment period duration • observed recruitment data • recruitment period elapsed	• the number of patients to be recruited within a fixed time period • the time required to reach the target sample size

	Waiting times are assumed to be exponentially distributed with a mean θ, the prior distribution of which is specified by the inverse gamma.	• times when each patient entered the trial • investigators confidence of completing the trial on time as a single value between 0 and 1	
	Jiang *et al* 2015 [64] Two adaptive Bayesian priors are proposed in monitoring accrual process, as an extension of the aforementioned Bayesian model [32] (i) accelerated prior (AP), where prior certainty is associated with the proportion of observed data, P=1-m/n (ii) hedging prior (HP), where prior certainty P is assigned a uniform distribution.	• sample size target • recruitment period duration • observed recruitment data • recruitment period elapsed • times when each patient entered the trial • accelerated prior: investigators confidence of completing the trial on time defined as P= 1-m/n • hedging prior: investigators confidence of completing the trial on time is specified by a uniform distribution • Tdecision to be defined by the research team as a stopping rule for a trial with slow accrual	• the trial completion time

	Zhang and Long 2010 [33] Use the Poisson process to model the average recruitment rate under the Bayesian framework. The patient accrual is modelled stochastically by using a Non-homogeneous Poisson process (NHPP), which characterises the underlying time-varying accrual rate using cubic B-splines.	• sample size target • recruitment period duration • anticipated maximum accrual rate • number of patients enrolled on a day • observed recruitment data • recruitment period elapsed • P confidence parameter with $P \in [0,1]$	• the duration of accrual to reach the planned sample size, by assuming that the accrual rate plateaus after the interim monitoring is conducted

	Lan *et al* 2018 [65]
	The method uses a statistical model for center initiation times. The within center accrual is assumed to be constant and then decreasing.
	
	• the number of centers initiated each month follows a Poisson distribution with a time dependent mean, which is modelled as a negative exponential variable and
	  ○ non-informative normal prior distributions are assigned to the parameters μ and δ of the aforementioned distribution
	• subject accrual within centre is modelled as a Poisson
	  ○ centre accrual rate is modelled as negative exponential after the steady period with coefficient $\boldsymbol{\eta}$
	  ○ centre enrolment rates are modelled as a sample from a gamma distribution to describe heterogeneity between centres
		• sample size target
		• number of centres
		• number of initiated centres
		• initiation time for each centre
		• observed recruitment data per month by centre
		• current month of recruitment
			• the number of monthly enrolled patients
			• the cumulative number of centres
			• the time required to reach the target sample size

	▪ a prior Gamma distribution is assigned to each of the parameters α and β of the aforementioned distribution and ▪ a truncated normal prior is assigned to the parameter **η**		
Sequential patient recruitment monitoring (SPRM)	**Kim *et al*** 2018 [66] The model estimates the probability of achieving the target enrolment under the assumption that the current trend continues. It also provides an opportunity for corrective actions. The SPRM method is based on the sequential probability ratio test, a hypothesis test for sequential samples.	• sample size target • recruitment period target • the optimal start time for monitoring to be determined (the first 10-15% of the target accrual is suggested to be used for initial estimation) Under the SPRM, after a decision is made, then the following need to be calculated • remaining sample size • remaining recruitment period • N(t) denotes the number of new recruits within a time period of length t • S_n denotes the time until n patients are recruited H_0 and H_1 are to be defined for each round.	• the probability of reaching the target sample size When the null hypothesis has been rejected, the SPRM method can be used to estimate: • enrolment rate required to recruit the remaining patients with a specific probability • shortage size in patient enrolment • the probability of reaching the sample size target by the end of the recruitment period • the possible extension of recruitment period, based on the assumption that the recent trend that triggered the warning will continue

Table 4: Models' presentation and description of parameters required for their implementation

4.3.2.4. Bayesian Models

Williford *et al* proposed a Bayesian approach to address a non-constant recruitment rate, which is an assumption of the Poisson model for patient recruitment [63]. They also used a Poisson model for the number of patients recruited. The method uses time intervals with a gamma prior distribution for the recruitment rate. The posterior distribution is updated using the conjugate properties of the gamma family to predict ongoing recruitment.

Gajewski *et al* also adopted a Bayesian framework. This model considers waiting times between patients recruited and assumes this follows an exponential distribution with mean θ, the prior distribution of which is specified by the inverse gamma defined as $\theta \sim IG(nP, TP)$, where n is the sample size target, T is the expected recruitment time and P is how confident the investigator is that n will be achieved by time T [32]. This model was initially presented in chapter 2 for its use at the design stage, while in this chapter the focus is on how, by combining accrual data and initial expectations, ongoing recruitment prediction could be improved. The method accounts for the uncertainty in the model parameter as well as the uncertainty in the accrual process. More details about the parameter estimation and additional features of the model are presented in Table 4 and Table 5.

Jiang *et al* extended the model by proposing alternative prior distributions, the accelerated prior and the hedging prior [64]. In the accelerated prior, the prior certainty P is defined as a proportion of the observed recruitment, $P=1-m/n$, where m is the number of patients already recruited and n is the recruitment target. This constrains the investigators prior beliefs according to recruitment progress with P declining linearly as more recruitment data are available and reflects the fact that posterior distribution is based more on accrual data than prior expectations as the trial progresses. In the hedging prior instead of assigning a single value to the variable P, a hierarchical model is used instead and the investigators confidence is specified by using the uniform distribution $P \sim U(0, 1)$, which indicates the similarity of the current trial with historical data. The "accrual" package in R [40] has been developed for the implementation of the Bayesian model introduced by Gajewski *et al* [32] and expanded by Jiang *et al* [64].

In addition, Baldi *et al* illustrate the methods described by Gajewski *el al* [32] and Jiang *et* al [64] using accrual data from cardiovascular trials retrospectively [68].

While Liu *et al* [69] implement the same models [32, 64], to monitor accrual in a research portfolio of a University Cancer Centre by linking to the clinical data management system and generating accrual reports. The process of accrual computation uses R software and starts with importing daily Clinical Trials Office data and ends with an export of the accrual report in Hypertext Markup Language (HTML) format. The accrual prediction is visualised with recruitment graphs, which demonstrate the predicted completion date with a 95% prediction interval and the posterior predictive distribution.

Zhang *et al* [33] also proposed a nonhomogeneous Poisson process within a Bayesian framework to model accrual over time and predict patient recruitment. Taking into account that in most clinical trials enrolment typically starts slowly and builds to a plateau, the authors proposed to project the future accrual pattern by assuming that the accrual rate plateaus after the interim monitoring is conducted. They use a regression spline approach to describe the accrual rate against time. The prior distribution of the B-spline coefficients is specified as a multivariate normal, $b \sim MVN(\mu, \Sigma)$, where the estimation of parameters is based either on a fully data-driven approach using the data before the interim time point or by asking investigators opinion about the anticipated average accrual rate once patient recruitment stabilises. The results showed that the projection tends to be more accurate when more accrual data have been used to update the posterior distribution.

Lastly, Lan *et al* described a simulation-based prediction model, which takes into account the key features of patient accrual such as the staggered initiation of new centres, the variability in centre size, and changes in accrual within centres [65]. The aim is to estimate the time to recruitment completion and produce prediction intervals around the estimated time. Patient recruitment is described in two stages; in the first stage the rate of initiation of centres is defined, while in the second stage the rate of subject accrual within centre is defined.

The number of centres initiated each month is assumed to follow a Poisson distribution with the mean depending on the month since trial initiation; the initiation rate usually declines after an initial surge of activity and therefore the monthly centre initiation rate is modelled as a negative exponential of the study time with parameters μ and δ. A non-informative normal prior distribution is assigned to each parameter.

On a patient level, centre accrual in a specific month is Poisson with mean $\lambda_c(u)$. The pattern of recruitment model allows for each centre recruitment rate to be 0 prior to its initiation, remain constant for a period of months after initiation and thereafter it declines and can be modelled by the negative exponential distribution. To consider heterogeneity between centres, the baseline rates are modelled as a sample from a gamma distribution with parameters α and β, each of which has a gamma prior distribution.

For an ongoing trial, the future of the accrual is projected by first predicting the number of centres and their initiation times and then the subject accrual within each centre. The steps for this procedure are listed in Table 4. This hierarchical model is implemented using accrual data from two case studies.

Comparison of the proposed model [65] with two conventional models, the constant-rate recruitment model and the moving average method, which estimates future accrual by using the average rate from the six months preceding the prediction time only, indicated that the predictions from the proposed model had a better fit to the overall recruitment curve and reflected the uncertainty better with larger standard errors. The authors conclude that even though the model can fit past accrual rates very well, it is not guaranteed that it will predict accurately future rates and this is because of the many unanticipated factors having an impact on patient recruitment [65].

4.3.2.5. Sequential patient recruitment monitoring (SPRM)

Kim *et al* proposed a new approach that combines monitoring and prediction for patient recruitment, the Sequential Patient Recruitment Monitoring (SPRM), which is based on the sequential probability ratio test (SPRT), a hypothesis test for sequential samples [66]. This method allows for continuous monitoring of the rate of enrolment and gives an early warning when the recruitment is unlikely to achieve the recruitment target. The entry times of participants recruited are organised into a series of packet data, which are non-overlapping groups of observations. For an adequate packet size, the Central Limit Theorem is used and the inter-arrival times between patients are considered as independent and identically distributed (iid) variables with a common Normal distribution, where the mean and the variance are finite positive parameters.

The null hypothesis H_0 stands that the average waiting time between patient recruitment is equal to the expected recruitment time divided by the target sample size (T_0/n_0), while under H_1 it is considered bigger ($T_0/n_0 * 1/\delta$), where δ ($0<\delta<1$) is the

design parameter. By re-parametrisation the hypotheses above are converted to the following ones:

$$H_0: \theta = 0 \; vs \; H_1: \theta = \theta_1, \text{ where}$$

$$\theta_1 = \frac{\sqrt{m}}{\sigma}\frac{T_0}{n_0}\left(\frac{1}{\delta} - 1\right), \theta_1 > 0 \text{ , where m is the packet size.}$$

If the distribution functions for N (0, 1) and N (θ_1, 1) is G_0 and G_1 respectively, then the approximate distributions of $Z_j = \frac{X_j - \mu}{\sigma/\sqrt{m}}$ under H_0 and H_1 are G_0 and G_1,

where $X_j = \frac{1}{m}\sum_{i=1}^{m} Y_{i+m(j-1)}$ represents the sample mean of the j[th] packet of size m and Y_i is the inter-arrival time between patients.

The log-likelihood ratio statistics l_n for given values $z_1, z_2, \ldots$ is

$$l_n := \sum_{j=1}^{n} \log g(z_j) = \sum_{j=1}^{n} \theta_1 (z_j - \frac{\theta_1}{2})$$

Let $R_1 = inf\{n \geq 1: l_n < -\text{b } or \; l_n > \text{a}\}$ then H_0 is rejected only if $l_{R_1} > a$, and it can be accepted only if $l_{R_1} < -b$. The boundaries *a* and *b* depend on the desired type I and type II error, and can more generally be calculated as a=log (γ_1/α) and b=log (γ_0/β) where γ_0 and γ_1 are the Laplace transformations of the excess limiting distribution under the null and alternative hypothesis respectively [70].

After a decision is made by either accepting or rejecting the null hypothesis, a new test is proposed with updated hypotheses and a new parameter, in which T_1 and n_1 represent the remaining recruitment time and sample size respectively. Only the recruitment data newly available from the last decision are being used to test the new hypothesis. Subsequent hypotheses and tests are designed in a similar way.

When the null hypothesis has been rejected, the SPRM method can be used additionally to estimate the size of shortage in patient enrolment, the probability of reaching the target enrolment, and the possible extension of recruitment period, based on the assumption that the recent trend that triggered the warning will continue.

According to the authors, this method has two limitations; the first is that the implementation of the SPRM requires the target sample size to be more than 200 participants, since the effective sample size is reduced by the factor m, which represents the packet size, and the second limitation is that it takes some time to make

the decision to reject or not the null hypothesis, and this can endanger missing the warning signal.

Author		Target number of patients (input), Yes/No	Target number of centres (input), Yes/No	Initial Expected duration of the trial (input), Yes/No	Estimated Expected Duration (output), Yes/No	Constant/average (Aver) AND/OR Time variation (TV) AND/OR Centre variability (CV) recruitment rate	Model counts for seasonality	Recruitment thresholds to stop the trial	Corrective actions suggested	Implementation	
										Programming code provided, Yes/No	Model validation/implementation* using Real (R) and/or Simulated data (S)
Lee [27]	1st model	Y	N	Y	N	TV	Y	Unsuccessful Interim goals	- add more centres - lengthen the recruitment duration	N	R
	2nd model	Y	Y	Y	Y	TV & CV	N	Unsuccessful Interim goals	- add more centres - lengthen the recruitment duration	N	R
Lai [60]		Y	N	Y	N	TV	N	A high probability, e.g. 85% or 95% of reaching the required sample size	N	N	R
Zhang & Lai [61]		Y	N	Y	N	TV	N	A probability of reaching the	N	N	R

							required sample size on time			
Anisimov [38]	Y	Y	Y	Y	arrive at different centres with time-constant rates, TV & CV	N	the prespecified probability, e.g. 80% of reaching the recruitment target on the remaining time	- additional centres required to accomplish the study recruitment	N	R&S
Mijoule [62]	Y	Y	Y	N	TV & CV	-Only worked days considered and -closure of centres for holidays is considered	The probability of ending the study in time is high, e.g. 80%	- prolong the study - the different centres to increase their rate of inclusion up to the maximum estimated lambda - more centres to be open to finish on time	N	R
Williford [63]	Y	N	Y	N	TV	N	N	- extension of the intake period - revised recruitment goals	N	R
Gajewski [32]	Y	N	Y	Y	TV	N	95% probability of the median prediction, the lower limit	-revise the study -stop early the trial for futility	Y	R&S
Jiang [64]	Y	N	Y	Y	TV	N	$T_{decision}=\delta T^{1}$	-evaluate whether or not to continue the trial	Y	R&S

Zhang and Long [33]	Y	N	Y	N	TV	no patient accrual occurs on weekends	N	-speed up the accrual or -revise the original accrual plan	N	R&S
Lan [65]	Y	Y	Y	Y	TV & CV	N	N	- continue to invite and initiate clinical centres throughout the recruitment period.	N	R
Dong-Yun Kim [66]	Initial target & Remaining number of new recruits needed	N	Y	-remaining duration & - potential extension of accrual period	Average accrual rate / average daily rates	N	75% of the target is often used as an informal benchmark	- giving incentives to existing centres Or - adding new centres & - determine how much extension is needed to reach the target recruitment with high probability.	N	R&S

Table 5: Statistical Models to predict ongoing recruitment: Factors defining model flexibility and assumptions

** Model validation was done either by using actual recruitment data and comparing them to the accrual data resulting from the statistical model assumed, or by using simulated data resulting from the statistical model suggested to describe patient recruitment.*

[1] The prediction interval produced by this model provides a rule for stopping a trial with slow accrual. $T_{decision} = \delta T$. The 95% confidence interval is being calculated for the total accrual time ($\hat{T}_{0.025}$, $\hat{T}_{0.095}$). If $\hat{T}_{0.025} > \delta T$ the trial should be stopped with a NOGO decision. If $\hat{T}_{0.025} < \delta T$ the decision is GO. In the examples of this article δ is set up as 1.25.

4.4. Discussion

4.4.1. Main findings

It is necessary when predicting recruitment at the design stage to make a number of untestable assumptions. However, the data to test the accuracy of these assumptions accrues during the recruitment period. The accrual data collected from the recruitment period elapsed, can produce more accurate projections about the time of recruitment completion or the probability of reaching the target sample size on time.

Poisson model is a well-accepted approach, which models the inherent fluctuation in the accrual, and has been broadly used. Yet, there is a concern associated with this model, and that is the constant rate restriction, which is not a common phenomenon for the majority of clinical trials [63]. However, when constant rate can be assumed for a specific time interval, then the contagious Poisson model can be used, allowing the current rate depending on the observed rate so far and adding frequent interim recruitment goals to monitor accrual progress and make sure that recruitment target is met [27].

While in the Poisson model all the observed recruitment data are being used to inform future prediction, in BM and FBM models the initial accrual data are discarded because they are not considered representative of the recruitment process [60, 61]. Thus, future prediction is based on data accumulated from rather stable periods when many centres are already open. This is a limitation on when the models can be used, which may render it too late to take remedial actions. This approach was further extended by Lai *et al* where the authors suggest that the FBM combined with moving linear regression is better than the linear regression used to model the simple Brownian motion [60]. Moving linear regression is a trend following indicator that plots a dynamic version of the linear regression indicator.

The model proposed by Lan *et al* [65] was compared to a Poisson model with a constant recruitment rate and the moving average method. While in the Poisson model with the constant rate, the same average rate calculated from all the accrual data up to the time of prediction is used for the future projection, in the moving average model, only the 6-month accrual data preceding the prediction time is used to define the average recruitment rate to be used for the future prediction. The results indicated that the model proposed by Lan *et al* was more accurate mainly because the Bayesian model provided wider prediction intervals; however when moving away from

recruitment initiation date, such as month 20, the moving average method performed comparably to the proposed Bayesian model, but with smaller interval width.

In most of the articles included, both centres' initiation and patient accrual are expected to increase with time, and the overall recruitment rate to reach and preserve an approximate constant value once all centres are open. The approach proposed by Lan *et al* [65] differs as it suggests that the initiation of centres declines after an initial surge of activity, modelling the monthly centre initiation rate as a negative exponential of the study time. The same happens with the recruitment rate within centre, which after a period of steady recruitment declines gradually, thus modelled as a negative exponential, including also a parameter for the centre size. This model may have greater potential for use in studies where patients are recruited from a known existing pool. While the model proposed fitted the observed accrual rates adequately, the authors acknowledged that the prediction in both case studies was conducted when the recruitment rate reaches the steady state, and accurate prediction for future rates cannot be guaranteed.

The contribution of centre performance in patient recruitment was acknowledged in the article of Anisimov V. and Fedorov V. by extending the Poisson model to Poisson-Gamma model [38]. While the number of patients enrolled can still be modelled based on the Poisson process with time-constant rates, centres' heterogeneity in multicentre trials can be captured by assigning a gamma distribution to the rates. The observed accrual data from the recruitment period elapsed are used to estimate the parameters of the gamma distribution in this model. When the number of centres is more than twenty then instead of estimating an individual rate for each centre, the Bayesian paradigm is used, estimating the overall number of patients to be recruited by all centres. This is done by combining investigators' prior beliefs of recruitment rates at the design stage and the observed recruitment rates.

The benefit of the Bayesian approach is in monitoring and prediction of ongoing patient recruitment. As more data are collected, the Bayesian model places less weight on the prior distribution and the posterior estimation is defined accordingly. It is worth mentioning here that even if the Bayesian models take into account the impact the centres have in patient recruitment by assigning a distribution to the rates to mimic the different recruitment patterns among centres, when it comes to prediction, the output is the aggregated (across all centres) number of patients to be recruited and not a

centre-based recruitment metric. In addition, accrual uncertainty in a Bayesian model is reflected with wider prediction intervals. While this is helpful in realising that there are some unknown factors influencing centre opening and hurdling patient recruitment, which have not been considered when designing the trial or during monitoring when reassessing the recruitment figures, it provides limited guidance in practice.

The amount of accrual data required to produce an accurate prediction was a discussion point in some of the articles included. The main result from this discussion was that the projections tend to be more accurate when more accrual data are available [33, 61, 63, 65]. In case of the SPRM method, an ad-hoc range of 10-15% of recruitment data is suggested for the estimation of the standard deviation for the normal distribution [66]. However, as discussed in the article, a more formal technique is desirable to determine the optimal start time for monitoring.

There are only two models suggesting a decision threshold [64, 66]. Jiang *et al* proposed a decision-making threshold $T_{\text{decision}} = \delta T$, where δ is a tolerance coefficient defined by the research group [64]. In the examples used in the article, the decision point was set to $1.25T$, which represents a delay large enough to threaten the successful study completion. The trial should be stopped with a NOGO decision if the 95% posterior predictive interval for the time to complete recruitment excludes 1.25 times the planned trial duration. The probability that the predicted total accrual time is less or equal to the cut-off time, P ($T_p \leqslant \delta T$) was also estimated.

The method proposed by Kim *et al* [66] is using the sequential probability ratio test with stopping boundaries to monitor continuously patient accrual. Apart from calculating the probability of reaching the target sample size based on the recruitment period elapsed, this fully sequential approach allows one to estimate the shortage in patient recruitment, the desired average waiting time between patient recruitment for the remaining patients and the additional recruitment time needed, which are considered important metrics during accrual monitoring for the evaluation of future predictions.

Failure to meet the recruitment goal usually results in the extension of the study [63] or, in the case of multicentre studies, the addition of centres [38, 65], or both [27, 62, 66], and as a result this leads very often to a cost overrun. Funder's role is also

important at this stage, as they need to be aware of and approve the upcoming changes regarding the extension of the recruitment period and any additional funding required to complete the trial. No matter what causes the delay in the recruitment process, efficient monitoring gives researchers the opportunity to detect and address the problem in a timely manner. Subsequently, the more accurate the new recruitment plan is, the easier it will be for both the research team and the funder to be prepared for the requirements of the additional period needed to complete patient recruitment.

4.4.2. Strengths and Limitations

This review is the first to our knowledge of statistical models to be used for the ongoing recruitment prediction. The value of the accruing data can inform ongoing conduct and identify accuracy of initial predictions.

The search strategy utilised in chapter 3 to identify the eligible articles, was also used in this review for the period before and after 2016, namely the ORRCA database and citation tracking through Web of Science respectively. The limitation in relation to the different sources used is identical to that described in chapter 3.

4.4.3. Summary

Successful recruitment needs constant monitoring. Early warnings when patient accrual is lagging behind the target, will allow researchers to take appropriate corrective actions on time. Otherwise, as described in chapter 3, when corrective actions are not considered adequate to reach recruitment target on time, a reprofiling of the recruitment plan is required.

The models described in this chapter, if broadly implemented, could help investigators and funders evaluate the present recruitment situation and make informed decisions about the future of the trial. Understanding the size of additional resources needed to successfully complete patient recruitment will help in assessing whether it is worth putting in more effort and money to complete the trial or use these resources in more promising trials. However, it is very important to mention here that this decision very much depends on the number of centres open to recruitment and the amount of recruitment data available; thus deciding the timing for the model's implementation requires a lot of consideration.

The following chapter focuses on exploring the reporting of recruitment experience in different trials and in how much detail this is described in the recent publications of

high impact journals. This investigation was considered important since the implementation of statistical models requires the definition of the model parameters, which can be informed by various data sources, when those are adequately reported in the final publication of studies.

Chapter 5: A cohort investigation of RCTs exploring how patient recruitment has been reported in five major journals

Preface

A randomised controlled trial is the most powerful single study design to compare the effectiveness of an intervention. The success of a trial is related to adequate patient recruitment, which depends on many factors. An important factor in planning the design of the trial are the sources of information available to the research team, which can be used to predict the rate of patient recruitment. This knowledge could arise from the personal experience of the investigators and/or the published literature. The level of information about patient recruitment issues at the early stage of a clinical trial and the challenges accompanying it, are not frequently reported in the final publications. In chapters 2, 3 and 4 we described the available statistical models and other simple methods for the prediction at the design stage, monitoring of patient recruitment and ongoing prediction during the conduct of clinical trials respectively. However, the implementation of statistical models at the design stage prior to the start of patient recruitment, requires the definition of the model parameters, which can be informed by the previous knowledge gained from successful and unsuccessful patient recruitment. When the effort spent on the recruitment of patients by the research team is not communicated, then no knowledge is gained and as a result, investigators cannot benefit from others' past experience when designing new studies. In this chapter, we review a cohort of RCTs to establish the level of information published in relation to the recruitment process.

5.1. Introduction

Recruitment of patients in clinical trials is a demanding and time consuming procedure. When researchers design the trial and apply for funding, they need to define the expected duration for the recruitment period based on the required sample size. This level of information can be extracted from relevant published studies describing the process of patient enrolment, where available. Whether the published study's research team achieved the recruitment goal in the predefined time frame and any description about the difficulties they experienced during this process can provide very important information about the feasibility of recruitment in past clinical trials. When designing a new trial, this degree of detailed information could be very useful

to inform future researchers of the difficulties in recruiting the sample size required and in informing the development of an alternate plan in case patient recruitment does not go as expected.

Clear and detailed reporting of participant flow is essential to assess the performance of the trial with regards to the number of patients screened and recruited in the time required. The Consolidated Standard for Reporting of Trials (CONSORT) criteria first published in 1996 [71] and last revised in 2010 [72], contains a 25 item checklist and a flow diagram, to assist authors in clear and transparent reporting of randomised controlled trials. Many leading medical journals and major international editorial groups have endorsed the CONSORT statement, which has been shown to improve standards of reporting [73, 74]. This version of the CONSORT 2010 Statement includes a revised flow diagram, which contains at the enrolment stage, the number of patients assessed for eligibility, the reasons for those excluded and the final number randomised, and for the after-randomisation stage, there is one box displaying each of the following figures for each arm; allocation of intervention, follow-up and analysis of participants.

The majority of research on implementation of CONSORT statement has focused on post-randomisation reporting [73].

A systematic review conducted by Toerien *et al* including RCTs published during the July-December 2004 period, identified that the majority of RCTs reported the flow of participants after randomisation although only two-thirds included a complete flow chart [75]. However, this was previous to the last CONSORT amendment, which now includes pre-randomisation figures. To our knowledge, this has not been considered following the amendment, yet the importance of this data is in the planning and design of the future RCTs.

Jones *et al* investigated the use of systematic reviews in the planning, design and conduct of randomised controlled trials and they found that the main areas in which systematic reviews were used, were in the selection or definition of an outcome, the sample size calculation, the duration of follow up and the approach to describing adverse events [1]. Only two applications used information from systematic reviews to inform planning of patient recruitment; one application justified the consent rate assumed in the study based on relevant previous trials in the systematic review; the

second application used poor recruitment rates reported in a systematic review to determine centre selection criteria. This demonstrates the limitation in how the recruitment information is being used.

The BeWEL trial unusually provides information on aspects of expected recruitment which are not often reported, “To achieve the recruitment target, we estimated that a pool of 558 patients would be required from which to recruit, to allow for an expected eligibility rate of 81% (n=452), a recruitment rate of 70% (n=316), and a subsequent drop-out rate of 16% (n=266)” [76]. The figures reported in the CONSORT flow diagram allow a comparison of those rates, however there is no information on the expected duration of recruitment or variation at centre level. It may be considered too great a level of detail within the main trial publication, but it could be included in the supplementary material.

In another example of a pilot study of cardiac rehabilitation in patients with bowel cancer, the estimated and actual recruitment figures describing the process of moving from the admissions to the eligible number of patients (% of admission) and finally to the number of patients randomised (% of eligible patients) are reported in detail for each centre [77]. However, this is a pilot study and its reporting is to determine the feasibility of the main trial.

Taking into account how useful this level of information could be, in this chapter we focus on publications of main trial results to determine:

- the level of information provided on recruitment prediction
- the level of information provided on observed recruitment

5.2. Methods

5.2.1. Eligibility criteria/Study selection

The latest 25 published RCTs were selected and evaluated from each of the following journals: British Medical Journal (BMJ), The Journal of the American Medical Association (JAMA), The Lancet, New England Journal of Medicine (NEJM), and The National Institute for Health Research Health Technology Assessment (NIHR HTA) library. I searched the website of each journal in April 2019 for the latest RCT publications to identify the most recently published eligible publications.

I included all RCTs designed to estimate intervention effectiveness in improving health outcomes. If the study was not a RCT (e.g. observational studies, reviews,

systematic reviews and meta-analysis), or was a cluster RCT, where the randomisation is not at participant's level, then it was excluded.

5.2.2. Data extraction

A data extraction form was developed and agreed following piloting. The areas of extraction were:

Recruitment planning: recruitment target, any adjustment made for attrition, revised recruitment target.

Recruitment prediction: initial estimate of recruitment period, initial estimate of the number of centres, expected initiation rates of centres such as staggered initiation times, and any description about the method used for recruitment prediction (including statistical models, if any).

CONSORT diagram including: number of participants assessed for eligibility, number of patients randomised and number of patients lost to follow up.

Actual recruitment: date trial opened to recruitment, date trial closed to recruitment, actual number of centres open and number of countries participating in the trial.

In addition, if the trial was terminated early, any reasons reported were included in the data extraction.

I undertook the data extraction for each article and 16% of the articles had independent data extraction in duplicate. An Excel spreadsheet was used for data extraction. I completed the data extraction, which was then checked and discussed with SD, RR and CG.

5.3. Results

125 RCTs were identified across the five journals. The publication date range for each journal's 25 RCTs is provided in the table below.

Journal	Most recent date of publication	Earliest date of publication
BMJ	February 20, 2019	April 07, 2017
JAMA	April 16, 2019	November 13, 2018
The Lancet	April 17, 2019	February 2, 2019
NEJM	April 18, 2019	January 24, 2019
NIHR HTA	April, 2019	March, 2018

Table 6: Range of publication dates for each journal's included RCTs

5.3.1. Recruitment planning and prediction

5.3.1.1. Recruitment target

The target sample size was reported in the main publication in 99.2% of included studies, see Table 7 below. One publication referenced the protocol for the sample size and the attrition rate. In more than two third of the studies (69.6%), prospective adjustments were made to the target sample size to account for attrition. Attrition rate adjustments varied from 1% to 40%. Two studies reported adjusting for attrition but did not provide the percentage, however this could be determined indirectly.

Recruitment items reported	**BMJ n (%)**	**JAMA n (%)**	**The Lancet n (%)**	**NEJM n (%)**	**NIHR HTA n (%)**	**Overall, N (%)**
Recruitment target	25 (100)	24 (96)[1]	25 (100)[2]	25 (100)[3]	25 (100)	124 (99.2)
Adjustment for attrition	16 (64)	14 (56)	20 (80)	16 (64)	21 (84)	87 (69.6)
Sample size re-estimation	4 (16)	4 (16)	3 (12)	2 (8)	11 (44)	24 (19.2)

Table 7: Recruitment target, attrition adjustment and revision of the recruitment target

[1] The recruitment target was reported only in the protocol, which was referenced in the main study report.
[2] In one RCT instead of the required sample size, the number of expected events was reported.
[3] In one RCT both the required sample size and the expected number of events were reported

In 19.2% of the studies included in this cohort, the sample size was recalculated during trial conduct. Recommendations led to either an increase or a decrease in the sample size target, see Box 1 for details.

In addition to the studies in which target revision was implemented, there were two studies where the final sample size was greater than the initial target, without this being scheduled in advance. Thus, these 2 studies are not included in Table 7 under the category "Sample size re-estimation", while the reasons leading to this modification are provided in the Box 1 below under the section "In addition".

A list of Reasons for Recruitment Target Revision

Revision led to an increase of the sample size

- Sample size increased from 120 to 214 following planned interim data monitoring meeting [78]
- Sample size increased from 423 to 491 participants, following review of early data to support a per protocol analysis with 90% power in addition to the primary intention-to-treat analysis [79]

- Sample size increased to 510 versus the initial 500 following blinded review of the combined proportion of patients with consent withdraw or lost to follow-up [80]
- Sample size increased due to low event rates, with the original target being 700 versus the amended 855 participants [81]
- Sample size increased from 658 to 714 to allow for a dropout rate of up to 24% versus the initial dropout rate of 15% [82]
- At the interim analysis, the data and the safety monitoring board recommended increasing the sample size to 400 versus the initial 350 [83]
- Inclusion criteria modified due to slow recruitment, which increased the sample size target from 750 to 1250 patients [84]
- Due to faster than expected recruitment, the DMC advised increasing power to 90% (1320) versus the initial 80% (950) [85]
- The original sample size (840 women) was based on a Cochrane review, but after the publication of an updated Cochrane review where the anticipated effect of the intervention was revised, the new sample size required 1300 women to be recruited [86]
- The sample size calculation was revised from 6,000 to 8,000 without any knowledge of interim results to give a greater power to investigate any differential effectiveness of oxygen compared with control within subgroups, in particular those with more severe disease [87]
- Sample size was increases from 150 to 200 to allow for increase in attrition at funder's request; it is unknown whether this is prior to or during trial conduct [88]
- A protocol amendment was made close to the end of recruitment period to allow over-recruitment beyond the initial recruitment target of 396 patients, in order to allow centres to recruit in waves because of the nature of the intervention and run intervention groups with sufficient participants, concluding in the recruitment of 414 participants [89]

In addition

- In one RCT, the final sample size was not the same as the initial target with the reasons including prespecified post-randomisation exclusions, valid consent not being appropriately documented and withdrawal. Thus, at the end of the trial, 3,236 women were randomised instead of the required sample size of 3,000 [90]
- In another study, because of an erroneous value used as a parameter for the sample size calculation, the sample size recruited in the end (246) was approximately 25% larger than the minimum sample size required [91]

<u>Revision led to a decrease of the sample size</u>

- Sample size decreased from 500 to 366 patients because of slow recruitment and limited study period available, with the revised sample size providing 80% power to detect the same effect size under the same assumptions [92]
- Sample size was decreased from 3656 to 2464 pregnant women, due to budget limitations and because the follow-up rate was better than expected [93]

- In accordance with a slower-than-projected accrual of study patients, the steering committee decided to recalculate the original sample size of 270 patients, thus including a further prolongation of the study period and a reduction of the sample size to 156 participants [94]
- Due to slow enrolment and lower than expected aggregated event rates, the data and safety monitoring board recommended modifying the trial design, thus a reduction in the sample size to 2200 was suggested versus the initial target of 3,000 patients [95]
- Because of the difficulty in reaching the initial target sample size and possible overestimation of cardiovascular risk in the control group, the target sample size was reset to 972 versus 1,600 [96]
- The actual rates of recruitment were lower than anticipated, so the recruitment period was extended and the target sample size was reduced to 114 from 154 initially planned [97]
- Because of the slow recruitment and after the request of the trial funder, the primary outcome was changed and the required sample size was reduced to 770 versus 940 participants [98]
- After the pilot trial phase it was apparent that the sample of 300 participants was not achievable and thus the target sample size was reduced to 100 patients [99]
- The results of the internal pilot phase contributed to the research team realisation that the possible benefit may have been underestimated and the fact that they showed that an enhanced intervention could be delivered, leading thus to a revised power calculation and as a result the sample size for the full trial was reduced from 1,800 to 600 participants [100]
- Owing to the interim event rate for the primary outcome being higher than estimated, the power calculation was revised and the sample size was revised from 2300 to be between 1,750 and 1,850 participants [101]
- Owing to the challenges in trial setup and associated poor initial patient recruitment, and reassessment of important end points, the primary outcome measure was changed from a binary to a continuous outcome. This allowed a reduction in sample size to 477 from 870 patients, while still ensuring a trial of clinical relevance [102]
- Because of poorer than expected recruitment, the TSC recommended that the target for power should be revised to 80% versus the initial 90%, based on which 2,444 couples were required for the primary analysis instead of the initial sample size of 3,700 [103]

Box 1: Reasons for Recruitment Target Revisions

It is of note that of the 12 studies in which the sample size was reduced, this was a consequence of lower than expected participant recruitment rates for the nine out of 12 studies.

5.3.1.2. Recruitment prediction

Recruitment prediction is a very important stage in the design phase of the clinical trial. However, this information is seldom available in the final publications of the RCTs. Assumptions made to enable recruitment prediction can be summarised by specific factors, which are listed in Table 8 below. This table demonstrates the level of information provided within the RCTs cohort examined.

Recruitment Prediction reported	BMJ n (%)	JAMA n (%)	The Lancet n (%)	NEJM n (%)	NIHR HTA n (%)	Overall, N (%)
Expected number of patients	25 (100)	24 (96)	25 (100)	25 (100)	25 (100)	124 (99.2)
Expected number of centres	0 (0)	0 (0)	0 (0)	0 (0)	13 (52)	13 (10.4)
Expected recruitment period	0 (0)	1 (4)	4 (16)	0 (0)	14 (56)	19 (15.2)
Centres' expected opening rates	0 (0)	0 (0)	0 (0)	0 (0)	2 (8)	2 (1.6)
Recruitment variation expected over time	0 (0)	0 (0)	1 (4)[1]	0 (0)	1 (4)[2]	2 (1.6)
Expected variation in centres' recruitment rates	0 (0)	0 (0)	0 (0)	0 (0)	6 (24)	6 (4.8)
Use of a statistical model for prediction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 8: Recruitment Prediction Factors considered

[1] *A constant recruitment of 64 eligible patients per treatment group (plus four early dropouts per group) was assumed over 2 years of expected recruitment period.*
[2] *4 participants were expected per centre per year*

Reporting of recruitment prediction is considered complete when all the parameters listed in the Table 8 above are provided. None of the RCTs in this cohort described a statistical model for recruitment prediction. The prediction included mainly assumptions based on the average recruitment rate, which were formulated either per centre, or per month or per centre per month.

It is mainly the NIHR HTA reports, in which there usually is a section dedicated to patient recruitment, where some of the parameters describing recruitment prediction are discussed. Recruitment prediction is partially described in the text, but NIHR reports often attach the recruitment graph in the main report. The level of information presented in these graphs about recruitment prediction is variable with some providing the expected number of centres and the expected number of patients per month, or in its simpler version includes only the cumulative number of patients expected per month.

The same recruitment graph can be used to extract information about the estimated recruitment period when this is available in the NIHR reports. The examples from

JAMA and The Lancet on the other hand, describe the expected accrual period in combination with the overall trial's duration, which includes the follow-up period, e.g. "the protocol anticipated 4 years of accrual and 1 year of further follow up", "enrolment period of approximately 26 months and minimum follow-up period of 19 months after completion of enrolment was assumed", "assuming that 80 patients per year could participate in this trial, the accrual period was estimated to be 5 years to enroll 400 participants, with a follow-up period of 2 years after enrollment, the total duration of the planned trial was 7 years".

An additional factor that could contribute to a more complete recruitment planning in a multicentre trial is the number of centres and the rate of their initiation and whether this was taken into consideration when designing the trial. Yet, this aspect was only evident in the NIHR reports with half the studies either stating the number of centres expected to open to recruitment or presenting this information in a recruitment graph. Expected opening rates for the centres were presented only in the recruitment graph of two studies, where staggered initiation times were considered [97, 104]. The expected variation in centres' recruitment rates was discussed in six studies, with one study specifically displaying in a table the target expected for each centre [88], in the other two a suggestion was made that the target per centre was expected to be different [97, 98], while in three studies the target recruitment was (1) 97 per centre [105], (2) 80 per centre [106] and (3) 4 participants per year at each centre [100], implying no variability at centre level.

5.3.2. Reporting of observed recruitment across centres

The CONSORT flow diagram, which is reported with different names (such as study flow chart; study profile; flow of participants through study, screening, enrolment, randomisation, and follow-up of study participants etc.) displays essential figures about the recruitment process, including the number of patients screened and the number of participants randomised. Participants flow diagram was provided in 88.8% within the body of the main publication, and for the remainders, this was available in a supplementary material (NEJM journal) and cross-referenced to the publication of one NIHR HTA report.

In 15 out of 125 studies (12%), the number of patients screened was not reported. In seven of these, a reason was provided regarding the ability to capture screening log information.

Table 9 presents all the recruitment items describing the patient flow from the time they were contacted and assessed for eligibility, moving on to randomisation and follow-up period until the study is complete, as they were reported in the publications by each journal.

Participants Flow diagram and Items Reported	**BMJ n=25**	**JAMA n =25**	**The Lancet n=25**	**NEJM n=25**	**NIHR HTA n=25**	**Overall N=125**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**N (%)**
Consort Diagram/Flow Diagram included in the main paper	25 (100)	25 (100)	25 (100)	12 (48)	24 (96)[1]	111 (88.8)
Consort Diagram/Flow Diagram included as Supplementary material	0 (0)	0 (0)	0 (0)	13 (52)	0 (0)	13 (10.4)
Number of participants assessed for eligibility	22 (88)	22 (88)	22 (88)	22 (88)	22 (88)	110 (88)
Number of patients randomised	25 (100)	25 (100)	25 (100)	25 (100)	25(100)	125 (100)
Number of patients lost to follow up	25 (100)	25 (100)	25 (100)	25 (100)	24 (96)	124 (99.2)

Table 9: Participants Flow diagram and recruitment items reported

[1] *In one NIHR report the original paper was referenced for the flow of patients in the study*

The number of participants lost to follow up was reported in all publications that included the flow diagram (99.2%). As reported in Table 7, in 87 studies prospective adjustments were made to the sample size to account for possible attrition, with the expected attrition rates varying from 1% to 40%. 11 out of those 87 studies were terminated earlier, while in ten studies there was no observed attrition. Attrition expectations were proven accurate for 53 trials, 5 trials had less than 5% higher actual attrition, while in 8 studies actual attrition was more than 5% higher than expected.

5.3.3. Reporting of observed recruitment at centre level

In addition to the number of participants randomised, observed recruitment can be reported at centre level too, by including the actual recruitment period, the number of centres open to recruitment and their initiation rates and the number of countries participating. Whether the trial was completed or stopped earlier is also reported here.

The number of activated centres was reported for 98.4% of the RCTs. 92% of the RCTs included in this cohort were multicentre and 6.4% were conducted in one single centre, while there were two studies (1.6%) where the number of centres was not specified because of a different approach used to reach the potential participants. In

particular, in one study recruitment was done from workplaces, social media platforms, schools, word of mouth etc. and in the other study participants were referred to the study by healthcare professionals at their primary and secondary care centres or participants could self-refer to the study.

Actual Recruitment Figures reported	**BMJ n (%)**	**JAMA n (%)**	**The Lancet n (%)**	**NEJM n (%)**	**NIHR HTA n (%)**	**Overall, N (%)**
Recruitment period of the trial (date trial opened and closed to recruitment)	25 (100)	25 (100)	25 (100)	25 (100)[1]	24 (96)	124 (99.2)
Number of centres open	23 (92)	25 (100)	25 (100)	25 (100)	25 (100)	123 (98.4)
Initiation rates of centres	0 (0)	0 (0)	0 (0)	0 (0)	4 (16)	4 (3.2)
Number of countries participating	25 (100)	25 (100)	25 (100)	25 (100)[2]	25 (100)	125 (100)
Trial was terminated early	2 (8)	4 (16)	2 (8)	3 (12)	7 (28)	18 (14.4)

Table 10: Actual recruitment figures observed

[1]*A household census was conducted in June 2014 and the household census was repeated in May 2015 and May 2016 (seasonal malaria chemoprevention)*
[2] *The number and list and of countries participating in the trial for one study is only reported in the supplementary material.*

The trials were conducted in a single centre or in multiple centres within the same country or in multiple centres in more than one county. The number of different countries taking part in a multinational clinical trial varied from 2 to 41.

5.3.3.1. Trial's early termination

One of the main roles of the Trial Steering Committee is to evaluate trial's performance regarding adequate recruitment in the planned accrual period and the feasibility of outcomes. Decision to stop the trial early may occur when it is highly unlikely that the trial will recruit the planned number of participants, if there is evidence of benefit or harm, or because of a prespecified criterion for futility. In this cohort of RCTs, eighteen trials (14.4 %) were terminated early and the reasons are presented in the Box 2 below.

Early termination of trials: Reasons provided
• Motivated by considerations of the beneficial effect of laparoscopic cholecystectomy and concerns about negative outcomes in the percutaneous drainage group, the data safety monitoring board recommended termination of the trial after 142 high risk patients were recruited versus the required sample size of 284 patients [107] • Because of slow recruitment and financial constraints, the decision was made to stop patient recruitment by December 2014, when an expected 260 women would be included instead of the target sample size of 400 women [108] • The trial was stopped after recruiting 426 infants versus the initial target sample size of 600, following a prespecified review of adverse outcomes [109] • On the recommendation of the data and safety monitoring committee, recruitment was discontinued on December 21, 2017, after recruiting 440 participants versus the target sample size of 618, because a prespecified futility criterion for efficacy was met [110] • The trial was stopped early for benefit on its primary outcome [111] • Further recruitment was stopped because the dropout rate was lower than expected, and the minimum required sample size (n=350) for the primary outcome analysis was achieved [112] • The trial stopped at 286 participants instead of the initial sample of 308, because of the completeness of primary outcome data and the fact that attrition was lower than anticipated [113] • Early termination was decided because of a lower-than-planned event rate and the time needed to accrue 425 events would be much longer than expected [114] • At the time of the second interim analysis, the data and safety monitoring board advised that the trial should be stopped for futility. At that time 5,400 patients were recruited versus the initial target of 10,600 [115] • The trial was terminated at the recommendation of the data and safety monitoring committee because of futility for finding superiority. At the time of trial termination, enrolment had been completed and 1,454 patients had been recruited [116] • The DMC advised the steering committee members that the prespecified efficacy criteria for early cessation had been achieved and recommended that the trial be stopped. At that time, 4,401 patients had undergone randomisation [117] • Recruitment to the trial was halted based on the results of the second interim analysis, showing that there was significant evidence that adalimumab was more

effective than placebo. At the time IDSMC made the recommendation to stop recruitment, 90 patients were randomised versus the required sample size of 154 [97]

- Recruitment was stopped early, after 387 of the intended 600 participants had been randomised, when the TSC concluded that there were signs of harm with the treatment being evaluated and, at best, a result of futility would be expected if the trial were to continue [100]

- Based on the number of centres opened and observed recruitment rates, recruitment to November 2017 would have been required to reach the target of 477 patients, at an additional cost of £450,000. Consequently, the Health Technology Assessment programme monitoring panel withdrew funding in November 2014; the trial closed to recruitment in December 2014, when only 122 patients were enrolled [102]

- Owing to higher follow-up rates than expected (82% at the time), recruitment was stopped after 404 participants were randomised versus the initial target of 428. This decision was made with the approval of statisticians involved with the trial and agreed on by study collaborators and the TSC [118]

- Owing to the slower than expected accrual, recruitment was terminated in September 2014, when 352 patients had been randomised instead of the 400 initially planned, with approximately 70% power to identify the target treatment effects [119]

- The trial was stopped early on the recommendation of the DMC after recruitment of 3,096 participants versus the target sample size of 4,100 [120]. The advice to stop was based on three observations:
  (1) the presence of a significant increase in major bleeding in participants randomised to intensive antiplatelet therapy,
  (2) the absence of a significant reduction in the primary outcome and
  (3) a conditional power analysis suggested that the trial was highly unlikely to demonstrate a significant difference in the primary outcome.

- The trial was terminated early due to insufficient recruitment caused by numerous problems. The required sample size was 300 participants, and after screening 1,175 patients, only six were recruited. The numerous problems are described in a dedicated chapter in the report [121]

Box 2: Reasons for early termination of the included studies

The reason for trial termination in four out of 18 studies was insufficient recruitment. Some of the challenges the research team faced during the recruitment stage were the overestimation of patient recruitment, which was based on clinician judgement rather than audits, the underestimation of the centres' set-up period, staff changes across centres, recruitment extension being too long and prohibited additional costs to complete the study.

5.4. Discussion

5.4.1. Main findings

In this chapter we investigated the level of information provided on recruitment prediction and on observed recruitment in the final publications of five high impact factor journals. Whether the research team achieved the recruitment goal in the predefined time frame and any description about the challenges they experienced during this process, can provide very important information about the feasibility of recruitment in past clinical trials and improve planning of future studies. It is essential that researchers designing new trials and searching the literature to identify relevant studies, are able to find that information about the recruitment process and use it to design a feasible recruitment plan for their trial.

The results show that recruitment target was reported in all studies either in the main publication or by cross-referencing the protocol. In more than half the studies (87, 69.6%) adjustments were made to take into account potential attrition because of loss to follow-up, withdrawals, non-adherence, loss of consent, death etc. In addition, in 24 clinical trials (19.2%) the research team needed to re-evaluate the sample size during the conduct of the trial, mainly because of slower than expected recruitment. This is an indication of overoptimistic expectations of the research team about how easily they could open the centres and recruit the required sample size.

In a multicentre clinical trial, the research team usually consider the number of centres that will contribute to patient recruitment and thus an estimation about the potential recruitment period could be made. However, in this cohort of RCTs, while the target sample size is well defined, initial estimates about the number of centres to be included in the trial and the expected recruitment period are rarely described. This lack of information makes it impossible to evaluate the recruitment performance of the trial, since no comparison can be made between the expected and the actual recruitment figures.

The word count restriction in some journals could prevent the authors from providing more information about that stage of the study, yet this could be included as supplementary material. The fact that recruitment prediction was partially described in more than half the NIHR HTA studies where there is no restriction about the length of the report, in comparison to the other four journals, is an indication about what is considered important to be reported in a final publication.

Patient flow in the study could be very informative in relation to recruitment challenges, when it also considers the number of patients screened before moving to the randomised participants. Describing the process of moving from the number of patients assessed for eligibility to the number of patients randomised (% of eligible patients) and the reasons for ineligibility, has been identified as an important factor which contributes to a better understanding of recruitment problems, which is why this has been included in the revised CONSORT 2010 Statement [72]. In this cohort, the number of patients screened was reported in 88% of the studies with the number randomised reported in all the studies.

The completeness of reporting about centre contribution in patient recruitment was limited. Even though the number of centres contributing to recruitment was reported in 98.4% of the studies, the actual initiation rates of centres were only provided in four NIHR HTA studies [97, 100, 104, 122]. In the NIHR HTA reports, it was more common to find information about the recruitment per centre and/or dates of the first and last randomisation per centre, rather than the actual initiation date for each centre. Provision of recruitment curves detailing centre and participant level information for predicted against observed can provide detailed information succinctly.

As explained in chapter 2 where we present the statistical models that can be used for recruitment prediction at the design stage of the trial, for the statistical models to work properly, we need to provide reasonable estimates of the parameters required. These parameter estimates can be elicited from experience and previous published data on recruitment.

Valuable evidence about the recruitment process could be found not only in completed trials but also in trials that were stopped earlier. Trial performance regarding adequate recruitment based on the planned accrual period is evaluated at different stages. One of the reasons to stop the trial early may be when it is highly unlikely that the trial will recruit the planned number of participants. There were examples in this cohort where the trials were terminated early and the reasons behind the slow accrual were described in details. The challenges the research team faced were in relation to loss of recruiting centres, moving of staff, time and financial constraints, centre set-up taking longer than anticipated, overestimation of centres' activity leading to overestimation of recruitment rates etc. Even if not all of these issues could be considered when designing the trial, it is very important to report them and let the research community

know about all the potential problems that are likely to happen during a clinical trial in relation to recruitment.

5.4.2. Strengths and Limitations

To the best of our knowledge this is the first cohort of RCTs investigating the level of information reported in the final articles in relation to recruitment prediction and observed recruitment figures. The importance of this cohort lies in the fact that these data could be proven very useful when designing new studies.

Recruitment reporting in this cohort of RCTs could have been more complete if the first version of the protocols of these studies were available and a comparison was made between what the research team was planning to do in relation to recruitment and how they described this in the protocol and what was reported in the final publication. However out intention was to investigate what is reported in the final publication and point out how useful this could be when available, to inform future trials.

Given the number of important details trials need to include within the main publication, it could be argued that is unreasonable to request this level of information even within the supplementary material. This may have been presented within grant applications and potentially within early versions of protocols. While grant application access is restricted, 83.2% of these RCTs have a protocol available. However, those published were often later versions and again suffered from restrictions on word count. For future work, we will look at how the recruitment prediction is described within protocols and within grant applications.

5.4.3. Summary

Factors affecting patient recruitment may be complex and many; thus, a complete reporting of recruitment prediction and detailing the assumptions that were made against the observed recruitment can help to develop greater understanding. Lessons can be learned when comparing what was expected in relation to the number of centres, the number of patients, recruitment duration and other factors contributing to the process, which are required when designing the study, with the actual recruitment figures. For example, if trials do not allow for staggered centre initiation rates are they more likely to have lower than predicted recruitment rates, and when predicting the rates, knowing how many centres could be initiated per month on average should be information that is available from previous trials.

When comparing the level of information provided in the final publications about recruitment prediction and observed recruitment at centre and patient level, reporting of prediction is quite incomplete and no statistical model has been used in any of the studies in this cohort. Greater transparency is needed to support the implementation of statistical models. Researchers should be clear about factors considered at the design stage of the trial and data sources used to inform their prediction.

In the next chapter, we will present the results from two surveys we conducted to investigate patient recruitment prediction and monitoring, one with chief investigators and one with statisticians. Some of the questions are in relation to the sources of data they use to inform their recruitment prediction and the use of statistical models. This is to highlight the importance of complete reporting in literature, which is then used in combination with personal experience to inform future trials.

Chapter 6: Investigating current practice in recruitment prediction and monitoring of patients in clinical trials within UK and European Networks

Preface

Chapters 2, 3 and 4 systematically reviewed methods to predict and monitor recruitment. In chapter 5, a cohort of published RCTs was examined to investigate the level of information provided on predicted and observed recruitment. This showed that despite the importance of recruitment, publications of clinical trials contain very limited content relevant to recruitment and this has negative consequences to learn and inform future trials.

To identify current practice for recruitment prediction and monitoring within clinical trials, a survey of chief investigators and a survey of statisticians were undertaken across a UK network and a European network. The chief investigators' survey targeted information not obtainable from publicly available sources, such as data sources used to predict recruitment and how these were applied to trial and centre requirements. The statisticians' survey across Clinical Trials Units registered within the UK Clinical Research Collaboration (UKCRC) network and members of the European Clinical Research Infrastructure Network (ECRIN) targeted the investigation of current practice and knowledge and implementation of the available statistical models. This is the first time that current practice on methods to predict recruitment in clinical trials have been reported and raises hypotheses about different practices in UK compared to Europe. Work arising from this chapter has been published in Journal of Clinical Epidemiology (JCE, 2020, open access) (Appendix A: Publications). Sections of this chapter include direct excerpts of the published manuscript. I wrote the original draft of the published manuscript, which was edited by senior authors and has been subject to peer review.

6.1. Introduction

Clinical trials are a major financial investment with the time to recruit to the required sample size being a key driver of associated costs. Failure to successfully recruit the required sample size as that was predicted at the design stage has many negative consequences. These range from incurring increased costs and time to answer the clinical question of interest to abandoning the research with the question remaining

unanswered. There may also be negative impact on the planning and roll out of future research, where the use of historic data is necessary to inform future studies and produce a more feasible recruitment plan.

As mentioned in chapter 2, recruitment prediction was identified as a top ten priority area in a prioritisation exercise, which aimed to identify uncertainties related to trial recruitment as a focus for future methodological research [20]. Despite the fact that every clinical trial will require such predictions to be made, little is known about how this is achieved either in terms of data sources or methods used. This is unlikely to change given that reporting requirements for recruitment within a main clinical trial article are minimal [72] and as reported in the previous chapter the level of information provided on predicted and observed recruitment in the final publications is very limited.

To determine current practice within the UK and Europe we undertook a survey of chief investigators and a survey of statisticians across a UK and a European network.

6.2. Methods

6.2.1. Design

I led the design of each survey with input from SD and CG. Questions targeted data sources and methods used for recruitment prediction, identifying team members contributing to the process, and awareness and implementation of the statistical models (statisticians survey only). Multiple choice answers were informed by the systematic review of Barnard *et al* [13] and the results of our systematic review (chapter 2) about statistical models, and other simple approaches that could be used for recruitment monitoring (see chapter 3), as well as by a number of factors that could have an impact on recruitment rate and should be considered [46, 47, 55, 123].

6.2.1.1. Chief Investigators' survey

The chief investigators' survey targeted those collaborating within UK and European research infrastructures. The survey aimed to be brief to maximise return rates collecting information not available from publicly available sources covering data sources used to predict recruitment at the design stage and how these were applied to trial and centre requirements. The survey was reviewed within the study team prior to circulation across the UK and the European Clinical Research Infrastructure Network (ECRIN, https://www.ecrin.org/).

A prize equivalent to £75 in vouchers was offered as an incentive to participation. The full list of survey questions and the invitation email are provided in the Appendix C.

UK Chief Investigators

UK chief investigators of recently funded clinical trials were surveyed as identified from the National Institute for Health Research (NIHR) journals library (https://www.journalslibrary.nihr.ac.uk/programmes/hta/ searched in May and October 2018). The NIHR is the largest funder of health and care research within the UK. To be eligible for inclusion projects were required to be randomised with the trial status listed as '"waiting to start". I obtained the contact information of the Chief Investigators from the projects' website and contacted each of them via email, which contained an invitation to participate and the survey attached as a word document. CIs were also given the option of delegating survey completion to a trial team member. If no response was obtained within two weeks then a reminder email was sent and a further reminder followed three weeks later, within which we gave them the option to answer the survey via a phone call. A final attempt was made to contact non-respondents by phone to ensure the correct contact details.

European Clinical Research Infrastructure Network (ECRIN) Chief Investigators

I also surveyed chief investigators working in collaboration with ECRIN, a non-profit distributed infrastructure that supports the conduct of multinational clinical research in Europe. The ECRIN European Correspondents (EuCos), based within each member or observer country, distributed the survey within their respective countries. I explained the survey context and purpose to the EuCos via a web-based meeting prior to contacting CIs of ECRIN supported studies via email. The email contained an invitation to participate and the survey as an attached word document. I sent two reminders to the EuCos requesting recirculation of the survey.

6.2.1.2. Statisticians' survey

I surveyed statisticians within UKCRC registered CTUs and ECRIN. The aim of the survey was to establish current practice, and knowledge and implementation of available statistical models. The survey was reviewed within the study team and piloted with a senior statistician prior to circulation across the UKCRC registered CTU Statistics Group and ECRIN. A prize equivalent to £75 in vouchers was offered as an incentive to participation.

The full list of questions for the online survey and the invitation email are provided in the Appendix C.

UK CTU Statisticians

The UKCRC registered CTU secretariat distributed the survey via email to the nominated senior statistician within each registered CTU. The email contained an invitation to participate and a link to an online survey, which was constructed using SelectSurvey.NET (http://selectsurvey.net/). The statistician could discuss responses within the wider statistical team of their CTU but only a single response per CTU was required. E-mail reminders were sent after one, two and four weeks. Non respondents also had the opportunity to respond by completion of a paper copy of the survey distributed during the UKCRC registered CTU Statistics Operational Group Network statisticians meeting in October 2018.

ECRIN Statisticians

The EuCos at ECRIN circulated the email invitation with the link to the online survey to the statisticians identified within their national network. The same procedure was followed as for the CIs' survey with the EuCos sending two reminders.

6.2.2. Ethics approval and consent to participate

Ethical approval for both surveys was granted from Health and Life Sciences Committee on Research Ethics (Human participants, tissues and databases) at The University of Liverpool on 5 September 2018 (reference 2282) (see Appendix C). All survey participants were provided with full written information prior to survey commencement with the act of completing the survey providing a demonstration of consent.

6.2.3. Analysis

Quantitative data from closed-ended questions were analysed using R, version 3.5.0 [124]. Due to the restricted sample sizes, statistical testing was not planned and results are reported as frequencies and percentages. I reviewed the responses to open-ended questions with SD and CG, and the themes identified within the free text answers were then categorised in groups.

6.3. Results

6.3.1. Chief Investigators' Survey

The CIs' survey was conducted between 24 October 2018 and 30 November 2018 within UK and between 18 October 2018 and 8 March 2019 within ECRIN with results summarised in Table 11. Thirty-two studies were identified as eligible for inclusion in the UK cohort and 17 responses were received (53%) from the chief investigators contacted. Two CIs completed the survey twice each allowing for the multiple trials, which they led as the chief investigator. Nineteen studies were identified via the ECRIN EuCos with six responses (32%) received.

Question	**Answers**	**UK N =17**	**ECRIN N=6**	**Overall N=23**
		n (%)	**n (%)**	**n (%)**
1) In determining the disease or condition prevalence, what sources of data were available to you to use? *Please select all that apply.*	Population based data on Geographical areas covered by sites	9 (53)	5 (83)	14 (61)
	Disease/condition incidence data	8 (47)	6 (100)	14 (61)
	Audit data from a single site	5 (29)	3 (50)	8 (35)
	Audit data from multiple sites	14 (82)	4 (67)	18 (78)
	Estimates obtained from sites based on their experience/perceptions rather than available data	5 (29)	3 (50)	8 (35)
	Feasibility or pilot study	5 (29)	3 (50)	8 (35)
	Previous RCTs in similar populations	7 (41)	4 (67)	11 (48)
	Other: Please specify[1]	4 (24)	1 (17)	5 (22)
2) In considering the translation of these data sources to your trial population which of the following adjustments did you make within your grant application to predict recruitment in to your study? *Please select all that apply.*	Estimated impact of specific eligibility criteria	15 (88)	6 (100)	21 (91)
	Ethnic minorities	0 (0)	0 (0)	0 (0)
	Seasonal effects	4 (24)	2 (33)	6 (26)
	Consent rate	13 (76)	3 (50)	16 (70)
	Other: Please specify[2]	6 (35)	1 (17)	7 (30)
	None	1 (6)	0 (0)	1 (4)
3) Within your trial's recruitment period, did you assume that all sites would be open for the same length of time?	Yes	2 (12)	5 (83)	7 (30)
	No: Please specify	15 (88)	1 (17)	16 (70)
4) Within your trial's recruitment period, did you assume that all sites would	Yes	4 (24)	0 (0)	4 (17)
	No: Please specify	13 (76)	6 (100)	19 (83)

have the same average recruitment rate?				
5) In considering recruitment to your trial, were you aware of any trials recruiting at the same time that would compete for the same patient population?	Yes: Please specify any strategy employed to allow for the impact on your recruitment	6 (35)	3 (50)	9 (39)
	No	11 (65)	3 (50)	14 (61)
6) Did you search a trial registry for competing trials?	Yes	11 (65)	6 (100)	17 (74)
	No	6 (35)	0 (0)	6 (26)
7) Is your trial open to co-enrollment (e.g. patient enrolment to more than one trial)?	Yes: If yes, what restrictions apply?	9 (53)	2 (33)	11 (48)
	No	8 (47)	4 (67)	12 (52)
8) In estimating your recruitment rate, there may be a need to be optimistic about your recruitment rate for the trial to be attractive to the funder. Do you feel that this issue impacted the recruitment rate used?	Yes	6 (35)	3 (50)	9 (39)
	No	11 (65)	3 (50)	14 (61)

Table 11: Survey results of the Chief Investigators' survey (UK & ECRIN)

[1] Local patient survey; data compiled by a specific NIHR biomedical research unit; national data on disease a activity; multiple sources
[2] Difficulties in recruiting; logistics of recruitment; availability of research nurses; data on rates of recruitment from previous studies; a general rule: 50% of what the Principal Investigator estimates; eligible Vs consent rate, e.g., we expect the recruitment to be something between 30 and 50% of the eligible population depending on the trial question; impact of recruiters.

The data source most commonly used to predict trial recruitment was audit data from across multiple centres with the impact of specific eligibility criteria being the most frequently adjusted factor (Table 11, Question 1). While no respondents reported adjusting for ethnic minorities, one respondent even though provided "No" as an answer to this question, elaborated that not adjusting for this factor negatively impacted their predictions.

Allowing for variation in recruitment rates at individual centres was also common (13/17 UK, 6/6 ECRIN) with comments supporting the need for this practice based on variation in patient numbers and knowledge of centre research activity infrastructure and experience. The majority of UK respondents (15/17, 88%) did not assume that all centres would be open for the same length of time in comparison to only one of the six ECRIN respondents (17%). Free text responses reported staggered opening times to reflect variation in time required at each centre to obtain approvals.

Eleven (65%) UK respondents searched a trial registry for competing trials compared to 100% of ECRIN respondents (Table 11, Question 6). Thirty-five percent of UK and 50% of ECRIN respondents were aware of other trials competing to recruit the same patient population. Co-enrolment was considered for only half of UK and one third of ECRIN respondents. A third of UK and half of ECRIN respondents reported a need to be optimistic about the predicted recruitment rate for the trial to be attractive to the funder. Free text comments emphasised the difficulties this practice would lead to during trial conduct. Additional comments stated that the estimates were reflective of recruitments rates if things went well, accepting that this may not be the case with an inability to accurately predict researcher performance and stability of local clinical services.

6.3.2. Statisticians' Survey

The survey was conducted between 18 September 2018 and 6 November 2018 among the 51 UKCRC registered CTUs of whom 50 (98%) responded (46 responses completed online, 4 responses completed at the network meeting). The ECRIN EuCos circulated the survey between 13 November 2018 and 29 January 2019 to 53 participants of whom 19 (36%) responded.

Table 12 below summarises the survey results.

Question	**Answer**	**UK, N =50**	**ECRIN, N=19**	**Overall, N=69**
		n (%)	**n (%)**	**n (%)**
Introductory questions				
1) Who usually leads recruitment prediction for a clinical trial within your unit? *Please select all that apply.*	Chief Investigator	33 (66)	13 (68)	46 (67)
	Trial Coordinator	28 (56)	5 (26)	33 (48)
	Statistician	29 (58)	10 (53)	39 (57)
	Other (e.g. IT team, Senior staff)	6 (12)	1 (5)	7 (10)
2) Do you believe a statistician should be involved in the recruitment prediction process?	Yes	43 (86)	13 (68)	56 (81)
	No	3 (6)	6 (32)	9 (13)
3) When predicting the recruitment rate at the pre-trial planning stage, where do you find the information about the prevalence of the condition being studied, the eligibility of patients, the	Published literature	28 (56)	10 (53)	38 (55)
	Research team experience	28 (56)	10 (53)	38 (55)
	Previous studies	22 (44)	4 (21)	26 (38)
	Registry data/audit data / patient databases /hospital data	22 (44)	5 (26)	27 (39)
	Feasibility surveys/ pilot studies / sites' questionnaire	24 (48)	5 (26)	29 (42)

Question	Answer	UK, N =50	ECRIN, N=19	Overall, N=69
		n (%)	n (%)	n (%)
consent rate of participants etc.? Please provide information[1]	Conservative interpretation of previous experience or consent rate	4 (8)	0 (0)	4 (6)
	PPI[2] engagement group	2 (4)	0 (0)	2 (3)
	Projections were not particularly evidence-based	1 (2)	0 (0)	1 (1)
	NA	0 (0)	1 (5)	1 (1)
4) In considering recruitment to trials in your CTU, are you usually confident that you are aware of other trials recruiting at the same time that would compete for the same patient population?	Not confident at all	0 (0)	1 (5)	1 (1)
	Not very confident	6 (12)	11 (58)	17 (25)
	Neither	10 (20)	1 (5)	11 (16)
	Fairly confident	28 (56)	5 (26)	33 (48)
	Very confident	6 (12)	1 (5)	7 (10)
Recruitment prediction				
5) In addition to the number of patients and the number and size of sites, what factors would you routinely consider when predicting rates of recruitment? *Please select all that apply.*	Staggered site openings	48 (96)	13 (68)	61 (88)
	Seasonal variation	24 (48)	9 (47)	33 (48)
	Holiday periods	21 (42)	9 (47)	30 (43)
	Other	9 (18)[3]	6 (32)[4]	15 (22)
6) Do you use any statistical model for recruitment prediction?	Yes	3 (6)	4 (21)	7 (10)
	No	47 (94)	15 (79)	62 (90)
7) Are you aware of any of the statistical approaches listed below for use in recruitment prediction? *Please select all that apply.*	Poisson model - assumes a constant average rate of recruitment	23 (46)	13 (68)	36 (52)
	Poisson Gamma model - which models variability in centre recruitment rates using a gamma distribution	13 (26)	8 (42)	21 (30)
	Bayesian approaches requiring a prior for recruitment to be specified	12 (24)	9 (47)	21 (30)
	Other	2 (4)[5]	2 (11)[6]	4 (6)
	None	24 (48)	4 (21)	28 (41)
8) Have you ever simulated recruitment data to support your pre-trial planning?	Yes, routinely	0 (0)	1 (5)	1 (1)
	Sometimes	16 (32)	6 (32)	22 (32)
	Never	34 (68)	12 (63)	46 (67)
9) If you do not use any of the approaches mentioned above for recruitment prediction, what is the	I prefer using a simple approach (e.g. using Excel) rather than assuming statistical distributions for recruitment prediction	22 (44)	8 (42)	30 (43)

Question	Answer	UK, N =50	ECRIN, N=19	Overall, N=69
		n (%)	n (%)	n (%)
reason for this? *Please select all that apply.*	I am not familiar with these models for recruitment prediction	17 (34)	2 (11)	19 (28)
	I am familiar with some/all of these models but I don´t know how to implement them for recruitment prediction	6 (12)	2 (11)	8 (12)
	I am not convinced of the value of implementing these models	27 (54)	2 (11)	29 (42)
	Other	8 (16)[7]	8 (42)[8]	16 (23)
Recruitment Monitoring and implementation of statistical models via web application				
10) How do you routinely monitor recruitment during the course of a trial? *Please select all that apply.*	Tables showing the expected and actual recruitment rates	43 (86)	14 (74)	57 (83)
	Recruitment Graphs showing the expected and actual recruitment rates	49 (98)	11 (58)	60 (87)
	Individual recruitment targets for each site	41 (82)	10 (53)	51 (74)
	Common recruitment target for all sites	24 (48)	9 (47)	33 (48)
	Comparison of overall recruitment rates for each site with recruitment rate over recent months	31 (62)	8 (42)	39 (57)
	Other	8 (16)[9]	0 (0)	8(12)
11) Are you aware of any software/web platforms for planning and monitoring patient recruitment?	Yes	3 (6)	2 (11)	5 (7)
	No	47 (94)	17 (89)	64 (93)
12) If a user-friendly web application implementing some of the aforementioned models became freely available, would you be interested in using it for predicting and/or monitoring of the trial recruitment? *Please select all that apply.*	No, I don't believe it is a statistical issue and it is best handled by the trial team	4 (8)	3 (16)	7 (10)
	Not for prediction but I would be interested in using it for monitoring	3 (6)	1 (5)	4 (6)
	Yes, I want to improve prediction of recruitment	14 (28)	5 (26)	19 (28)
	Yes, I want to use it for both initial prediction and monitoring of recruitment	27 (54)	11 (38)	38 (55)
	Other	18 (38)[10]	3 (16)[11]	21 (30)

Table 12: Survey results to closed-ended questions of the Statisticians' Survey (UK & ECRIN)

[1] Free text responses have been categorised into common themes
[2] Patient and Public Involvement
[3] Experience of working with sites; staff change-over; international sites, previous experience of sites in similar trials, network of co-ordinated sites with inbuilt resources; recruitment to other comparable trials; research nurse availability, past records of recruitment, interest levels of potential CIs; any information on consent rates in the participants group; funding restrictions, allowing a burn-in period; study setting (eg. hospital-based vs

community-based), staff resource availability; potential issues around consenting patients, e.g. in emergency settings

[4] Compliance of investigators in charge of recruiting; concomitant studies; experience of researchers; motivation of investigators; observed enthusiasm of contact persons in various sites; we do not usually have to face with that issue

[5] Multistate Markov model; point estimates once the trial is underway

[6] Using the most recent period to predict future recruitment; we are aware of statistical models for recruitment prediction, but with the information provided it is not easy to predict, so we do not usually use them

[7] It is so dependent on the quality of previous data; there is limited evidence of the benefit over the above practical feasibility modelling, given the capacity to do; I prefer spending the available time getting good information on number of potentially eligible patients at a centre (consent rates); models are used but not for pre-trial planning; often I am not involved in the recruitment prediction, often this comes from the site and the trial managers; there is usually not much time for this as the CI does not see this as needed; they would simply give a distribution of recruitment rates and we would need to pick a final number which would be the mean so simple multiplication would seem as appropriate given the uncertainty about the assumptions; within our trials unit, recruitment prediction is usually done by the trials team, with limited involvement from the statisticians. However, in the implementation of more complex early phase designs where recruitment will impact on the operating characteristics, there are more statistical involvement

[8] Our CTU will need to write a standardised package to do such predictions, which is generic enough that it could be used for all trials; I was so far rather dealing with small trials with small budget; lack of planning at the design stage and lack of time to carry out the required analysis; nobody expects and pays me to predict recruitment; we do not use models since the assumptions provided are too vague; we use East; we use also simple approaches; I have sometimes used some of the previous methods

[9] All the above tools are commonly used, however these are all calculated from a master recruitment chart; awareness of CRN (Clinical Research Network)/local targets, which are increasingly asked to reduce to ensure that sites remain green; different methods for individual trials – often the Trial Management Group knowledge about the centre and their likely recruitment potential is incorporated; it does depend on the particular trial, but for large trails we would generally use most of these; review of recruitment rates per centre-month; site recruitment information supplement, albeit typically common targets for all sites. This may vary by type e.g. feasibility trial or trial with internal pilot with progression rule based on recruitment, where they tend to have increased monitoring, including monitoring by site; interest and practicality from new centres

[10] Certainly would be interested; Don't really have the time and probably not something that a funder is willing to fund more statistician Full Time Equivalent for doing this activity; I believe it's largely about (1) the quality of previous data to inform predictions and (2) getting approvals in a timely fashion. Approaches based on reference limits – what ifs could improve this a bit but I remain to be convinced they make major impact; I think this probably has value, however something similar has already been developed here as part of our recruitment prediction and monitoring so this would be of little use to us; I would certainty investigate the utility of such tool (if available); I would like to test it alongside the method we already use to see if it is helpful; I would say yes if there was sufficient evidence that the tool has worked previously and would be beneficial; I'd certainly be interested in what the models could do; I'd want to see evidence that it is really worth the extra effort; it would be useful to have access to the experience of others about these issues; No requirement for separate software as we use our standard statistical software as required; No, I would not be interested in using such a web application as I believe that it would be better to spend time helping the trial team to identify ways to improve the recruitment rate if needed. Such as identifying the underperforming sites using central statistical monitoring so that one of the monitoring team can visit and provide assistance (for example by providing additional training about our pre-screening process to improve identification of eligible patients); No we see no need for this as we can easily implement the models ourselves and have greater versatility; Not sure, I would be interested in looking at it and playing around to see how it works but I wonder how much more effective it would be than using simple projections; perhaps, in specific instances for prediction; Sure I'd try using it, but no promise as to whether it would become our main tool; happy using Stata; it may be difficult to make this generic across types of trials e.g. recruitment at clusters Vs recruitment at patient level

[11] Yes, if sponsor/investigator asks me to do this and would pay for it. This is not very likely to occur at our institution, mostly running investigator-initiated small trials; I don't know; No-mostly I prefer doing it myself

The majority believe that statisticians should be involved in predicting recruitment (86% UK, 68% ECRIN); however, statisticians were reported to have been involved in leading the process in only just over half of the studies. The contribution of individual groups of chief investigators, statisticians and trial coordinators and their corresponding combinations in leading recruitment prediction are presented in Table 13 below.

Who usually leads recruitment prediction for a clinical trial within your unit?	UK (N=50) n (%)	ECRIN (N=19) n (%)	Total (N=69) n (%)
Chief Investigator	6 (12)	6 (31)	12 (18)
Trial Coordinator	5 (10)	2 (11)	7 (10)
Statistician	5 (10)	3 (16)	8 (11)
Chief Investigator & Trial Coordinator	6 (12)	1 (5)	7 (10)
Chief Investigator & Statistician	7 (14)	4 (21)	11 (16)
Trial Coordinator & Statistician	5 (10)	0 (0)	5 (7)
Chief Investigator & Trial Coordinator & Statistician	10 (20)	2 (11)	12 (18)
Other	6 (12)[1]	1 (5)[2]	7 (10)

Table 13: Detailed presentation of the responses in Question 1 of the Statisticians' survey (UK & ECRIN)

[1] A combination of the CI/PI and the senior trial managers; Colleague from operational team with previous trial experience in the disease area, Chief Investigator, Statistician; Operational staff, Chief Investigator, Statistician; Recruitment Coordinator, Chief Investigator, Trial Coordinator; Senior team when applying for the grant as it is an essential part of getting the funding right; Senior Trial Co-ordinator/Trials team leader, Trial Coordinator

[2] Scientific Director of the Medical Statistics core facility, Statistician

Respondents from ECRIN reported were less confident than UK respondents in their awareness of other trials competing to recruit from the same patient population (12% UK, 63% ECRIN) and were less likely to adjust for staggered centre openings (96% UK, 68% ECRIN).

Use of statistical models to predict recruitment was low overall (10%) but higher within ECRIN respondents (6% UK, 21% ECRIN) who also had greater awareness of the individual statistical approaches with 48% of UK respondents not aware of any method compared with 21% within ECRIN.

At the pre-trial planning, only 32% of respondents sometimes simulated data to support recruitment prediction, whereas 67% of them never did (Table 12, Question 8). The time investigators would need to dedicate to perform simulations is an additional challenge, especially if they are not convinced of their value.

The majority of respondents who sometimes simulated data are at least aware of the Poisson model (73%, 16/ 22), whereas six of them are not aware of any statistical model for recruitment prediction (27%, 6/22). On the other hand, almost half of respondents who never simulated data, are not aware of any model (48%, 22/46), whereas 43% of them are at least aware of the Poisson model (20/46). However, because of the small sample size, we cannot conclude a definitive correlation between knowledge of statistical models and use of recruitment simulations.

A sizeable proportion of respondents (44% UK, 42% ECRIN) preferred to use a simple approach rather than statistical distributions to predict recruitment. Slightly over half of UK respondents were unconvinced of the value of implementing these methods in comparison to only 11% of ECRIN respondents (Table 12, Question 9).

A minority of respondents were aware of existing software or web platforms to support planning and monitoring of patient recruitment with over a quarter of respondents being interested in such a resource for predicting recruitment and over half interested for both prediction and monitoring (Table 12, Question 12). Free text responses indicated that time to learn how to use such an application and funder willingness to support any associated costs were a concern. Other participants expressed an interest in comparing any methods alongside those already used in practice to determine whether any time or resource investment was worthwhile. One participant expressed concerns on whether the requirements of more complex clinical trials could be met by such a resource.

Response to the free text question about further practices, tools or resources that could potentially improve prediction accuracy are provided in Box 3, with suggestions for how funders/trial teams could monitor recruitment progress/milestones summarised in Box 4.

Question 13: Please give details of any further practices or tools/resources that you think could influence your future practice, in terms of prediction accuracy in patient recruitment.

Training (e.g. work with CIs to show the value of involving statistics for recruitment purposes before and during the trial / workshops for trial statisticians / challenge the clinicians etc.) (8/69, 12%)

Better engagement (e.g. with potential sites, using standard questionnaires to elicit proposed recruitment target / easily accessible & timely input from clinical communities & access to relevant patient groups etc.) (5/69, 7%)

Raising awareness of the available approaches (2/69, 3%)

Current challenges and conflict with NIHR CRN targets (e.g. sites come back and ask to change their local recruitment target to ensure they are not challenged / providing the funding for realistic timelines / building in flexibility with timelines for project management and funding / allowing for reallocation of research resources to new studies towards the end of the study etc.) (3/69, 4%)

Recommendations to improve prediction (e.g. building up a database of actual recruitment in our studies that could be referred to in future / use anonymised registry of patients with relevant disease along with demographic information / valid international data on disease incidence and prevalence / comparing predictions and targets to what actually happened so future predictions can be improved /comparing recruitment in pilot studies with that in full trials / getting funders to request more rigorous methods to estimate recruitment etc.) (10/69, 14%)

Tool/Model (a tool that automatically integrates recruitment predictions for individual sites in a multicentre trial into an overall prediction for the trial / simple, robust methods yielding accurate results / a smoothed time-autocorrelated prediction might be helpful / any tool that helps to maintain engagement/enthusiasm) (8/69, 12%)

Demonstrating evidence that these models actually work in practice (e.g. it is important to show that prediction ability of a model/tool is better than the simpler ways / it can be cumbersome to gather all information to feed into prediction tools and it would require further input from a statistician etc.) (2/69, 3%)

No response (35/69, 51%)

Response not clear (3/69, 4%)

Box 3: Further practices or tools to improve recruitment prediction

Question 14: Do you have any comments or suggestions on how funders/trial teams monitor recruitment progress/milestones?

Educate funders (e.g. Funders' expectations of trials set up and recruitment rate should be more realistic / they should be less rigid in setting targets and monitoring against those targets / funders want more for less / funding panels to define the feasibility of recruitment rates and convince the administrative funders that studies need more time to be successfully delivered etc.) (3/69, 4%)

Educate Chief Investigators (CIs tend to be overoptimistic / Methodologists/Statisticians usually try to be conservative but this is challenged by CIs etc.) (2/69, 3%)

Build on skills and experience gained from previous trials (e.g. pass on the skills and experience of trials teams that manage to recruit to time and budget / a sort of rule of thumb is that 20-40% of potentially eligible people approached to take part will consent to inclusion / in cancer trials we tend to expect about 50% of eligible patients to consent etc.) (2/69, 3%)

Take into account factors related to trial/outcomes/intervention/condition being studied (e.g. seasonal factors / clinic frequency/ TTE[1] considerations/ staggered entry assumptions etc.) (4/69, 6%)

Allow for delays outside of the control of the trial management team during the course of the trial (e.g. due to budgeting/staffing/resources/ new trials opening / delays in agreeing contracts / whole centres dropping out etc.) (2/69, 3%)

Central database with recruitment information from previous trials to accompany the online tool (1/69, 1%)

Uncertainty to be considered (e.g. any recruitment estimates at the onset of a trial will be based on assumptions, e.g. average recruitment rate per site or something similar / there are so many variables involved and I am not sure there are any decent ways of getting around that / initial recruitment predictions tend to be very inaccurate / any prediction or monitoring of recruitment using sophisticated modelling may not be any better than using simple projections etc.) (5/69, 7%)

Generic programming (programming something generic is important, because statisticians are already under a lot of time pressure and deadlines, so they want to avoid an overload of duties) (1/69, 1%)

No response (52/69, 75%)

Response not clear (3/69, 4%)

Box 4: Suggestions for monitoring recruitment progress

[1] *TTE: time to event*

6.4. Discussion

6.4.1. Main findings

This survey is the first to identify current practice on methods to predict recruitment in clinical trials and raises hypotheses about different practices in the UK compared to Europe and the perceived value of more complex statistical approaches.

Survey responses clearly indicate that the statistical models available are not being implemented. The absence of a robust demonstration of their benefits in comparison to simple approaches is a key barrier to their uptake. The statistical literature is restricted to the evaluation of these models in simulations or in retrospective trials [57, 65, 68]. It lacks a real-time prospective evaluation utilising the same limited information sources to support parameter estimation across models at the design stage, which are then used to monitor actual accrual. Furthermore, the survey suggested that this evidence is required prior to trial statisticians being able to justify the time required to understand and implement the methodology, suggesting that software availability on its own is insufficient to change practices.

There are many factors to be taken into account when predicting recruitment and in turn defining a trial's duration. Recruitment targets cannot be realised if based on overoptimistic expectations and unrealistic timelines. The overoptimistic expectations of the research team have been reported previously [12]; however, this survey highlights the tension felt by a sizeable proportion of investigators to be optimistic about their recruitment rates, for the trial to be attractive to funders. Despite this tension, there was a clear appreciation of the difficulties this would cause at later time points, with calls for funders' expectations of trial set up times and recruitment rates to be more realistic, less rigid and to allow for unforeseen delays outside the control of the trial management team.

The importance of adhering to the centre initiation schedule is key and our anecdotal experience is that deviations from this often explain a substantial proportion of under recruitment. The time required to complete the administrative arrangements which need to be made in order to open participating centres can vary and be impacted by centre engagement and capacity or by regulatory changes [125-129]. The survey indicated that staggered centre openings are more commonly allowed for within the UK than across the ECRIN network. However, while the rate of centre initiations may be informed by past experience, there is an inherent assumption regarding the stability of centre resources to deliver the research remaining stable throughout the trial. While a potential solution is to improve centre feasibility and capability assessments, the variables that need to be included and how they are utilised within resulting predictions, needs further scrutiny.

The survey demonstrates that investigators and statisticians are using a wide variety of information sources to predict their recruitment rates. However, in practice the extrapolation of these data to a specific multicentre trial often requires adjustments to be used. The size of the adjustments may be considered to be arbitrary or based on guess work and this may in part reduce the number of factors investigators feel able to include. In addition as the availability of routinely collected data increases to support clinical trial planning, the assessment of such sources and how they are used will be of increasing importance.

The main focus of our survey was the prediction of recruitment; however we also aimed to ascertain how this was monitored against observed accrual. The responses demonstrated that this information is considered in multiple ways per trial with comparisons of observed recruitment rates against those predicted in graphical or tabular form, at individual centre level and across all centres, and covering the entire recruitment period or restricting to recent months. Although eight respondents indicated “other” methods were used, the free text provided demonstrated that the approach was consistent with the closed response categories. The limitation with these approaches is that they do not allow understanding of whether the observed variation is within reasonable limits of the prediction. This may lead to delays in remedial actions. A potential benefit of using a statistical model is the pre specification of a quantile to act as a trigger when the observed recruitment rate is inconsistent with that pre specified. One respondent commented that the use of statistical models would

"simply give a distribution of recruitment rates from which we would need to pick a final number which would be the mean, so simple multiplication would seem as appropriate given the uncertainty about the assumptions". This suggests that even if the uncertainty they elude to is not welcome within prediction, there is potential for their use within monitoring.

In a survey of the UKCRC registered CTUs the top inefficiency from recruitment of first participant to publication of results, was identified as the failure to meet recruitment targets due to overoptimistic or inaccurate recruitment estimates [130]. Some statisticians reported being under pressure to project optimistic recruitment rates. This is likely due to the perception that realistic rates are associated with increased budgets, beyond what funders are willing to provide. This issue was raised by our survey respondents, with participants' suggestions that training should be provided for both CIs and funders. Increasing funders' flexibility in setting timelines would be helpful and reflects additional calls on requirements with adaptive designs [131].

The majority of our respondents believe that a statistician should be involved in the recruitment prediction process but do not model recruitment as a stochastic process. This may be in part explained by time pressures, as recruitment prediction is undertaken during the unfunded preparation time of a grant application. This will be compounded given investigators and statisticians are unconvinced that the models described in the literature are worthy of the additional time required to support their use. However, the survey demonstrates the majority would be interested if the benefits were found to justify the additional time and statistical expertise required.

6.4.2. Strengths and Limitations

This survey aimed to elicit current recruitment practice across the UK and Europe. The high response rates from the UK are a strength of the survey; however, this means that the findings predominantly represent current practice within the UK.

The network structure within the UK facilitated survey distribution in a controlled approach using the network secretariat ensuring a targeted delivery and response, while the ECRIN approach used a more fluid hub and spoke model where the CIs and the statisticians were contacted by the EuCos in each country. Other surveys targeting statisticians across the UKCRC CTU network have achieved similarly high response rates [132-134] and we have been unable to identify similar surveys across ECRIN.

The lower response rates from ECRIN may be a result of these different network infrastructures; however, they may also impacted by the survey being restricted to the English language.

The comparison of practices between the UK and Europe therefore needs to be interpreted with caution as this could reflect response bias within ECRIN with those with particular interests in recruitment prediction taking part. This may be an explanation for the greater awareness of the statistical methods in the ECRIN respondents.

Furthermore, the investigators in the UK survey were identified from the website of the largest public funder of clinical trials in the UK. The sampling framework for investigators across ECRIN was by identification of the EuCos and therefore not restricted to a funding source. However, knowledge of both Networks suggests that the portfolio of studies represented is restricted to non-commercial research. It would be of interest to understand differences in methods used in comparison with industry sponsored studies, with research suggesting recruitment for industry sponsored studies being less problematic [2]. Yet, it is likely that the resources allocated and incentives provided are dissimilar and this complexity of factors warrants further detailed exploration in future research.

6.4.3. Summary

Approaches used to predict and monitor recruitment remain frequently unreported. These surveys provide insight from statisticians and chief investigators on methods and data sources being used. The results of the surveys indicate that recruitment is generally not recognised as a stochastic process in the approaches used and that those involved in recruitment prediction prefer simple approaches. Barriers to uptake of the statistical models include complexity of their implementation and an absence of evidence that the time taken to implement them will result in improving the accuracy of recruitment prediction.

To address the complexity barrier, introduction of software and training courses may reduce the gap between the development of methodology and its implementation. In the next chapter, we present the Shiny application, which has been developed to facilitate the implementation of selected models identified in the literature and extend their availability for non-statistical users.

Chapter 7: Implementation of statistical models for recruitment prediction and monitoring: an interactive Shiny application

Preface

Statistical methods targeting advances in the prediction of patient recruitment in clinical trials have been developed, however application of the methods is limited. In chapters 2 and 4 we present the statistical models that can be used for recruitment prediction at the design stage of the trial and statistical models to predict ongoing recruitment utilising current accrual data. The survey presented in chapter 6 indicated that the use of statistical models for recruitment prediction was low and the main reasons reported being their complexity and investigators preference for simple approaches mainly because of lack of time and funding. Thus, a need to bridge the gap between the development of methodology and its implementation, has been identified. We developed a Shiny application to facilitate the implementation of selected models and extend their availability for non-statistical users. Shiny is a package from RStudio that is used to build interactive web applications with R programming language.

7.1. Introduction

An empirical analysis of clinical trials that closed in 2011 was conducted to determine the number of patients recruited in those clinical trials that were at risk of not addressing the primary research question due to insufficient patient accrual [135]. The investigators concluded that "Ethics bodies, investigators, and data monitoring committees should carefully scrutinize trial design, recruitment plans, and feasibility of achieving accrual targets when designing and reviewing trials, monitor accrual once initiated, and take corrective action when accrual is lagging".

Deterministic models have been broadly used in the clinical trials units for patient recruitment prediction as described in chapter 6. Calculating the expected recruitment period by dividing the required sample size with the number of patients expected to be enrolled during a specific time unit (e.g. month), does not consider the stochasticity and uncertainty which are an integral part of the recruitment process. These aspects can be taken into account by using statistical models that are available in the literature and described in chapters 2 and 4.

The Poisson process is a well-accepted stochastic approach that can be used to model patient recruitment in clinical trials, when the average number of patients to be recruited is expected to be constant during a time interval [24-27]. The homogeneous Poisson process can be used when the average number of patients is expected to be the same across the trial recruitment period, and so lambda defines the recruitment rate at which events occur. Whereas in multi-centre trials, where patient recruitment is related to the number of centres open, initially the number of patients is expected to be low and as more centres open, more patients will be recruited. Thus, patient recruitment can be better captured by using a non-homogeneous Poisson process, where the lambda is a time-varying parameter.

Bayesian models have also been used for the prediction of patient recruitment at the design stage and during trial conduct [32, 63, 64]. At the design stage, the investigators define the prior information in relation to the number of patients and the time required for their recruitment, which is based on their experience and the available literature. The benefit of a Bayesian approach is better depicted in prediction of ongoing recruitment, where investigators' prior belief is combined with observed recruitment rates to predict accrual for the remaining recruitment period.

There is software developed to implement the Bayesian constant accrual model for single centre recruitment including a web calculator and a smartphone application [39] and there are other publications [68, 69] describing how they used case studies to implement the Bayesian model introduced by Gajewski *et al* [32] and extended by Jiang *et al* [64].

We developed a web application to facilitate the implementation of selected models identified in two systematic reviews [13, 57]. The web application is written using the Shiny package in the R programming language [124].

The aim of this chapter is to present a guidance of how to use the Shiny application. The statistical models that have been developed in Shiny will be presented by using two clinical trials as illustrative examples.

7.2. Methods

7.2.1. Shiny application: Steps of Development

Shiny is an open source R package that provides a web framework for building interactive applications using R (https://shiny.rstudio.com/). The Shiny application is

developed by using two R packages, the "poisson" [136] and "accrual" [40] that can be implemented to model patient recruitment and provide prediction on future accrual. Those two R packages were identified when searching for available statistical models to be used for recruitment prediction. Their availability in R led to the decision to develop the Shiny application. The Poisson and the Bayesian models and how they have been used for recruitment prediction at the design stage and during trial conduct have been described in details in chapters 2 and 4. The aim in this chapter was to use what was already available and to create a user-friendly interface. Thus, the models described in literature could be used in practice and be evaluated.

Shiny is displayed in a platform where the user can define the study parameters required for each model and produce the recruitment graph with the number of patients expected to be recruited in a time frame, or the time required to recruit the prespecified number of patients. Two Poisson models are presented, the Homogenous Poisson Process (HPP) and Non-Homogenous Poisson Process (NHPP), and another four Bayesian models.

The steps followed to develop the Shiny application are described below.

Shiny application is a directory containing an R script called *app.R* that is made up of a **user interface object** and a **server function**. Initially I created an empty app.R and installed all the required R libraries and packages, "poisson", "accrual", "DT" to display R data objects such as data frames in a table format, "shiny", and "shinyjs" which allows the performing of useful JavaScript operations in Shiny apps (https://deanattali.com/shinyjs/).

User Interface

The user interface is defined by calling the function *fluidPage*, within which the following functions are specified:

- *titlePanel* to define the application title as "Patient Recruitment"
- *sidebarLayout* containing the arguments *sidebarPanel* and *mainPanel*, which are presented in details below, and *position* which simply indicates the position of the sidebar, left side in our application.
    - *sidebarPanel* contains the input elements
        - *selectInput*, where the models are listed (HPP, NHPP, Bayesian1_Subjects, Bayesian1_Time, and Bayesian2) with the

conditionalPanel function allowing to condition on the model and display one model each time. Once the model is chosen, by using the *sliderInput* function, the range of values for each model parameter can be determined (e.g. sliderInput(inputId="HPPnum.events", label="Number of patients:", min = 1, max = 600, value =50, step = 1)).

- *mainPanel* contains the output elements, each of which is presented in a different tab (*tabPanel*) by using the *tabsetPanel* function, which is useful for dividing output into multiple independently viewable sections.
  - The first tab is called "Model description" and provides a short description for each model as shown in Figure 9, which is defined by using the *conditionalPanel* function (e.g. condition="input.model==1" for the HPP model).
  - The second tab is called "Patient Enrolment Times" as shown in Figure 10 and presents the time in months when each patient was recruited in a tabular format accompanied by the 2.5% and 97.5% quantiles, e.g. *dataTableOutput* ("EventTimes").

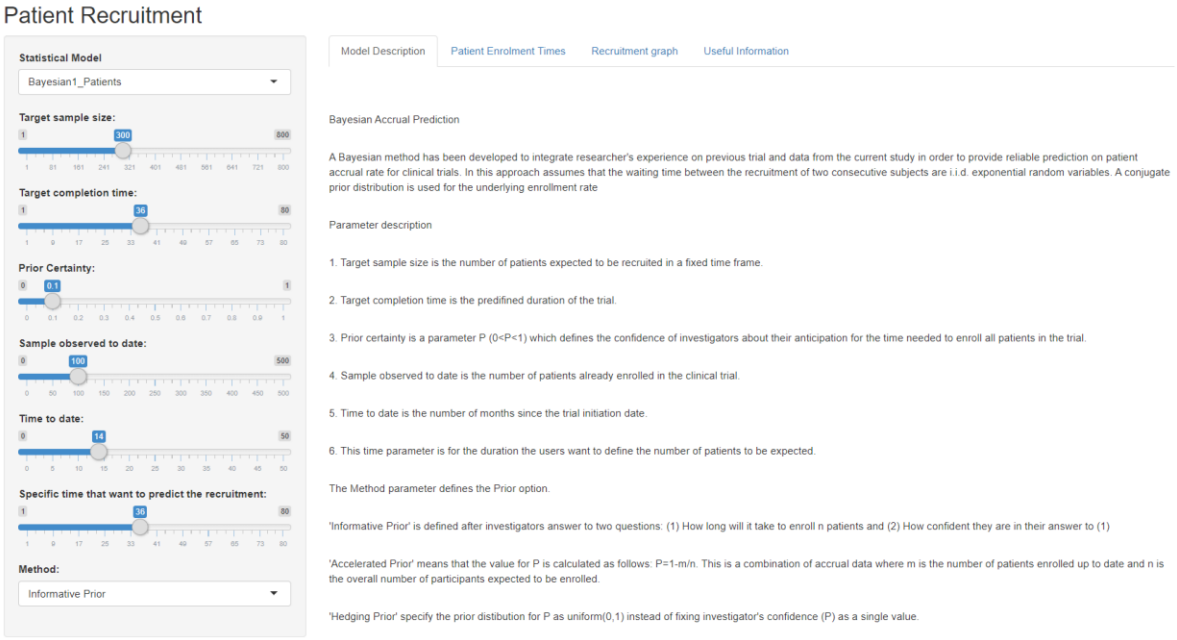


Figure 9: First tab in the Shiny web platform presenting the description for each model

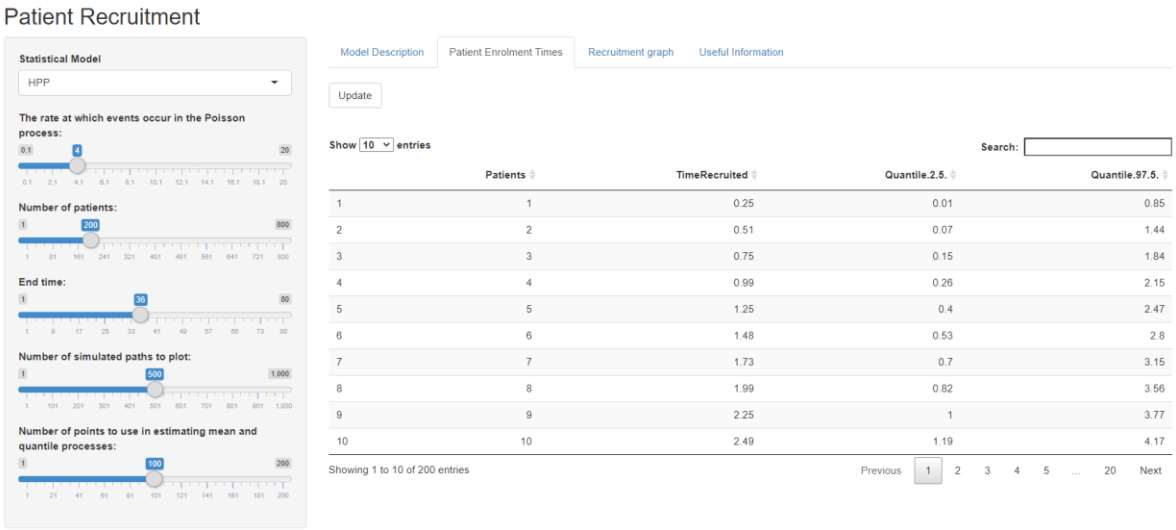


Figure 10: Second tab in the Shiny web platform, presenting patients' enrolment times for the Poisson models

The table with the enrolment times of patients and the quantiles is activated only for the two Poisson models, while this tab is not active for the Bayesian models. However, a brief summary of results, consisting of the median and 95% prediction interval for the final recruitment target, is presented in a table together with the recruitment graph in the following tab.

- The title of the third tab is "Recruitment graph", which is presented in Figure 11 below, where the recruitment graph is displayed by using the function *plotOutput*.
- The final tab called "Useful Information" contains supplementary material about the models as shown in Figure 12, such as the R packages, "poisson" and "accrual" and relevant publications.

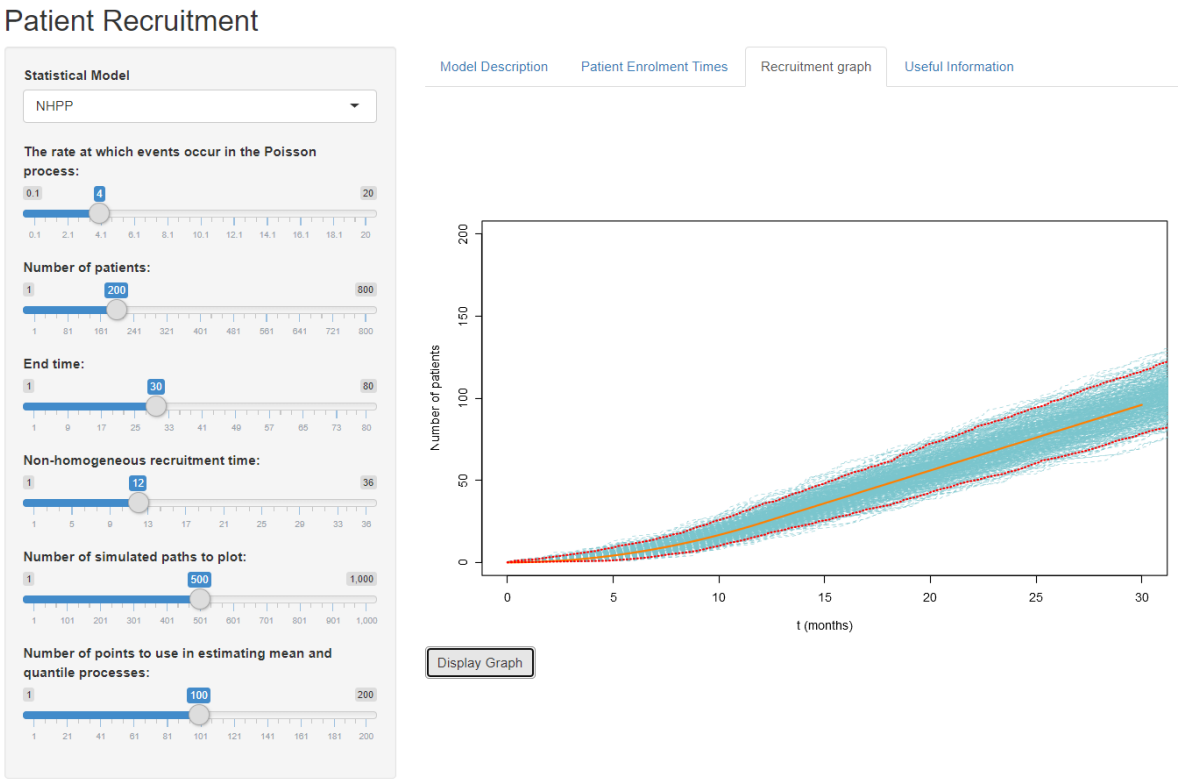


Figure 11: Third tab in the Shiny web platform presenting the recruitment graph for each model

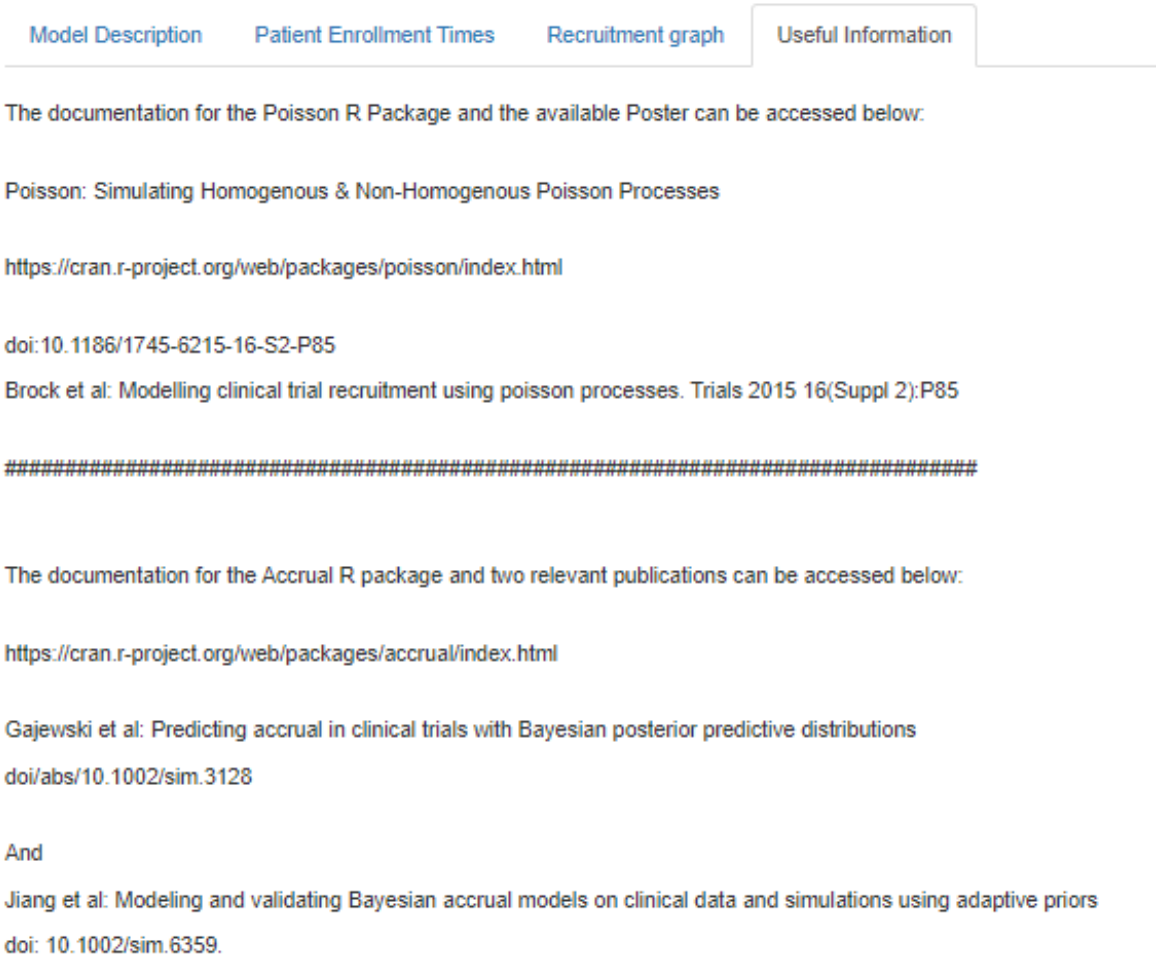


Figure 12: Forth tab in the Shiny web platform presenting some useful information and relevant articles for the models

Server Function

Server uses the command *function(input, output)* to define the two different outputs in the application. While the user interface is where the outputs are listed and categorised, the server function is where we specifically introduce the relevant functions from the "poisson" and "accrual" R packages to define the time when each patient is expected to be recruited (1st output) and to define the graph with the expected duration of recruitment in months and the expected number of patients (2nd output).

- The first output is the table presented in the 2nd tab with the patient recruitment times and the quantiles for HPP and NHPP models, which is built by using the *renderDataTable* function. This is a reactive function that returns a data frame and allows for searching, filtering and sorting of results.

- The second output is the recruitment graph created for each model. The function *renderPlot* is used in combination with the functions *hpp.plot*, *nhpp.plot*, *accrual.n.plot* and *accrual.plot.multicenter* from the "poisson" and the "accrual" packages to build the reactive plot for each model.

Finally, the *shinyApp* function is used to create the Shiny app object by combining the user interface object and the server function, *shinyApp* (*ui* = ui, *server* = server).

7.2.2. Poisson models

The "poisson" package was developed to model patient recruitment in clinical trials [136]. Depending on whether the recruitment rate is constant or time-dependent, there are two Poisson processes that can be used. The expected recruitment rate, which is referred to as lambda and represents the average number of events per unit of time, e.g. the average number of patients to be recruited in a month, is to be defined in each model.

The Poisson model is related to the exponential model. When the number of patient arrivals is expected to follow the Poisson distribution, then the time between patient arrivals is considered as an exponential distributed variable. If the frequency of patient arrivals in the clinical trial is the domain of interest for the researcher, then the number of patient can be modelled as a Poisson process, and the expected number of patients to be recruited in a specific time period can be calculated. However, if the time domain is of more importance for the investigator, then the inter-arrival times of patient enrolment can be modelled by using the exponential model. The average waiting time between patient recruitment can be calculated and it is equal to the expected recruitment time divided by the target sample size.

7.2.2.1. Homogeneous Poisson Process - HPP

In HPP the average accrual rate is considered constant. Patient arrival times in a clinical trial are considered random and there are examples such as single centre trials where the gap between patient enrolments is expected to be the same, on average, throughout the trial recruitment period. When these assumptions apply, patient recruitment can be modelled as a homogeneous Poisson process.

7.2.2.2. Non Homogeneous Poisson process – NHPP

Based on the NHPP approach, patient accrual initially is anticipated to increase linearly and after a predefined time point is assumed to be constant. In multi-centre clinical trials, for example, the gap between patient enrolments is expected to be large

at the beginning of the trial but it reduces as more centres are open to recruitment. Patient recruitment in these trials can be modelled by using non-homogeneous Poisson processes, where the recruitment rate is expected to increase linearly as more centres open, until the time when all centres are open and the recruitment rate is expected to reach its full capacity and remain constant after that. This time point in the model has been defined in the code with an intensity function
intensity ← function(t) pmin(t/input$month, 1), where the month until which the rate is expected to increase, can be defined by the user. In the Shiny application this parameter is defined as the "Non-homogeneous recruitment time". In addition, the user will need to define the maximum expected recruitment rate in the application.

The study parameters that need to be defined to implement the HPP and NHPP models are listed below:

- The rate at which events occur in the Poisson process (average rate for the HPP versus maximum rate for the NHPP)
- Sample size required, defined as "Number of patients"
- End time, which is the expected recruitment duration defined in the study protocol, while the start time is assumed to be zero ($t_0 = 0$)
- Non-homogeneous recruitment time (applicable to the NHPP model only) to be defined by the user as explained above
- Number of simulated paths to plot (range from 0 to 1,000; higher number of simulated paths will result in more accurate results about the mean and the quantiles). The drawback with a large number of simulated paths is the time required to process the simulations, which is longer when the number of simulations is larger. 800 simulated paths was deemed a reasonable number in the case studies following, to maintain the balance between the accuracy and the time required.
- Number of points to use in estimating mean and quantile processes (range from 0 to 200; the number of points used for the case studies was set to 100, following the suggestions in the "poisson" package).

7.2.3. Bayesian models

The "accrual" package [40] has been built to implement Bayesian models, where the expectations of the research team can be translated into prior information at the design

stage, whilst during trial conduct it can be combined with the real accrual data to update the posterior distribution and provide an updated prediction about future recruitment.

Gajewski *et al* [32] introduced a Bayesian model for recruitment prediction where they assume that the waiting times between patient arrivals w_i are exponentially distributed with mean θ ($w_i \sim \exp(\theta)$), where θ represents the average accrual time for the i^{th} subject. The conjugate prior for θ is the inverse gamma distribution as defined below.

The required sample size of patients is established after discussion within the team to answer the following questions:

- How long will it take to recruit the predefined number of patients? &
- On a scale 1-10, how confident are in your previous answer?

T is the answer to the first question and *P* divided by 10 is the answer to the second one. The prior distribution then for θ is defined as follows:

$\theta \sim IG(nP, TP)$ where *n* is the sample size target, where *P* as defined above can be considering to be a scaling parameter.

In the beginning of the trial, when there are no patients recruited, the posterior distribution of θ relies entirely on the prior specification.

As the trial progresses and accrual data are available, the posterior distribution can be updated by incorporating the initial expectations and the current accrual data. If m represents the number of patients recruited until the time of the revised prediction and t_m represents the recruitment period elapsed, the posterior distribution is

$$\theta/w \sim IG\ (nP+m,\ TP+t_m)$$

The posterior mean is

$$E[\theta/w] = \frac{TP + t_m}{nP + m - 1} \approx \left(\frac{nP}{nP + m}\right)\frac{T}{n} + \left(\frac{m}{nP + m}\right)\frac{t_m}{m}$$

which is the weighted average of the prior mean (T/n) and the mean of the observed data (t_m/m) and the weights are proportional to the prior and observed sample sizes respectively.

In a subsequent publication by Jiang *et al*, the authors provided a hierarchical extension to the model with different options about the prior distribution; (i) informative prior, (ii) accelerated prior and (iii) hedging prior [64] and these options for the prior distribution can be selected within the user interface.

7.2.3.1. Bayesian model with Informative Prior (IP)

The posterior predictive distribution for the number of patients yet to be recruited in the Bayesian model with the informative prior is defined as the negative binomial. A negative binomial is parameterised by the number of successes and the probability of a success. In this scenario the number of successes is set to equal the recruitment target and the probability of a success is defined as $Prob = \frac{(TP+t_m)}{(TP+T_p)}$

where T= Target completion time, P= prior certainty with a range 0-1 and t_m= recruitment time elapsed. T_p is the specific time at which we want to predict recruitment, for example when we would like to see how many patients we will be able to recruit during the first year of recruitment, then T remains the same while T_p equals 12 months. A common scenario is when T_p=T, which represents the overall recruitment target time.

- Setting prior certainty to 1 and assuming that T is large in comparison to t_m then the probability of success approximates 0.5.
- Setting prior certainty to 0 then the probability of success becomes the proportion of the accrual time spent such that the probability of success increases as time elapses.

From the formula for the probability of success, the impact of the prior certainty can be understood. The lower the prior certainty, the smaller the probability of success. If time observed to date is small in comparison to the recruitment period overall then the probability of success approximates 0.5 when certainty is set to 1; as a probability of success, this may be interpreted as a pessimistic.

The prior certainty controls the spread of the prior distribution in an inverse manner such that high values of this parameter result is low variance of the prior.

7.2.3.2. Bayesian model with Accelerated Prior (AP)

In the Bayesian model with the accelerated prior, the negative binomial is the posterior predictive distribution for the remaining subjects, with the probability of

success set to $Prob= (TP+t_m)/(TP+T_p)$ as shown in the previous model. However the prior certainty, *P* is defined in a different way in an ongoing trial; instead of giving the option to the user to define the value for the prior certainty from zero to one, now this depends on the number of recruited patients so far with the formula being as follows: $P=1-m/n$, where m is the number of patients up to date and n is the number of patients to be recruited overall.

When there are no accrual data available, then *P* is 1 and the use of an accelerated prior is the equivalent of the informative prior with prior certainty increased to 100%.

When observed accrual data become available, the predictive distribution becomes the weighted average of the prior distribution and the actual observed data. As more data are collected, the weighting of the current observed data increases, while the weighting of prior information decreases. The method above allows for the recruitment time passed and numbers recruited to date by deducting those totals from the overall values. In this approach, the observed values are used to determine the prior certainty.

7.2.3.3. Bayesian model with Hedging Prior (HP)

In the Bayesian model with hedging prior, patient enrolment is modelled as Poisson with parameter lambda (λ). In an ongoing trial, lambda is assigned a gamma prior distribution with shape and rate parameters Gamma ($nP+m$, $TP+t_m$). The prior certainty *P*, which indicates the similarity of the current trial with historical information, is assigned a uniform distribution (0, 1) in the hedging prior, thus adding a hierarchical level to the prior.

The posterior predictive distribution for the number of patients remaining to be recruited is the negative binomial, which results from multiplying the posterior distribution of theta $\theta|w \sim IG(nP + m, TP + t_m)$

with the distribution of the remaining subjects, which is Poisson $(\frac{T-t_m}{\theta})$ and where the prior certainty *P* is not a constant number but is assigned a uniform distribution, as described above. If the prior is off target, the hyperparameter converges to zero, representing a down weighting of the strength of the prior distribution.

As discussed in Jiang *el al* [39, 64] the closed-form solution provided indicated that for the remaining subjects to be recruited in a fixed time the posterior distribution is negative binomial, while for the time frame required to recruit a prespecified number

of participants, the posterior predictive distribution is inverse beta, with parameters $\alpha = n - m$ and $\beta = nP + m$, where alpha represents the remaining number of patients to be recruited and beta the sum of prior belief about the sample size and the actual number of patients recruited so far.

7.2.3.4. Bayesian model with Informative Prior in a multicentre study

In a multicentre clinical trial, the contribution of centres in overall patient recruitment is very important in determining whether or not patient recruitment will be completed on time. In this Bayesian model the user has the option to upload a csv file with the number of centres, the duration in months for which each centre has been active and the number of patients recruited so far from each centre. Each row in this file represents one centre.

Additionally, the target sample size and the target completion time need to be defined, as well as the prior certainty, which represents investigators' prior beliefs about the progress of recruitment in the formula of the informative prior, as described in the section 7.2.3.1. Bayesian model with Informative Prior (IP) above. All these parameters in combination with the information in the csv file uploaded, will be used to define the parameters of the negative binomial, which is the predictive distribution for the remaining number of patients and it is applied for each centre separately. The information about the number of centres participating (J), the time elapsed (T_m), the start date for each centre (T_{sj}) and the sample observed to date for each centre (m) can be extracted from the csv file. The parameter T_{pred} is specified as the time at which we want to predict recruitment; see section 7.2.3.1. Bayesian model with Informative Prior for more details. In the common scenario when we want to define patient accrual for the overall recruitment time, T_{pred} can be set as T. The parameters of the predictive posterior distribution are presented below:

$$r = n/J * P + m$$

which represents the number of subjects expected per centre and the probability of success

$$P = \frac{T * P + (T_m - T_{sj})}{T * P + (T_{pred} - T_{sj})}$$

which needs to be updated for each centre separately depending on the time when centre opened, the time elapsed and the expected recruitment duration. The output

from this model is a list which contains the median and the 95% Prediction Interval for each centre, as well as the vector resulting from the matrix with row=number of simulation and column=number of centres, which presents the overall number of patients expected to be recruited with the contribution of all centres. The results are presented in a tabular format and a recruitment graph.

7.2.4. Availability

The shiny application is hosted on the web with Shinyapps.io. (https://www.shinyapps.io/) and is available at the following website

(https://recruitment-prediction.shinyapps.io/Shiny_Recruitment_Prediction_2020/). The R code developed for the Shiny application is provided in the Appendix D. The application will be hosted in the main page of the Liverpool Clinical Trials Centre (LCTC) website http://www.lctc.org.uk/Home , together with the new web-based tool described in chapter 8 and will be available to the researchers involved in clinical trials.

7.3. Case Studies

Recruitment data from the EcLiPSE and ROAM clinical trials have been used for the demonstration of the models. Study parameters such as the required sample size, the expected duration of the trial and the monthly expected recruitment rate for the EcLiPSE trial, have been extracted and used for the illustration of the HPP, NHPP and Bayesian models at the planning stage of the trial, when no accrual data are available. Accrual data from ROAM study have been used at the interim point to demonstrate how the same models in the application can be used for the monitoring of patient recruitment and reprofiling of the recruitment curve.

7.3.1. EcLiPSE study

The EcLiPSE study, “Emergency treatment with Levetiracetam or Phenytoin in Status Epilepticus”, is a pragmatic randomised controlled trial of intravenous levetiracetam versus intravenous phenytoin in terminating acute, prolonged tonic-clonic seizures including convulsive status epilepticus in children [137]. The trial was inclusive of all males and females aged 6 months up to 18 years, who presented with convulsive status epilepticus that failed to respond to first-line treatment.

EcLiPSE planned to open approximately 25-30 Emergency Departments (EDs) in NHS secondary and tertiary hospitals in the UK. Eligible children were to be

randomised to receive either intravenous levetiracetam 40mg/kg or intravenous phenytoin 20mg/kg. The primary endpoint in the study was the time to cessation of all visible signs of convulsive seizure activity and the study duration per participant was 14 days.

The trial planned to include an 18-month internal pilot involving five centres; however additional centres were to be opened during this period.

The 18-month internal pilot was timed to enable the five centres involved to be opened, fully familiar with trial procedures and achieving the optimal recruitment rate. This time frame would also allow each centre a minimum of six months of active recruitment at the optimal level to demonstrate their recruitment rates and allow prediction of trial activity into the main phase of the trial.

Success criteria of the pilot based upon recruitment were:

1. If the predicted recruitment period is 36 months or less, proceed to main trial.
2. If the predicted recruitment period is between 36 months and 48 months, consider and introduce ways to reduce this e.g.:

   a. increase the number of centres

   b. address training needs

   c. determine whether new evidence suggests eligibility criteria could be widened.

Then proceed to main trial with amendments.

3. If the predicted recruitment period is more than 36 months, and no obvious solutions exist, abandon the plan for the main trial.

The study information required to implement the models proposed in this chapter for the EcLiPSE trial are listed below as they were provided by the EcLiPSE team:

- Expected initiation date for the first centre: March 2015
- Expected initiation for the 25 centres participating: March 2015 until February 2018
- Expected recruitment duration: 36 months
- Required sample size: 308 patients to be randomised, which will allow for 10% loss to follow up.
- Staggered initiation times for the centres have been incorporated

Table 14 below presents the month when each centre was expected to open and the average monthly target, as they were defined by the research team at the design stage of the study.

Centre	Month expected to open	Monthly target sample size
1	March 2015	0.71
2	April 2015	0.5
3	May 2015	0.36
4	June 2015	0.28
5	July 2015	0.58
6	August 2015	0.36
7	September 2015	0.51
8	October 2015	0.53
9	November 2015	0.62
10	December 2015	0.5
11	January 2016	0.68
12	February 2016	0.5
13	March 2016	0.69
14	April 2016	0.54
15	May 2016	0.57
16	June 2016	0.7
17	July 2016	0.63
18	August 2016	0.66
19	September 2016	0.47
20	October 2016	0.5
21	November 2016	0.46
22	December 2016	0.5
23	January 2017	0.53
24	February 2017	0.5
25	March 2017	0.54

Table 14: Expected opening dates and monthly recruitment target for each centre in the EcLiPSE trial

In addition to the staggered time openings, all centres were expected to start patient recruitment slowly; during the first month they would have 33% capacity, the following month 66% capacity and it is not until the third month that each centre

would reach full capacity for patient recruitment. This trend has been implemented to all centres in this study.

Routine data sources were used to identify the catchment areas of each centre and the size of the patient population. This was coupled with clinical knowledge of the expected event rate.

I. Homogeneous Poisson Process

At the design stage of the trial the plan was to recruit 308 participants from 25 centres in a period of 36 months. The HPP model assumes a constant average accrual rate throughout the recruitment period. The average recruitment rate is calculated as the target sample size divided by the expected recruitment duration, $308/36 \approx 8.5$ participants to be recruited on average per month, which defines the lambda for the HPP model.

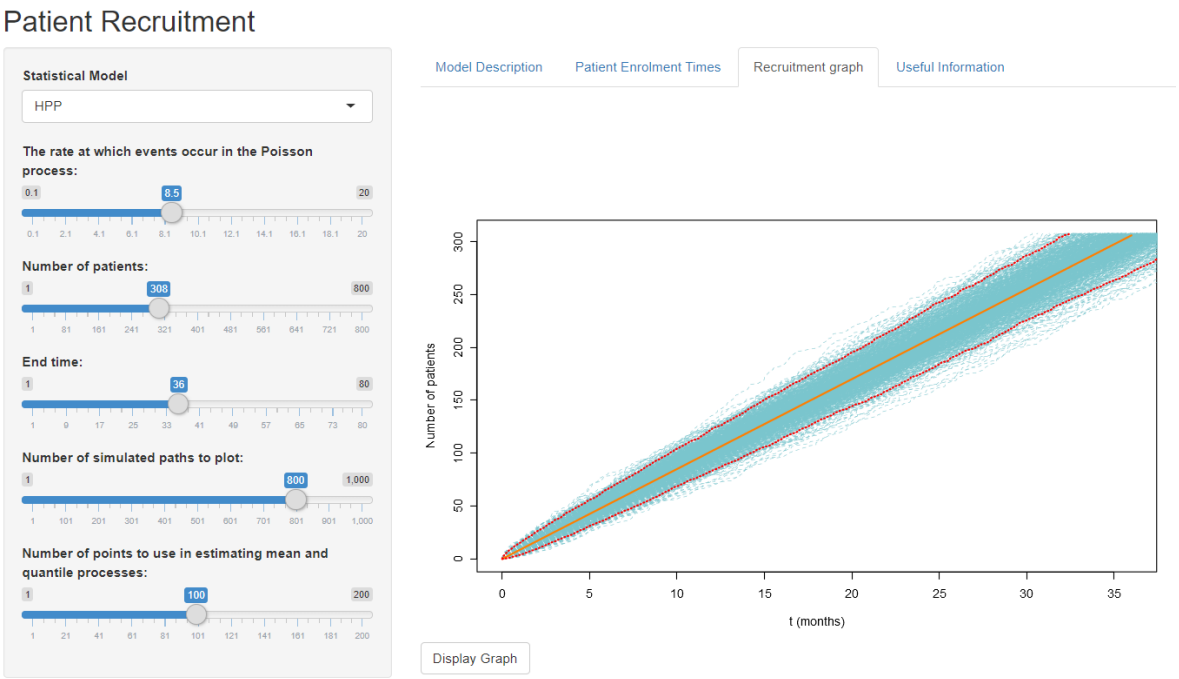


Figure 13: Homogeneous Poisson Process - EcLiPSE study

Based on this model, which assumes that the calculation of lambda is correct, the table with the patient enrolment times presented in the second tab shows that the average time of recruitment (orange line) for the first participant is approximately 3.6 days (0.12 month) and for the last patient is 36.26 months. The 2.5% and 97.5% quantiles presented in tab two reveals that the recruitment period may need to be set at 41 months to achieve the target sample size (32.27, 40.58) when the average recruitment

rate is set to 8.5 patients per month. While this method is simplistic, the parameter estimation is tangible and it improves on the deterministic approach by taking into account the uncertainty of the recruitment process and providing the mean and the quantiles to inform about the level of variance about the mean, allowing inference on best and worst outcomes, as shown in Figure 13 above.

II. Non Homogeneous Poisson process

In the NHPP model, it is assumed that for a multicentre study, the average recruitment rate will increase linearly from the first month until it reaches 100% as more centres are going to open. In the EcLiPSE trial, this non-homogeneous time period is defined as March 2015 – March 2017, by setting the non-homogeneous recruitment time parameter equal to 25 months. This period in the study represents the centre staggered initiation times. From April 2017 when all centres are expected to be open, the average accrual rate is expected to be constant, 13.4 participants on average per month and this figure results from the sum of the final column in Table 14 above.

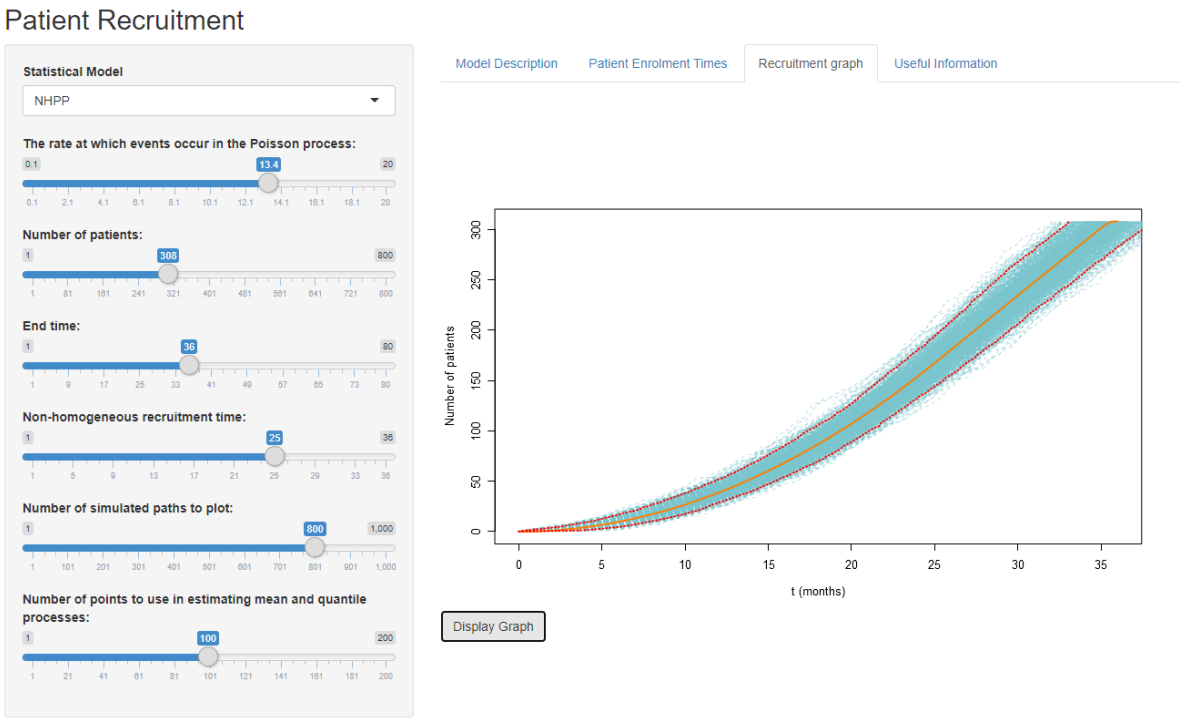


Figure 14: Non Homogeneous Poisson Process - EcLiPSE study

Based on the NHPP model, on average approximately 35.5 months of recruitment are required to achieve the target sample size as shown in Figure 14. The table with the patient enrolment times is presented in the second tab and the time of recruitment for

the first participant is approximately 52.2 days (1.74 month) and for the last patient is 35.49 months. The 2.5% and 97.5% quantiles show that recruitment period may be set at 38.2 months to achieve the target sample size (33.06, 38.21).

Patient recruitment is slower at the beginning in the NHPP model in comparison to the HPP, and this could be considered a more realistic situation in a multicentre trial where centres are expected to open at different times, thus the average number of patients to be recruited during the first period is lower. The early stages of recruitment are often used to demonstrate trial viability within an internal pilot. Therefore, overestimation of the recruitment predictions in this period increases the risk that the trial will be considered unfeasible. The advantage of the NHPP model is the definition of this non-homogeneous period, which if correctly defined by the user depending on the assumptions at the design stage, will potentially produce a more accurate recruitment plan.

III. Bayesian model with Informative Prior

The posterior predictive distribution for the number of patients to be recruited in the Bayesian model with the informative prior (IP) is defined as the negative binomial. A negative binomial as described in the section above, is parametrised by the number of successes and the probability of a success. In the EcLiPSE study the number of successes equals the recruitment target, which is 308 participants, and the probability of success is defined as

$$Prob = \frac{TP+t_m}{TP+T_p}.$$

At the design stage t_m=0, when no previous accrual data are available, T is set to 36 months, T_p is also set to 36 months defining the expected end of recruitment period, and the prior certainty is set to 50% assuming that the investigator is 50% confident that the accrual can be reached within the planned recruitment period. Note 50% used here is arbitrary; this may be a difficult parameter for the researcher to confidently set and natural inclinations may be to set this too high. The results are presented in Figure 15 below. The horizontal line indicates the target sample size. The white line is the estimate of the prediction and the grey funnel shows the prediction intervals. The histogram of estimated total accrual in 36 months is shown on the right side of the graph.

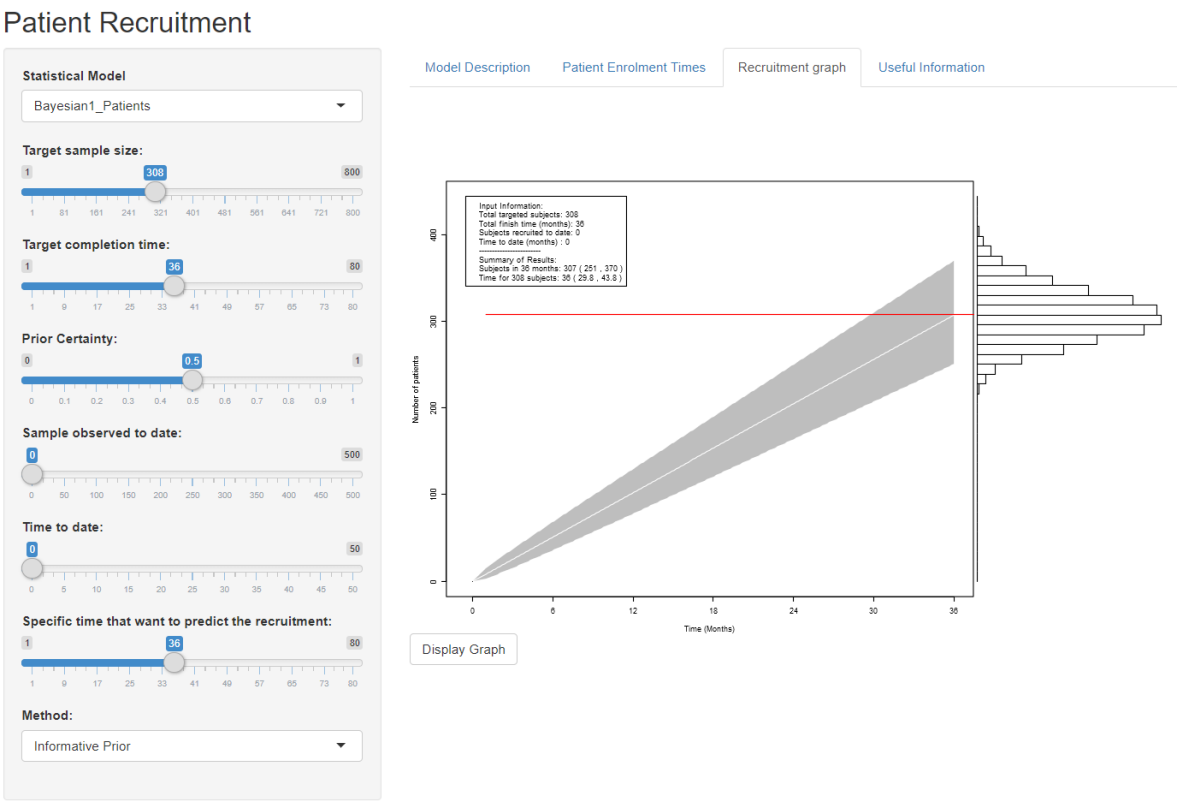


Figure 15: Bayesian Model with Informative Prior for prediction of the number of subjects that can be recruited in a fixed time frame - EcLiPSE study

In this example, there will be 307 patients recruited in 36 months, with 95% prediction interval (251, 370). It will take 36 months with 95% prediction interval (29.8, 43.8) for the investigators to recruit 308 patients. The relevant recruitment graph produced for the prediction of the time required to recruit a certain number of subjects is shown in Figure 16 below, which is defined as Statistical model = Bayesian1_Time in the Shiny application website.

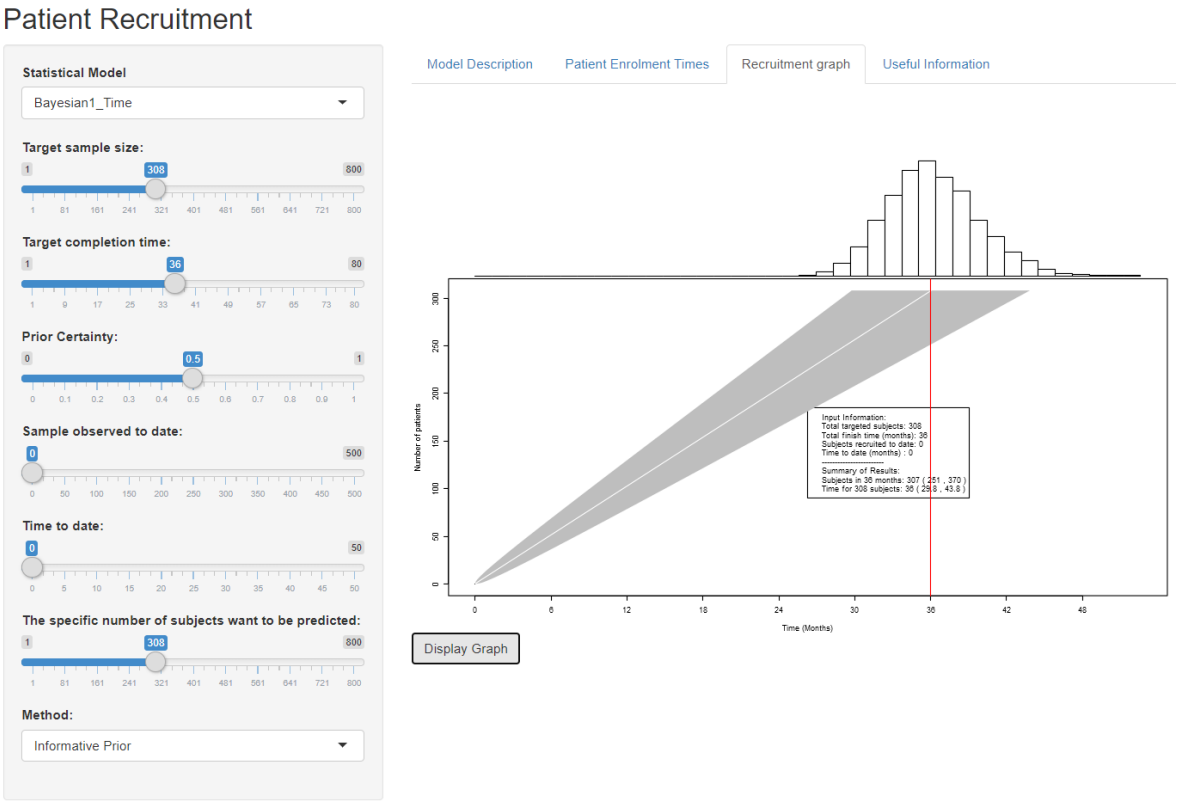


Figure 16: Bayesian Model with Informative Prior for prediction of the time required to recruit a certain number of subjects - EcLiPSE study

IV. Bayesian Model with Accelerated Prior

In the Bayesian model with the accelerated prior (AP), we need to define the number of subjects and the probability of success $Prob=\frac{TP+t_m}{TP+T_p}$. As in the previous model, the number of subjects to be recruited in 308, but the definition for the prior certainty in the probability of success formula is $P=1-m/n$, where m is the number of patients up to date, which is equal to zero in our example and n is 308. Thus, when there are no accrual data available, P is 1, t_m=0 and T_p=T.

Based on this model, the recruitment target of 308 patients will be reached in 36 months with 95% prediction interval (30.7, 42.2), or alternatively by fixing the recruitment period at 36 months to achieve the sample size target of 307 patients, a 95% prediction interval for the number of patients at that time is (261, 358). See Figure 17 below.

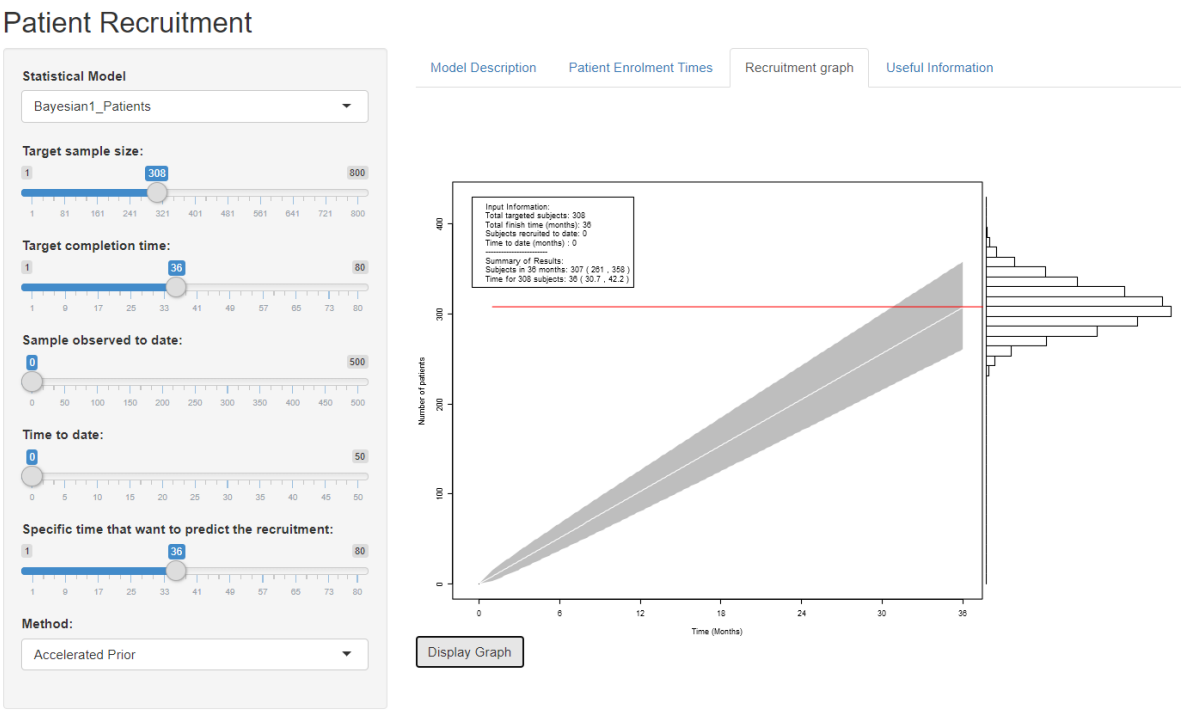


Figure 17: Bayesian Model with Accelerated Prior for prediction of the number of subjects that can be recruited in a fixed time frame - EcLiPSE study

V. Bayesian model with Hedging Prior

In the Bayesian model with hedging prior (HP) the number of successes is 308 patients, but the prior certainty P is not a constant number as it was in the two previous Bayesian models; instead is assigned a uniform distribution, $P \sim U(0, 1)$, which represents the investigators' confidence in the recruitment performance of the trial.

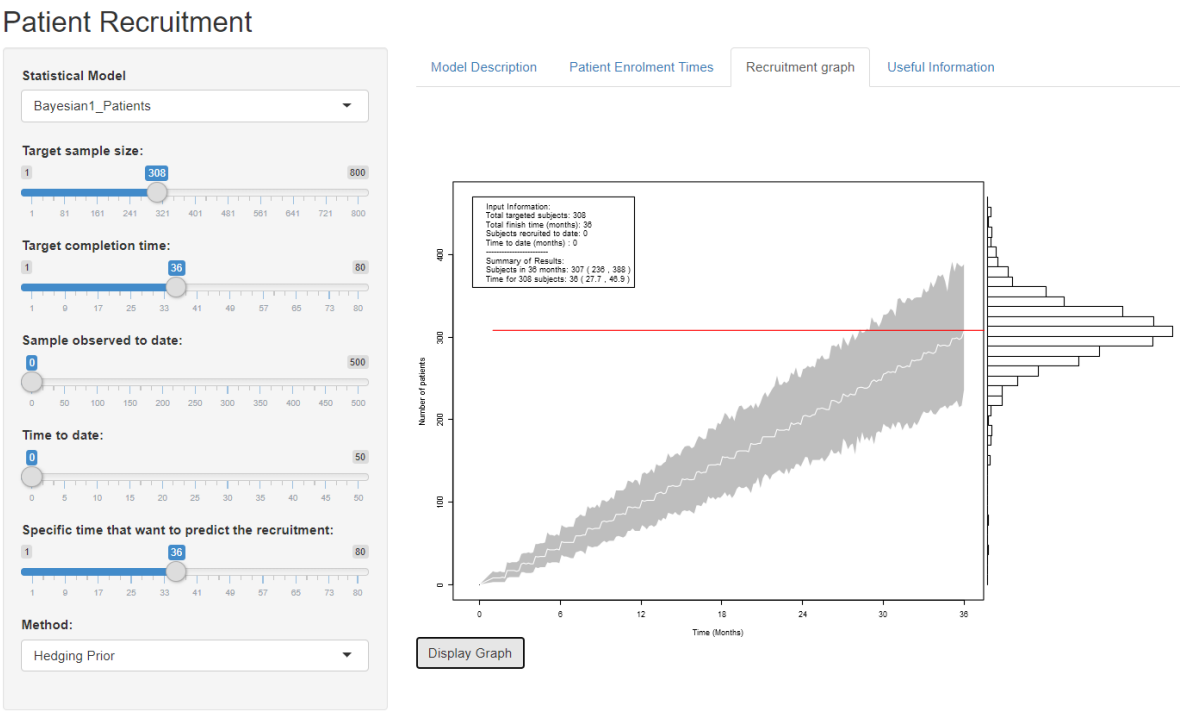


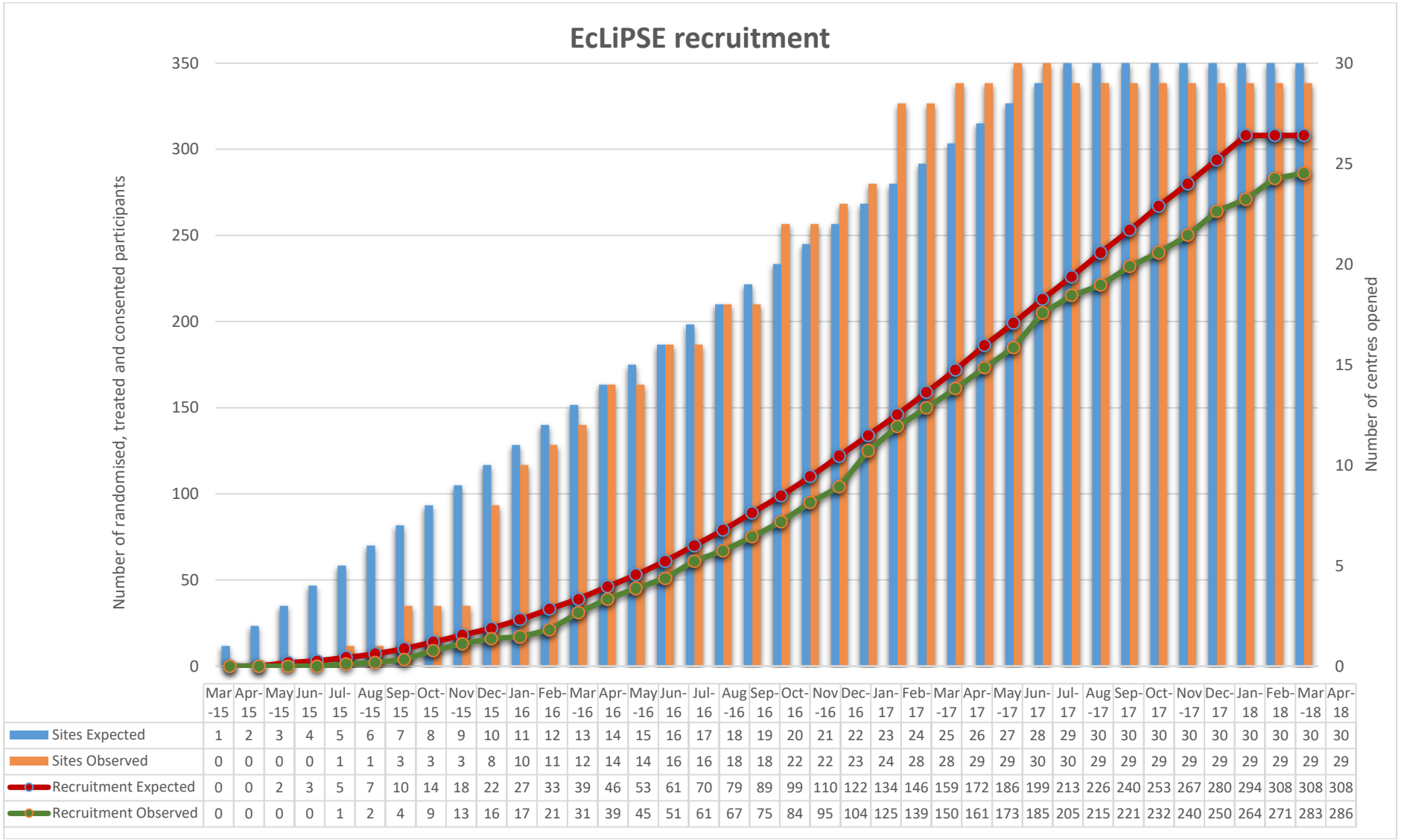
Figure 18: Bayesian Model with Hedging Prior for prediction of the number of subjects that can be recruited in a fixed time frame - EcLiPSE study

This model predicts that the recruitment target will be reached in 36 months with 95% prediction interval (27.7, 46.9) or alternatively, after 36 months we will have achieved the sample size of 307 participants with 95% prediction interval (236, 388), as shown in

Figure 18 above.

April 2019: Progress in comparison to the original prediction

Participant recruitment for the EcLiPSE study started in July 2015 when the first participant was recruited (17/07/2015) and was completed in April 2018 (as shown in Figure 19) after 286 participants were randomised with consent; the actual recruitment period for 286 participants was 34 months compared to the 36 months initially expected for recruitment of 308 participants (March 2015 - February 2018) [113]. The trial stopped at 286 participants following discussion with the Trial Oversight Committee as the adjustment for loss to follow up of 10% used to inflate the sample size calculation was not required.



	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18
Sites Expected	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	30	30	30	30	30	30	30	30
Sites Observed	0	0	0	0	1	1	3	3	3	8	10	11	12	14	14	16	16	18	18	22	22	23	24	28	28	29	29	30	30	29	29	29	29	29	29	29	29	29
Recruitment Expected	0	0	2	3	5	7	10	14	18	22	27	33	39	46	53	61	70	79	89	99	110	122	134	146	159	172	186	199	213	226	240	253	267	280	294	308	308	308
Recruitment Observed	0	0	0	0	1	2	4	9	13	16	17	21	31	39	45	51	61	67	75	84	95	104	125	139	150	161	173	185	205	215	221	232	240	250	264	271	283	286

Figure 19: Recruitment graph of EcLiPSE study

Note: during the first 8 months of recruitment, 6 sites had a temporary suspension to recruitment. This resulted in 2 days lost to recruitment in July 2015, 5 days lost in Aug 2015, 70 days lost in Jan 2016, and 43 days lost in Feb 2016.

In the EcLiPSE case study, the emergency setting of the paediatric trial requires patients to be randomised with informed consent obtained later. This is in contrast to the majority of clinical trials where there is sufficient time to approach participants prospectively for consent. This feature could have a positive impact on recruitment, leading to recruitment rates in line with the initial predictions.

In an attempt to evaluate the model's performance based on the initial plan, which was to recruit 308 participants, the use of the NHPP model allowed for slower recruitment at the beginning of the trial, which is to be expected in a multicentre study with staggered centre opening times. This trend is evident when comparing the NHPP and HPP recruitment graphs. Both models conclude approximately the same results regarding the number of months required to reach the target sample size, 36.26 months (HPP) versus 35.5 months (NHPP), with narrower quantiles in the NHPP model (33.06, 38.21) versus (32.27, 40.58) in the HPP model.

Comparing the Bayesian models, the Bayesian model with AP sets P at 100% in comparison to the Bayesian model with IP, where P can be determined by the user (and which we set to 50%). The 95% prediction interval in the Bayesian model with IP for the number of patients expected to be recruited in 36 months is (251, 370) while in the Bayesian model with AP is (261, 358) and this can be explained with the value of the prior certainty *P*. The 95% prediction interval is much wider in the Bayesian model with the HP (236, 388), which can be explained by the use of the uniform distribution assigned as the prior for P. This result is comparable to the Bayesian model with IP when the value for the prior certainty is approximately $P \approx 0.25$, meaning that in the production of the posterior distribution the prior would be given weight equivalent to one fourth of the proposed sample size.

Use of Bayesian models utilising observed accrual data from the internal pilot

The internal pilot was planned for 18 months (March 2015 – August 2016) and one of the aims was to use the demonstrated recruitment rates to inform prediction of trial recruitment in the main trial. As we have already discussed, the benefit of a Bayesian approach is in monitoring of patient recruitment, when observed accrual data are

combined with investigators' prior beliefs to predict future recruitment performance of the trial.

In August 2016, 18 centres were open and actively recruiting; 67 participants had been recruited versus 79, which was the expected number of participants to be recruited by this timepoint.

Question: Having already 67 participants recruited in 18 months, is it feasible to recruit the remaining 308-67= 241 participants within 18 months?

The accrual data from the internal pilot have been used to inform the Bayesian models and the results are presented in Table 15 below.

Model	**Target sample size**	**Target completion time**	**Number of patients expected to be recruited by month 36**	**Recruitment time to reach the target sample size**
Bayesian with Informative Prior Prior certainty *P* sets at 100%	308	36	192 patients, PI[1] = (168, 218)	52.7 months, PI = (47.5, 58.7)
Bayesian with Accelerated Prior	308	36	187 patients, PI = (163, 213)	54.1 months, PI = (48.5, 60.7)
Bayesian with Hedging Prior	308	36	137 patients, PI = (115, 161)	80.4 months, PI = (65.3, 101.8)
Bayesian with Informative prior in a multicentre study (18 centres considered) Prior certainty *P* sets at 100%	308	36	226 patients, PI = (196, 256)	Not applicable

Table 15: Results of ongoing recruitment prediction for EcLiPSE study

[1] *(2.5%, 97.5%) Prediction Interval (PI)*

The different values of the prior certainty *P* are explained below:

- In the Bayesian model with the informative prior, if the research team is confident enough that they will reach the target sample size on time, the value of prior certainty *P* could be set to 100%.

- In the second Bayesian model, the prior certainty is set at 78%, $P=1-m/n$, where m is the number of patients recruited to date (m=67) and n the overall number of patients expected (n=308).
- In the third Bayesian model, where the behaviour of the prior certainty is explained by the Uniform (0, 1) distribution, the observed data force the distribution of *P* downward, thus limiting the strength of the prior distribution. The expected number of recruited participants based on this model is far behind the target even if we consider the upper bound of the prediction interval, 161 versus 308 required.
- In the Bayesian model with the informative prior where the observed accrual data from each one of the 18 open centres have been incorporated and the value of prior certainty *P* is set to 100%, the prediction is more optimistic but still far from the desired target.

As we already discussed the trial was completed within 34 months after 286 participants were randomised with consent. The actual number recruited is not included in any of the prediction intervals of the Bayesian models. This could partially be explained from the low recruitment during the first 18 months of the trial, which was 67 instead of 79 expected, but arguably this difference is not particularly large. Even if the expected sample size (79), which was calculated using the deterministic approach, was reached after 18 months, the result from the Bayesian model with IP for example, demonstrates that 208 patients will be recruited by the end of 36-month period with the prediction interval being (183, 234). In fact for the Bayesian model to provide results predicting what was observed, then during the first 18 months, patient recruitment of approximately 154 participants (half of the target sample size recruited in half of the expected recruitment time) would be required, so that the Bayesian model with the informative prior where P=100%, would have predicted that 308 participants can be recruited in the next 18 months with the 95% prediction interval being (281, 337).

Providing a wider prediction interval for the recruitment target explains the uncertainty of the recruitment process, and this is acceptable at the design stage of the trial when no accrual data are available. However, in this case study even when accrual data have been used, in combination with the prior beliefs, to update future prediction, the results are not representative of the actual trial recruitment

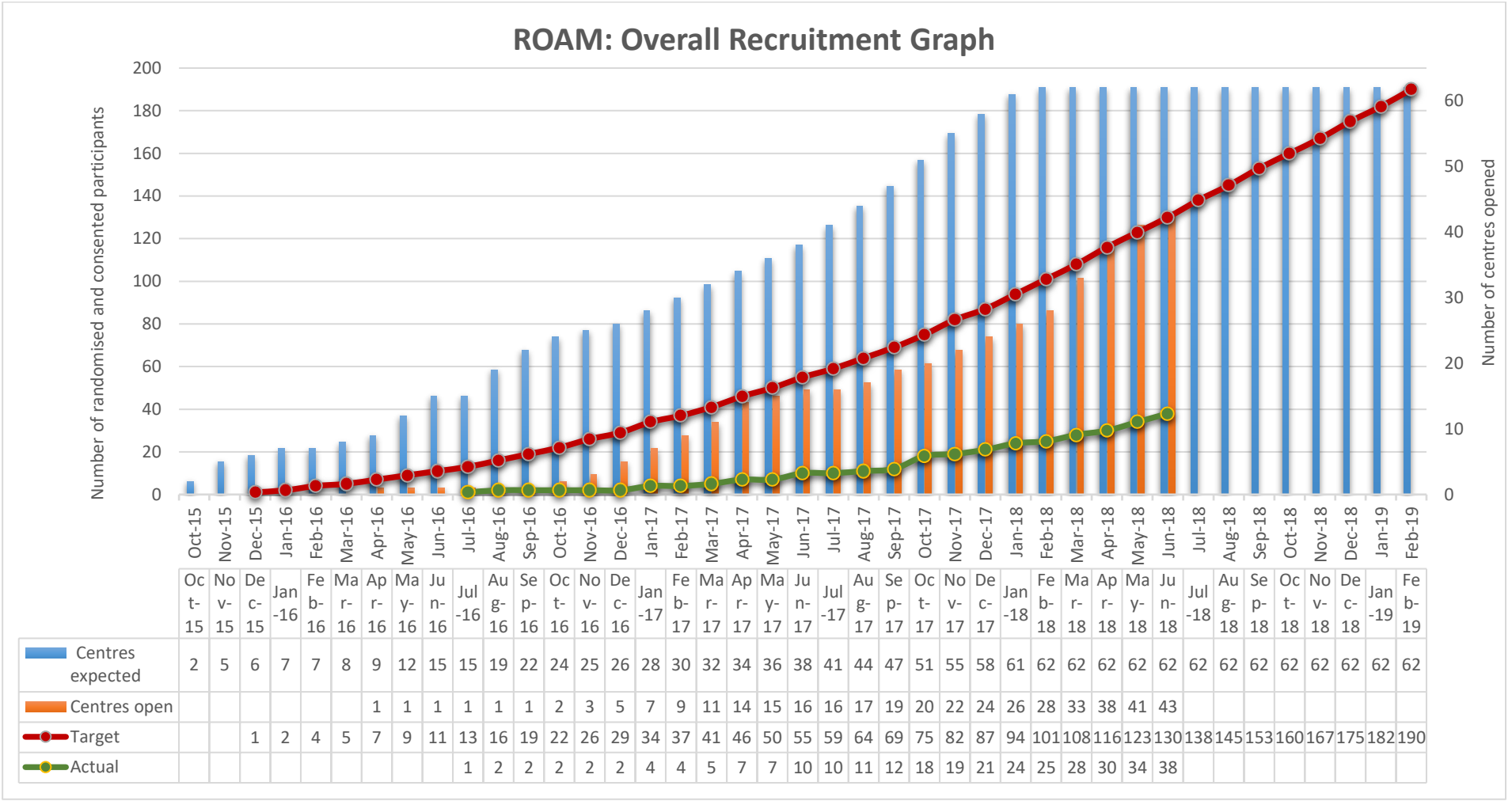
achievement. This is an important note to be made when considering the Bayesian models to evaluate recruitment figures and to make a decision of whether or not to proceed to the main trial. If the research team based their decision on any of the Bayesian models summarised in Table 15, there would have been an increased risk that the trial could be terminated.

7.3.2. ROAM study

The ROAM trial (Radiation versus Observation following surgical resection of Atypical Meningioma) is an international multi-centre, phase III, randomised controlled trial comparing early adjuvant radiotherapy (intervention) with observation (comparator) in patients who have undergone gross total resection of an intracranial atypical meningioma [138]. Patients with this rare condition were to be recruited from neurosurgical and oncology units in the UK, and via European Organisation for Research and Treatment of Cancer (EORTC) centres throughout Europe and TROG centres in Australia and New Zealand. Figure 20 below shows the centre initiation rates and recruitment rates across centres. The trial aimed to recruit 190 patients overall, with approximately 118 patients to be recruited in the UK. Patients will be followed for a minimum of 5 years post-surgery.

Initial planning

At the design stage of the trial, the plan was to recruit 190 patients from 62 (UK=22, EORTC=28 and TROG=12) centres in a period of 41 months beginning from October 2015 (October 2015 – February 2019). Figure 20 demonstrates staggered centre initiation times.



	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19
Centres expected	2	5	6	7	7	8	9	12	15	15	19	22	24	25	26	28	30	32	34	36	38	41	44	47	51	55	58	61	62	62	62	62	62	62	62	62	62	62	62	62
Centres open							1	1	1	1	1	1	2	3	5	7	9	11	14	15	16	16	17	19	20	22	24	26	28	33	38	41	43								
Target			1	2	4	5	7	9	11	13	16	19	22	26	29	34	37	41	46	50	55	59	64	69	75	82	87	94	101	108	116	123	130	138	145	153	160	167	175	182	190
Actual										1	2	2	2	2	2	4	4	5	7	7	10	10	11	12	18	19	21	24	25	28	30	34	38								

Figure 20: Recruitment graph of ROAM study

Progress in comparison to the original prediction

By June 2018, there were 19/22 UK centres open, 10 of which had randomised at least one patient. The EORTC had opened 16/28 centres and randomised 12 patients, and TROG had opened 9/12 centres and randomised one patient. This gave a total of 44 centres open, with an additional 18 centres remaining to be opened. The graph clearly demonstrates a delay in centre initiation rates.

Clearly having fewer centres open would impact the recruitment of participants. However, the screening data collected for the trial demonstrated that patient and clinician preferences, which were already allowed for in the recruitment rates proposed, were having a stronger impact than predicted. Qualitative research being conducted to tackle this issue is reported elsewhere [139].

Challenges for Ongoing Prediction

The expected accrual is heavily dependent upon centre initiations occurring as predicted. Eighteen centres are still to open with an additional 152 participants to recruit. In addition, centres that have recently opened have not had sufficient time to estimate a recruitment rate coupled with the difficulties of estimating recruitment rate in a rare disease. The following information will be used to re-profile patient recruitment.

Recruitment until June 2018

- 43 centres are open (one centre which opened in April 2017, closed in January 2018) with 38 participants recruited
- time elapsed= 24 months (July 2016 when 1st patient was randomised until June 2018 when the 38th patient was randomised)
- remaining recruitment period = 21 months (July 2018 – March 2020), with March 2020 being the new recruitment deadline
- 62-44=18 centres to be open
- 190-38=152 patients to be recruited

Future recruitment rates suggested

- July-September 2018, average rate= 4 patients per month
- October-December 2018, average rate= 5 patients per month
- January 2019-March 2020, average rate= 6 patients per month

These predicted recruitment rates reflect a reduction in those used within the original prediction. Clearly based on the observed recruitment rates, this number of patients per month is ambitious; however this represents a balance between satisfying funders and optimism that the patient preference issues could be addressed successfully.

I. Homogeneous Poisson Process for ongoing recruitment prediction

Question: Having already 38 patients recruited, is it feasible to recruit the remaining 152 participants within 21 months? The observed accrual data are used to make a more precise prediction about the average recruitment rate in the following months.

HPP model assumes a constant average accrual rate, which can be calculated as: (4*3)+(5*3)+(6*15) /21= 5.6 patients to be recruited per month, on average.

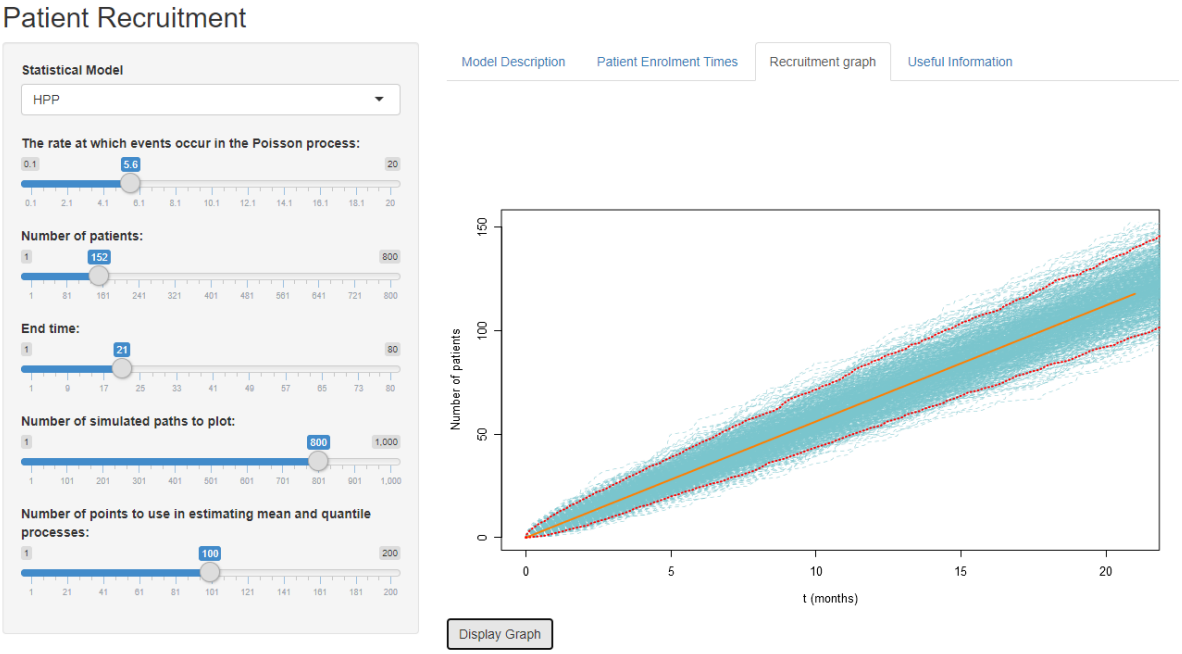


Figure 21: Homogeneous Poisson Process - ROAM study

Based on this model, the table with the patient enrolment times shows that the average time to recruitment of the first patient is approximately 5.1 days (0.17 months) and of the last patient (152) is approximately 27.14 months. The 2.5% and 97.5% quantiles (23.19, 31.53) presented in tab two show that the recruitment period may need to be set as high as 31.5 months to achieve the target sample size. Note that even the 2.5% quantile suggests that a longer period is required than the 21 months initially proposed.

II. Non Homogeneous Poisson process for ongoing recruitment prediction

In this model, the non-homogeneous time period is defined as the first six months of the recruitment period by setting the non-homogeneous recruitment time parameter equal to 6 months, as shown in Figure 22. In this example, this is the period from July to December 2018, where the recruitment rate increases linearly from zero until it reaches 100%. For ROAM the target recruitment rate increases from 4 to 6 patients per month. In the model the maximum recruitment rate of 6 is used and a probability is applied such that in the first month only one sixth of the events are observed, in the second month only two sixth of the events and so on, until the sixth month when recruitment rate reaches its maximum value and then all events following the 6-month period are admitted with probability 1 (month 6 included). This underestimates the numbers recruited over the first months. This underestimation will be present whenever this model is implemented for recruitment prediction at an interim phase, because the average recruitment rate does not begin from zero. However, in this example where there are still centres to open, this could be considered as a conservative approach; in any case the results from this model should be interpreted with caution.

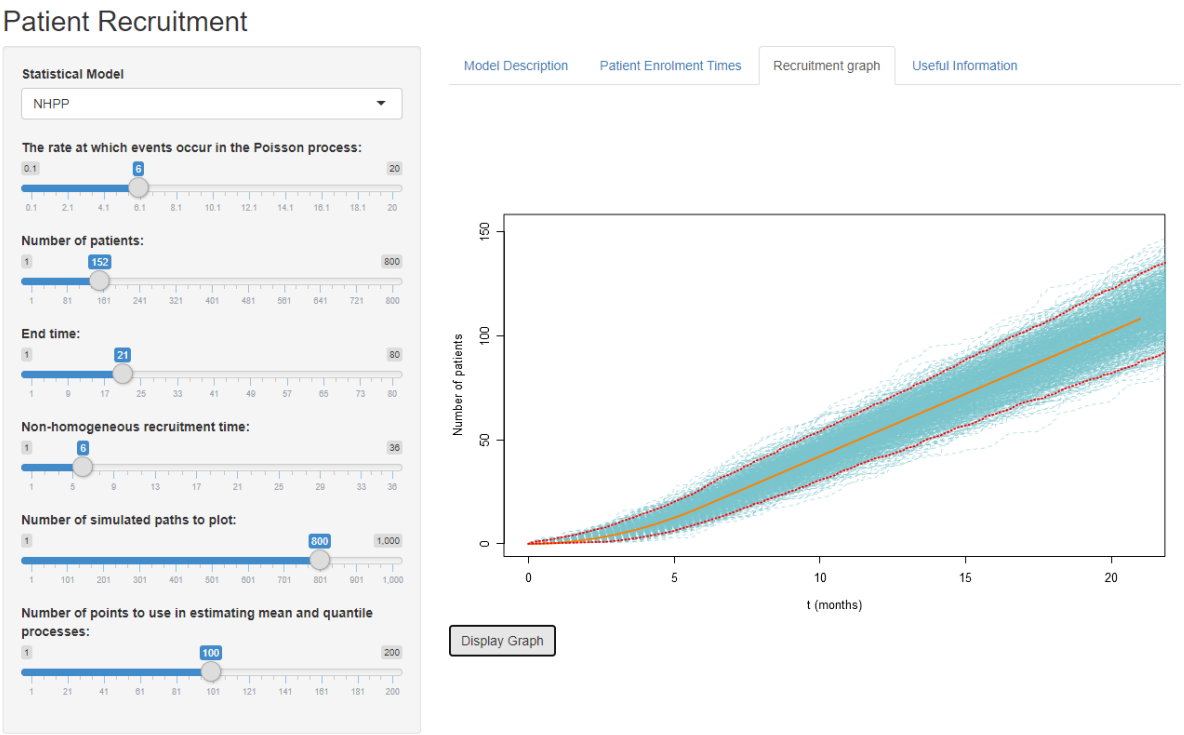


Figure 22: Non Homogeneous Poisson Process - ROAM study

Based on the NHPP model, approximately 28 (28.37) months of recruitment are required to achieve the target sample size. The 2.5% and 97.5% quantiles (24.2, 32.56) show that recruitment period may be set at 33 months to achieve the target sample size. The suggested average recruitment duration does not differ greatly between the HPP and NHPP models. This is a reflection of the short non-homogeneous recruitment period and the different expected rate used.

III. Bayesian Model with Informative Prior utilising observed accrual data

After recruiting 38 patients in a period of 24 months, we are expecting to recruit 152 patients in the following 21 months. The informative prior distribution is a negative binomial. A negative binomial is parameterised by the number of successes and the probability of a success. In this scenario the number of successes is set to equal the recruitment target and the probability of a success defined as

$Prob=\frac{TP+t_m}{TP+T_p}$ where T= 45 months, P= 0.5 to underline some uncertainty, t_m= 24 months and T_p is the specific time at which we want to predict recruitment, which can be simplified for the situation in which $T_p=T$=45 months.

Figure 23 below demonstrates that based on combination of the initial expectations and the accrual to date which is very slow, the recruitment target (190 patients) will be reached in 77.2 months with 95% prediction interval (66.1, 91.2) months. Alternatively, if the trial recruitment was required to be completed in 21 months (45 months in total), then the predicted number of patients will be 98 with 95% prediction interval (81, 117), well short of the desired 152.

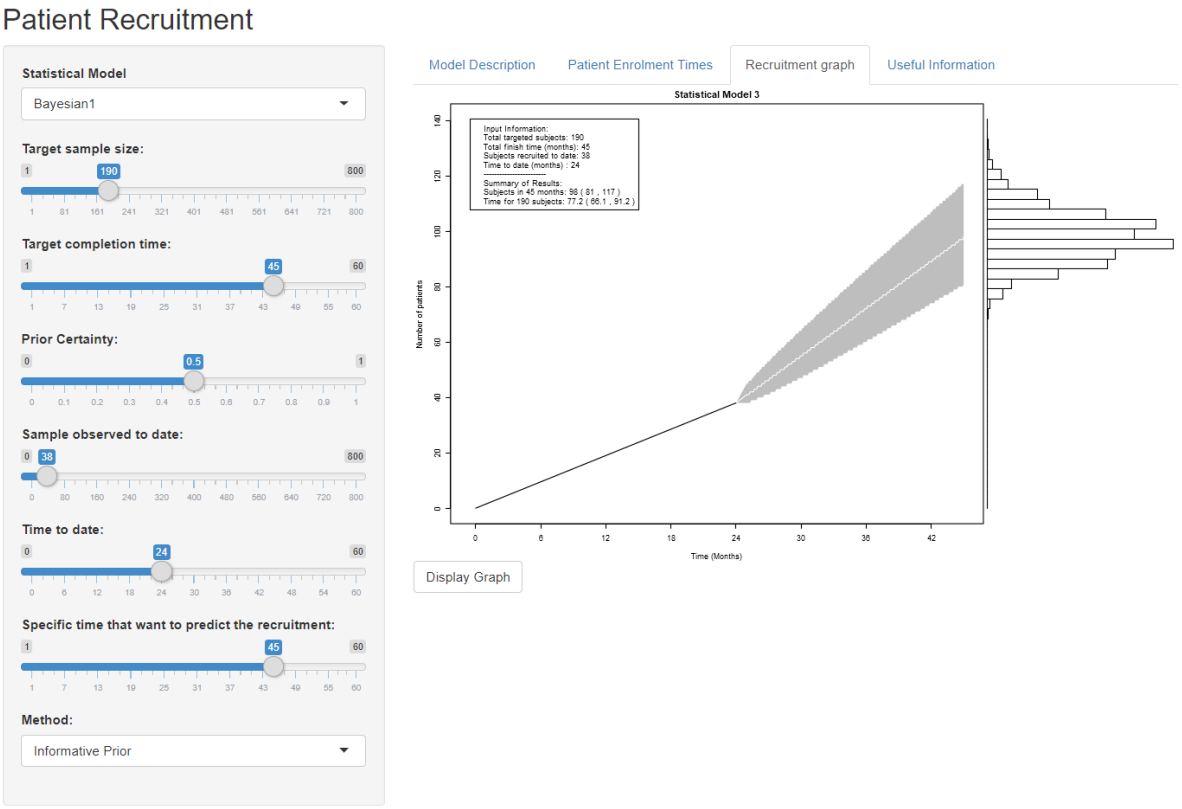


Figure 23: Bayesian Model with Informative Prior for prediction of the number of subjects that can be recruited in a fixed time frame - ROAM study

IV. Bayesian Model with Accelerated Prior utilising observed accrual data

This model allows for the calculation of the recruitment time passed and numbers recruited to date by deducting those totals from the overall values. In this approach, the observed values are used to determine the prior certainty. The prior certainty is set at 80%, *P=1-m/n*, where m is the number of patients recruited up to date (*m*=38) and n the overall number of patients expected (*n*=190), and the period of recruitment observed to date is truncated to start from first participant randomised (24 months).

When we are at the beginning of the clinical trial e.g. 6 months of recruitment in a trial of more than 3 year recruitment period, then the parameter t_m is small which means that the value for the fraction $Prob = \frac{TP+t_m}{TP+T_p}$ defined as the probability of success, will be lower in contrast to the value of the probability of success when further recruitment time has elapsed. In the second case the value for the t_m will be higher, so the value for the fraction will be bigger. The meaning behind a small/big value for the probability of success is that, when we are closer to the target, completion time reflects greater confidence in the prediction than when we are at the

beginning of the trial. In the ROAM study where the time elapsed is 24 months, the target completion time is 45 months, and not all centres are open to recruitment, we could say that we are approximately halfway through the study, which means that there is still uncertainty around recruitment, which should be considered.

Figure 24 demonstrates that at the end of recruitment on average 104 participants would be recruited (87, 124) demonstrating a likely shortfall in recruitment target with the time required to achieve the target requiring a considerable extension to allow a total recruitment period of 72 months (62.7, 83.4).

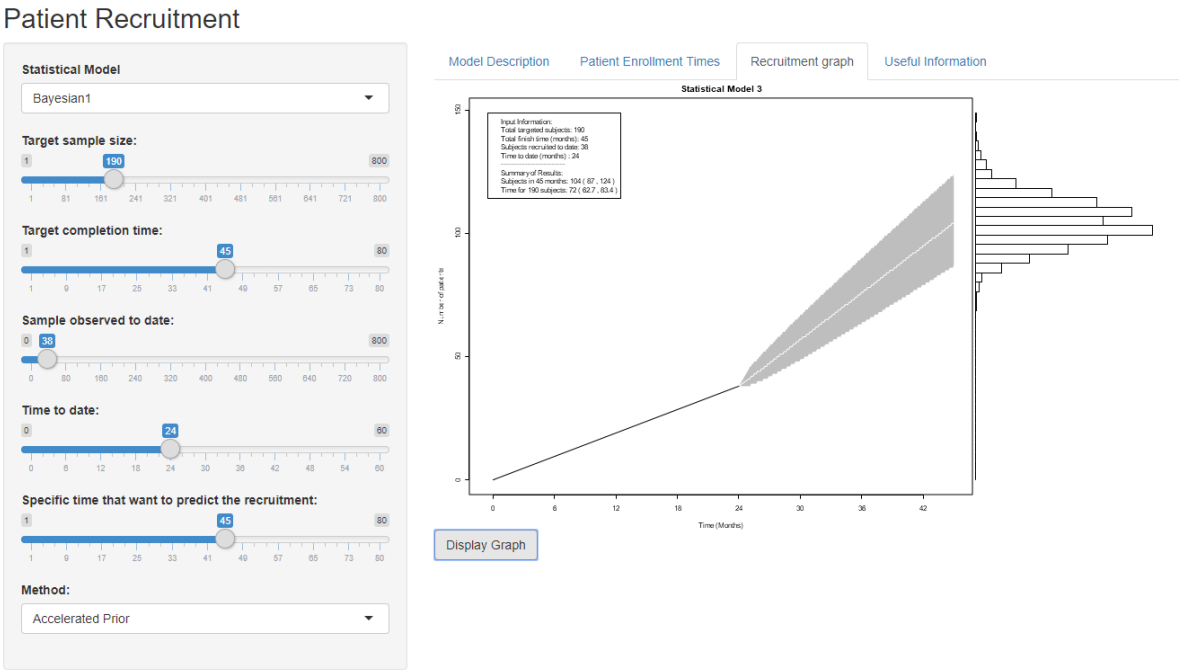


Figure 24: Bayesian Model with Accelerated Prior for prediction of the number of subjects that can be recruited in a fixed time frame - ROAM study

V. Bayesian model with Hedging Prior utilising observed accrual data

In the Bayesian model with hedging prior (HP), the prior certainty P is not a constant number as it was in the two previous Bayesian models, but is assigned a uniform distribution, $P \sim U(0, 1)$, which represents the investigators' confidence in the recruitment performance of the trial. The accumulated observed accrual data will force the distribution of P downward, if the prior is off target, limiting the strength of the prior distribution. All the other parameters have been defined as in the previous two Bayesian models.

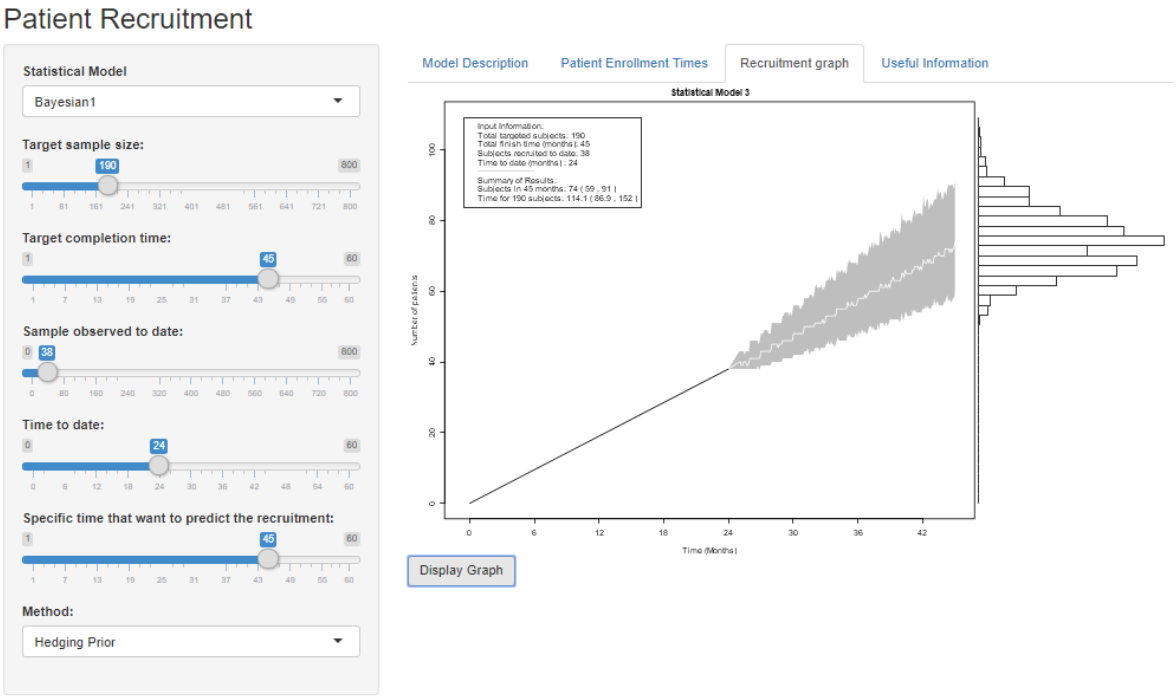


Figure 25: Bayesian Model with Hedging Prior for prediction of the number of subjects that can be recruited in a fixed time frame - ROAM study

As shown in

Figure 25 above, the recruitment target will be reached in 114 months with 95% prediction interval (86.9, 152) or alternatively, after 21 months (45 in total) we will have achieved the sample size of 74 participants, with 95% prediction interval (59, 91). This approach describes an extreme scenario for the ROAM study. This can be explained by the fact that the observed accrual data do not agree with the initial expectations, which means that the value of P is very small, and the strength of the prior distribution is controlled by the parameter P. This scenario could be compared with the Bayesian model with an informative prior where the value for the prior certainty is approximately $P \approx 0.03$, which represents the mean of the distribution of P in the HP. The value of P consequently has an impact in the probability of success, the value of which is approximately Prob=0.54, even if we have observed accrual data from a 24-month recruitment period. There is still considerable uncertainty about the future recruitment prediction based on accrual to date, and this is depicted in the values of the prior certainty and the probability of success.

VI. Bayesian model with Informative Prior in a multicentre study utilising observed accrual data

Overall, by June 2018, in the ROAM study there were 43 centres open (one centre which opened in April 2017, closed in January 2018) and 38 patients recruited, which meant that some of the centres hadn't recruited any patients by this point.

While 24 months had elapsed since recruitment of the first patient, 27 months had elapsed since the first centre opened to recruitment. By June 2018, 43 centres were open with 18 remaining to open. Table 16 provides the observed recruitment data, including the number of centres, the month when each centre opened, and the number of patients recruited per centre until June 2018. In the previous models, any lag between centre initiation and recruitment of the first participant could not be incorporated, but this model incorporates this lag. For this reason, the target completion time was updated to 27+21=48 months instead of 24+21=45 months.

This information in a csv file format was then used in the Bayesian model with the informative prior as described in section 7.2.3.4. Bayesian model with Informative Prior in a multicentre study.

Centre	Actual month when each centre opened	No of patients recruited until June 2018
1	1	9
2	7	0
3	8	0
4	9	3
5	9	2
6	10	3
7	10	0
8	11	3
9	11	0
10	12	1
11	12	0
12	13	0
13	13	1
14	14	0
15	15	1
16	17	3
17	18	0
18	18	0
19	19	4
20	20	1
21	20	0

22	21	0
23	21	1
24	22	0
25	22	3
26	22	1
27	23	1
28	23	0
29	24	0
30	24	0
31	24	0
32	24	0
33	24	0
34	25	0
35	25	0
36	25	1
37	25	0
38	25	0
39	26	0
40	26	0
41	26	0
42	27	0
43	27	0

Table 16: Observed accrual data for the ROAM study

The target remained the same; to recruit 152 patients in the remaining 21 months. The model used the information in Table 16 to update the parameters for the negative binomial distribution, which is used to describe patient recruitment in each centre. The same number of centres used in the csv file, were used for the prediction of future recruitment.

The recruitment prediction for the number of patients to be expected in the subsequent 21 months is presented in Figure 26 below. Note that this prediction does not take into account that an additional 18 centres were scheduled to open during the remaining 21 months.

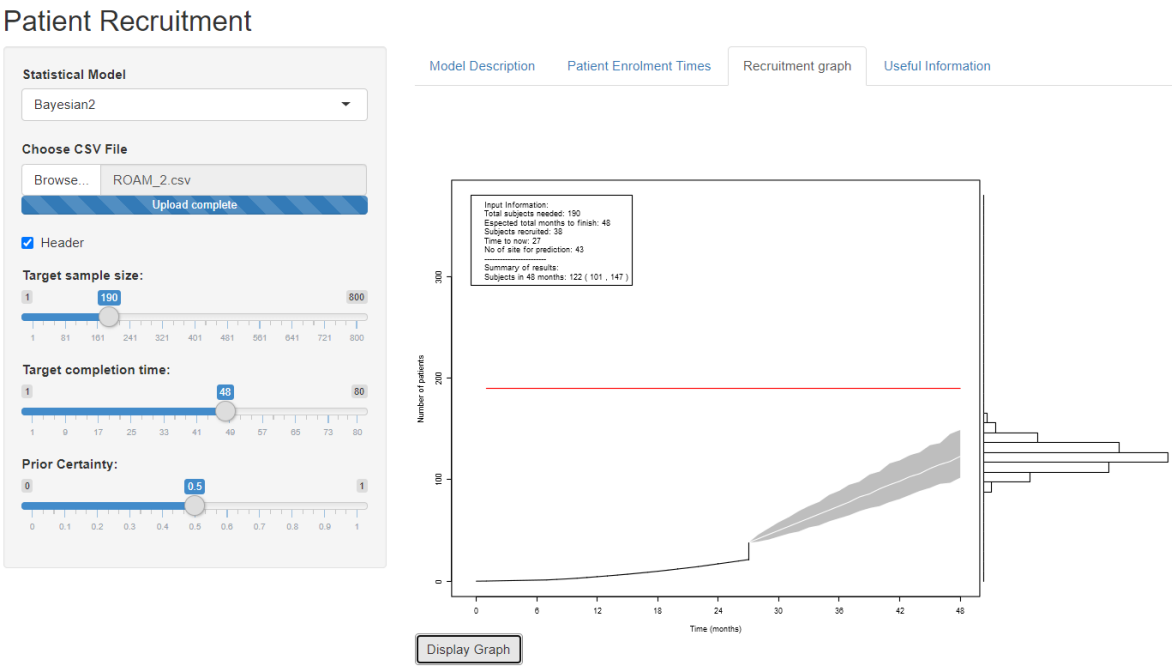


Figure 26: Bayesian model with Informative Prior for prediction of the number of subjects that can be recruited in a fixed time frame in a multicentre trial - ROAM study

As shown in the summary Box 5 below, by incorporating the observed accrual data until June 2018 from the 43 open centres, and the initial expectations of investigators with a prior certainty of 50%, the prediction for the future recruitment was that the number of patients expected to be recruited in 48 months is 122 with 95% prediction interval (101, 147).

Input Information:
Total subjects needed: 190
Espected total months to finish: 48
Subjects recruited: 38
Time to now: 27
No of site for prediction: 43

Summary of results:
Subjects in 48 months: 122 (101 , 147)

Box 5: Summary of results - ROAM study

The results from the implementation of all models described at this interim phase for the ROAM trial, are summarised in Table 17 below.

Model	Target sample size[1]	Target completion time[2]	Number of patients expected to be recruited by month 21	Recruitment time to reach the target sample size
HPP	152	21	118 patients 21 months, Q[3] = (18, 25)	27 months, Q = (23, 32)
NHPP	152	21	108 patients 21 months, Q = (18, 25)	28 months, Q = (24, 33)
Bayesian with Informative Prior	190	45	98 patients, PI[4] = (81, 117)	77 months, PI = (66, 91)
Bayesian with Accelerated Prior	190	45	104 patients, PI = (87, 124)	72 months, PI = (63, 83)
Bayesian with Hedging Prior	190	45	74 patients, PI = (59, 91)	114 months, PI = (87, 152)
Bayesian with Informative prior in a multicentre study (43 centres considered) Prior certainty *P* sets at 50%	190	48	122 patients, PI = (101, 147)	Not applicable

Table 17: Results of recruitment prediction for ROAM study

[1] The HPP and NHPP are using the remaining number of patients to be recruited, 190 minus the 38 already recruited, while the Bayesian models use the total of 190.
[2] The HPP and NHPP are using the remaining period for the recruitment, while the Bayesian models use the total period (past and future), with the final two Bayesian models incorporating lag between initiations.
[3] (2.5%, 97.5%) Quantiles (Q)
[4] (2.5%, 97.5%) Prediction Interval (PI)

As of March 2020, the overall number of patients recruited in the ROAM study was 115 with 56 centres open to recruitment. Thirty-eight patients were recruited within a period of 24 months following the trial initiation time, and an additional 77 patients were recruited in the subsequent 21-month period. With the target sample size being 190 participants, patient recruitment remained lower than the target; however due to

the Coronavirus (Covid-19) pandemic recruitment has been halted until it is safe to restart.

7.4. Discussion

7.4.1. Main findings

Conducting clinical trials can be very challenging and part of this challenge is the phase of patient recruitment. The difficulties of randomised clinical trials concerning recruitment lie within the variability of centres' opening dates, variable patient recruitment within a centre and sometimes the rare condition of the disease, as the ROAM case study described above. All these parameters need to be evaluated when designing the study and applying for funding. Prediction of patient recruitment is a key feature of trial design and monitoring, for which deterministic approaches have mainly been used so far [140]. There is also the option of using statistical models, which however is accompanied by difficulties in the models' implementation.

While the importance of statistical models has been acknowledged, there is a lack of useful tools, which could be used by the research team for the widespread implementation of these models. This chapter describes the development of the Shiny application to provide an easy to use approach for implementation of a range of statistical models, where the user can implement the models by defining the parameters required as described above. The models included in the developed Shiny application are implemented on two case studies with the results from the simulations displayed in the recruitment graph.

With the availability of these methods in the Shiny application, the decision on which model to implement can be based on factors beyond model complexity. A key factor is the determination of the parameter values and their intuitive interpretation. The parameters needed are described within this chapter with some aspects of the Bayesian approaches being less intuitive than the frequentist approaches.

A further key issue for consideration relates to the model constraints when applied to the trial itself. For example, the HPP model may be best placed for a single centre trial, while the NHPP allows for multicentre trial with staggered centre opening times. However, while the NHPP model requires a linear increase in the recruitment rate, the Bayesian approaches provide more flexibility when this is not the case.

The use of these models can be considered at the start of the trial or during recruitment as shown in this chapter.

Both Poisson models can be used only to predict remaining recruitment, thereby limiting the use of the information of the recruitment data collected so far beyond the users' estimation of the parameters.

In the Bayesian models, investigators' prior beliefs of recruitment performance are combined with observed recruitment rates to predict participant accrual for the remaining recruitment period. However, when the investigators are not sure about the progress of recruitment, they define a lower value for the prior certainty P, which leads to the decline of the probability of success and wider prediction intervals about the average number of patients expected to be recruited. Yet, wider prediction intervals do not lead to more accurate prediction; they just depict the uncertainty of the recruitment process.

In the NHPP accrual model the impact of centres' staggered initiation times can be introduced by defining the non-homogeneous recruitment period, resulting in a recruitment graph where the slow recruitment during the first stage of the study is noticeable. While, in a Bayesian model this information when available is used to inform the parameters of the distribution, which is used to model patient recruitment and it is not directly depicted in the recruitment graph. The complexity of some models does not allow the parameter estimation to be intuitive and being able to translate the available information could be very useful when planning patient recruitment.

In chapter 6 the statisticians' survey demonstrated a need for researchers to be convinced of the benefit of using these methods in place of the deterministic methods currently used. For the ROAM example the methods yielding results closer to that observed are the HPP and the Bayesian model with the informative prior in a multicentre trial, when 43 centres were used. However, these methods were implemented at the time of the request for a no cost extension from the funder. The funder did not find the uncertainty expressed for the recruitment period needed helpful as indicated by their response: "Regarding recruitment predictions, while we appreciate that recruitment is subject to a lot of uncertainty, it would be reasonable to

make a linear prediction based on what you achieve over the next few months to estimate when you are likely to hit 190."

There are many factors influencing recruitment in a clinical trial, not all of which can be predicted with any accuracy at the start. The funder response to the ROAM reprofiling demonstrates that while uncertainty can be incorporated, it reaches a point at which it becomes unhelpful. In the case of ROAM, the concern was whether a 12 or 27 months extension would be required for recruitment. Taking into account the demonstrated 15-month loss of recruitment due to delays in centre initiations, the research team requested an 18-month no cost extension, which was approved by the funder. In addition, many researchers would find it difficult to set the *P* for the Bayesian models to a low value representing their uncertainty when funders clearly require greater confidence on what is being proposed.

The Shiny application is easy to be used, and while there is increasing flexibility across the suite of models, ultimate flexibility can be achieved using the deterministic approach implemented by many in an Excel spreadsheet. The disadvantage is the absence of the recognition of the stochastic process.

7.4.2. Strengths and Limitations

The Shiny application is an interactive tool, which has been developed here to implement statistical models for recruitment prediction. User-friendly software can be considered an essential complement to the models' development, which can then be easily used by the research team without requiring a specific background in statistics.

This application easily allows the user to understand the impact of parameter changes on the recruitment results and the uncertainty around them as reflected in the stochastic process. This is particularly beneficial when parameter estimates are intuitive.

The limitation of these models is that they are not fully flexible and the level of uncertainty expressed may be too wide to be helpful.

7.4.3. Summary

The use of statistical models to predict recruitment depends on the availability of software and tools for their implementation. The development of this Shiny application provides a user friendly interface to support the uptake.

There are many factors to be considered when predicting recruitment and many of these have uncertainty around them. However, as demonstrated within ROAM, although uncertainty can be included, it can reach a point of being unhelpful, such that a hybrid approach allowing for a stochastic process while pushing the researchers to give milestones against which they can be held accountable, maybe desirable.

Thus, in the next chapter we introduce a hybrid approach to maintain the flexibility of the determinist method while allowing for some uncertainty.

Chapter 8: A Flexible approach to a Non-Homogeneous Poisson Model for Predicting, Monitoring and Re-profiling of patient recruitment in clinical trials

Preface

The available models and approaches that can be used for recruitment prediction and monitoring of patient in clinical trials, have been identified and categorised accordingly in the chapters 2, 3 and 4. In chapter 7, we describe the Shiny application we developed in order to provide a user friendly interface for the implementation of selected statistical models without requiring a statistical background for the user. While this application is easy to be used, it is lacking flexibility in relation to the number of factors the user could initially define for the study. The results from the two surveys described in chapter 6, indicated that there are many factors that the investigators need to take into account when designing the trial, such as variation in the times of initiation of centre (staggered centre openings) and in centre patient volume (variation in recruitment rates at individual centres), seasonality depending on the disease area, all of which contribute to a different expected recruitment rate per month per centre. None of the models described in the previous chapter allow the user to define all those parameters in a straightforward and direct way when designing the study. Considering the nature of patient recruitment in clinical trials and all the factors (expected and unexpected) that could influence the overall recruitment, flexibility is a very important feature that should be provided by a statistical model. In an attempt to address these limitations, we have developed a new model where the user could define all the parameters mentioned above and be able to construct a different recruitment rate per month as needed. The new approach is implemented in a web-based tool, which extends specification of the simple approach used so far as described in chapter 6, to incorporate variation via the Poisson model.

8.1. Introduction

Aiming to determine how the CIs and statisticians predict and monitor patient recruitment in clinical trials and whether the methods developed (see chapters 2, 3 and 4) are being utilised in practice, I developed two surveys and asked them about their experience and current practice (see chapter 6). The main reasons why the statistical models are not being used in recruitment prediction, are their complexity, the absence

of demonstration of their benefits in comparison to simple approaches and investigators' time pressure. Actual patient accrual is monitored against the expected in a graphical or tabular form, at individual centre level and/or across all centres. The limitation of these approaches is that they do not allow understanding of whether the observed variation is within reasonable limits of the prediction. This may lead to delays in corrective actions, which sometimes need to be taken to bring patient recruitment back on track.

The advantage of the deterministic model is its simplicity to implement within a spreadsheet package whilst providing maximum flexibility. The disadvantage is its inability to incorporate uncertainty reflected in a stochastic approach. We therefore developed an approach, which brings together simplicity, flexibility and stochasticity via the Poisson process. Poisson process is a well-accepted stochastic approach that can be used to model patient recruitment, when the average rate of patient recruitment is expected to be constant during a time interval [24-27].

In this chapter, we describe the design and the implementation of the new web-based tool based on the Poisson model, introduce a set of features accessible via this interactive application, use real recruitment data to demonstrate how this model works and conclude with a discussion of the benefits and limitations of the new approach. The web application can be used for three stages of the clinical trial; (a) the design stage, (b) the monitoring stage and (c) the re-profiling stage by inputting the relevant information available each time and saving the results in the History section.

8. 2. Methods

8.2.1. The statistical model

The number of patients recruited in a trial can be modelled based on the Poisson model by defining the lambda parameter, which represents the average number of patients recruited in a specific time interval. In the non-homogeneous model described in chapters 2, 4 and 7, the time period was split to allow recruitment rate to be modelled as a linear function during the non-homogeneous period. Here we estimate lambda on a monthly basis to allow the user to consider the effects on lambda across a number of parameters, providing maximum flexibility.

The user can input the trial parameters, such as the recruitment target, expected recruitment time, the expected recruitment start date, the number of participating

centres, the staggered initiation times and additionally allow for variation in recruitment such as slower recruitment in early months, seasonality relevant to the condition of interest and impact of holiday periods.

Based on the input information, the monthly recruitment rate from the contribution of all centres is then calculated and used in the Poisson model to produce the expected number of patients to be recruited per month. Using the inverse cumulative function of the Poisson distribution, for a specified value of *lambda* we output the median for each month and the 1st and 3rd quantiles.

The quantile function in R returns the value of the expected observation *x*, with a pre-specified probability *p*. The median, as the expected number of patients per month, and the 1st and 3rd quantile are plotted in the recruitment graph. An additional percentile, the "Acceptability threshold" defined by the user as the lowest acceptable limit for the expected number of patients to be recruited monthly is also plotted in the recruitment graph. This measure is intended to be used during the monitoring phase of the trial to indicate the lowest acceptable recruitment target.

The R script with the Poisson model used in the web application, is provided as supplementary material in Appendix E.

At the design stage, the only information available is the expected recruitment rate per month, which is defined based on previous similar clinical trials and investigators' experience. Parameters that will impact the overall monthly recruitment rates are the number of centres open to recruitment and their performance, which is introduced in the website in a tab labelled "Velocity", and seasonal factors such as holiday periods where a lack of staff and a limited number of patients to be recruited may be expected, which is presented in another tab labelled as "Seasonality". If the research team expects more factors to impact recruitment rate, they have the option to add more tabs and define those factors. The recruitment graph is then constructed based on the cumulative expected rates per month including also the number of centres expected to be open to recruitment.

At the monitoring stage, the user can add the actual number of patients recruited per month per centre. The cumulative number of patients per month is then compared with the corresponding expected number in the recruitment graph and the user specified minimum acceptable recruitment curve. Decision making is based on the results of

this evaluation and corrective actions should be taken if patient recruitment is not going as anticipated.

The reprofiling of recruitment is a necessary step if the research team, after evaluating the accrual up to that date, believe that the corrective actions will not be enough to bring patient recruitment back on track. They need to consider then updating the expected recruitment plan by taking into account the available information provided from those centres, which have been recruiting patients. Improving recruitment within centres by providing more training to the staff, investigating the reasons for the slow recruitment and taking actions as necessary and adding more centres are some of the remedial actions, which could be made. If they are not considered to be adequate, then the extension of the recruitment period is inevitable.

8.2.2. The framework of the web application

A bespoke web application has been created using Microsoft's .NET framework in conjunction with the R programming language.

Phase I involves creating a basic prototype that collates the necessary data to drive the statistical model, process the model and display the output in a graph format. The application comprises the following stages as shown in Figure 27 (a) and the following pages as shown in Figure 27 (b).

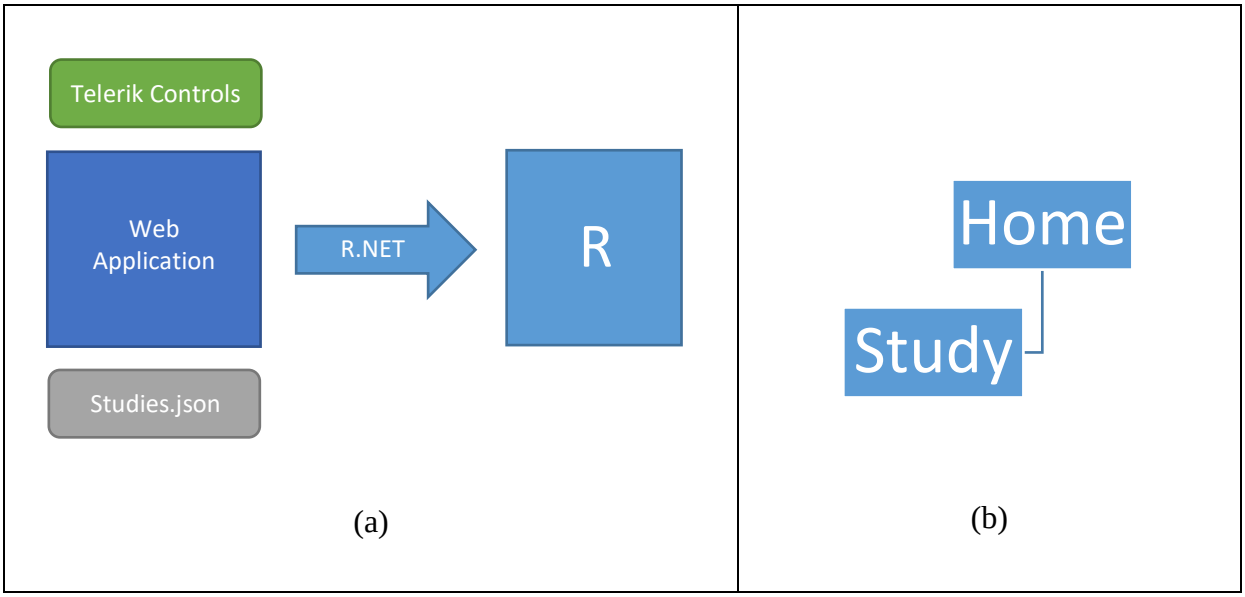


Figure 27: (a) Stages of the application. (b) Pages of the application

The web application utilises the statistical model by running the R script using the R.NET framework. This allows .NET code to pass data into and read data out of R.

This could be improved in the future by focusing to leverage Microsoft SQL Server and the Machine Learning extension, which will allow R to be executed in a scalable way. Telerik's UI control suite is utilised to create the graphs.

8.3. Tool usage

8.3.1. Web Application - Home page

The title of the web application is Patient Recruitment in Clinical Trials (PRCT). The home page lists the studies that have been registered in the system; they are read from the studies.json file. In a later release, the investigators will have the ability to login and view only their own studies.

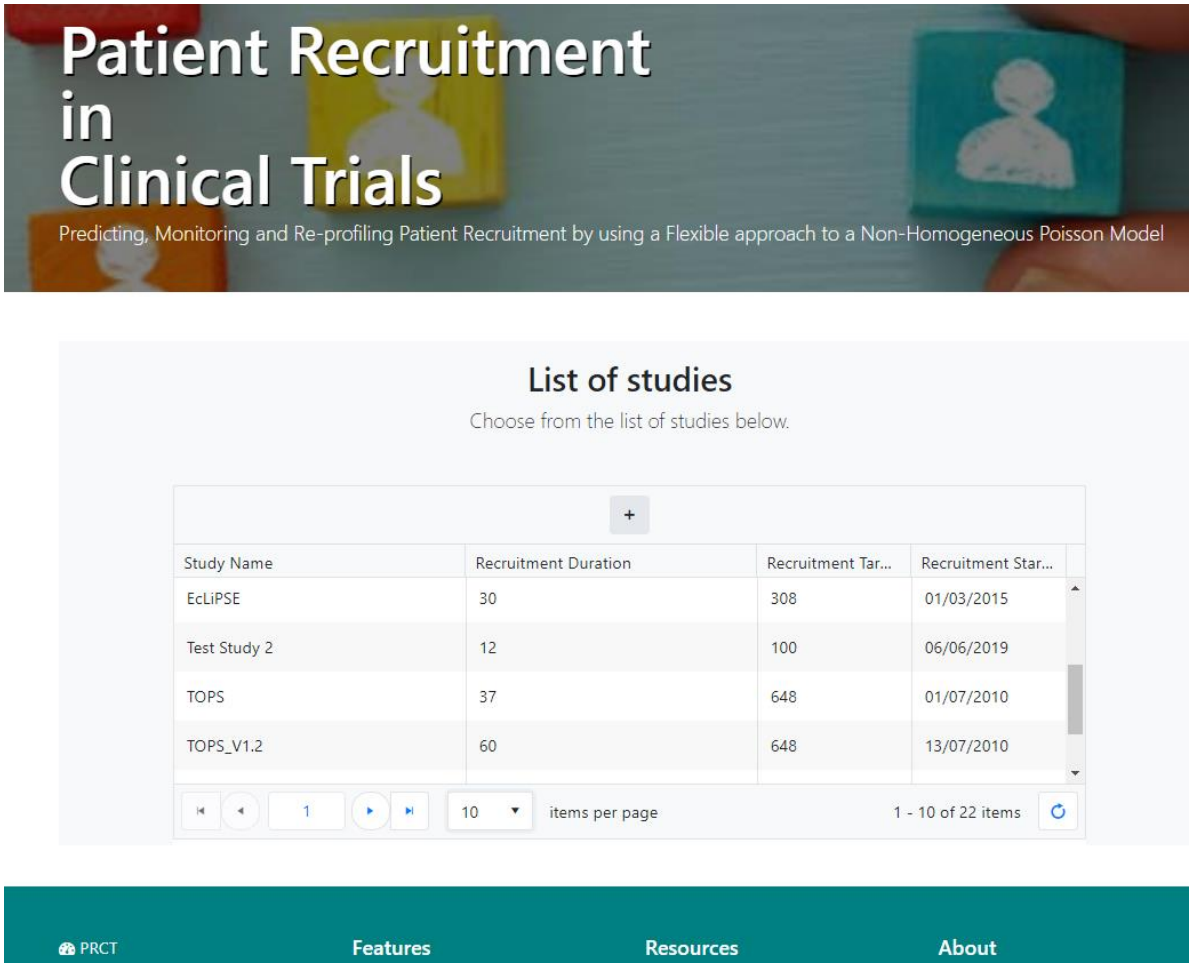
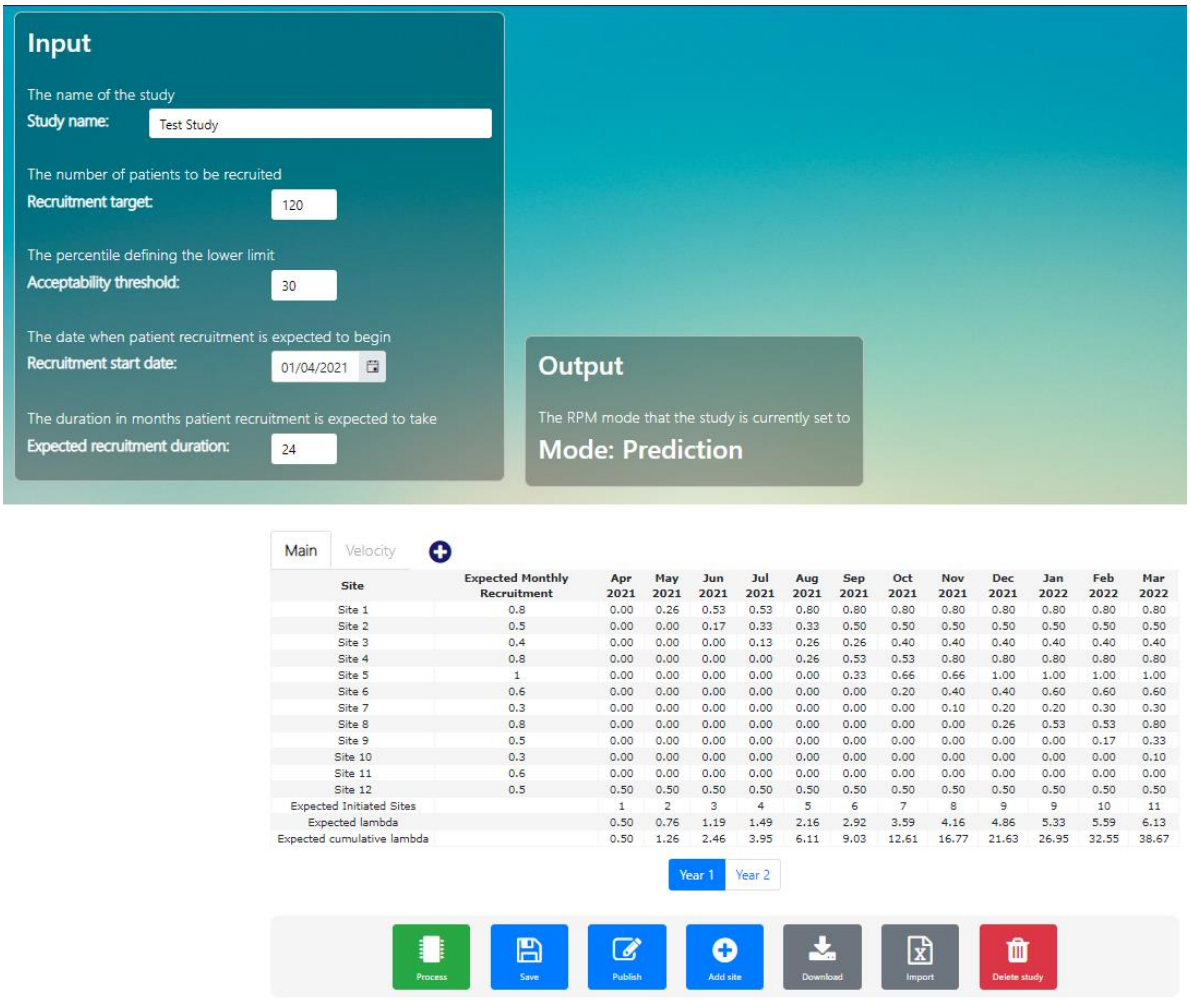


Figure 28: Home page of the PRCT web application

Here the user can add a new study by pressing the plus (+) button, or select an existing study by clicking on the corresponding grid row. Both options will take the user to the Study page.

8.3.2. Web application – Study page

The application for recruitment prediction will present the following web page, once the user logs into the system and chooses to add a study.



Site	Expected Monthly Recruitment	Apr 2021	May 2021	Jun 2021	Jul 2021	Aug 2021	Sep 2021	Oct 2021	Nov 2021	Dec 2021	Jan 2022	Feb 2022	Mar 2022
Site 1	0.8	0.00	0.26	0.53	0.53	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Site 2	0.5	0.00	0.00	0.17	0.33	0.33	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Site 3	0.4	0.00	0.00	0.00	0.13	0.26	0.26	0.40	0.40	0.40	0.40	0.40	0.40
Site 4	0.8	0.00	0.00	0.00	0.00	0.26	0.53	0.53	0.80	0.80	0.80	0.80	0.80
Site 5	1	0.00	0.00	0.00	0.00	0.00	0.33	0.66	0.66	1.00	1.00	1.00	1.00
Site 6	0.6	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.40	0.40	0.60	0.60	0.60
Site 7	0.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.20	0.20	0.30	0.30
Site 8	0.8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	0.53	0.53	0.80
Site 9	0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.33
Site 10	0.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10
Site 11	0.6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Site 12	0.5	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Expected Initiated Sites		1	2	3	4	5	6	7	8	9	9	10	11
Expected lambda		0.50	0.76	1.19	1.49	2.16	2.92	3.59	4.16	4.86	5.33	5.59	6.13
Expected cumulative lambda		0.50	1.26	2.46	3.95	6.11	9.03	12.61	16.77	21.63	26.95	32.55	38.67

Figure 29: Study page of the application

The user will need to fill the introductory information for the study as shown below:

- name of the clinical study
- recruitment target
- recruitment start date
- expected recruitment duration in months and
- an acceptability threshold

The acceptability threshold defines the lower acceptable limit pre-specified and agreed across stakeholders about the number of patients to be recruited. This limit will define the green (go), amber (amend) and red (stop) areas in the recruitment graph when comparing actual with expected recruitment at the monitoring stage. Boundaries for

these areas should be agreed between the investigators and the funder early enough to take into account the impact on recruitment duration.

8.3.3. Design stage

At the design stage, the user will be able to input information in to the website including the following:

- names and number of centres to be expected
- expected monthly recruitment rate per centre
- expected performance of each centre for all the months of recruitment (Velocity tab)
- any seasonality issues expected (Seasonality tab)

by filling the cells in the relevant tab.

Velocity tab

Velocity tab can be used to define the performance for each centre. Proportions from 0 to 1 can be entered into the cells of the relevant months with the following interpretation:

- a value of 0 means that during that month the centre will be inactive, and this is the case at the beginning of the trial when investigators have not yet managed to open all centres; this phenomenon is described as staggered centre opening times
- a value of 0.33 means that during that month the centre is expected to be recruiting at 33% of its ultimate capacity and
- a value of 1 means that the centre is expected to recruit at full capacity during that month.

Limited performance at centres can happen often at the beginning of the trial while centres are in a learning phase and at the end of the trial when investigators maybe suffering from fatigue. However, some trials may open utilising an existing known pool of patients and thereafter move to recruitment of new cases only. In this situation, recruitment rates will be higher in the early months and subsequently decline.

Seasonality tab

The same principle is followed for the Seasonality tab, where proportions from 0 to 1 are used to describe instability, for example during Christmas and summer holidays.

During these periods some centres are not expected to be open or will be underperforming. An example for the proportion interpretation is presented below:

- a value of 0 means that even if the centre is open, the reduced personnel and/or the limited number of patients expected will result in zero recruitment
- a value of 0.3 could mean that the investigators do not expect they will have many patients coming to the hospital as they could be on vacation
- a value of 0.5 could mean that the centres will have limited staff so they can perform with 50% capacity.

Seasonal change in the incidence of infectious diseases is another reason why seasonality needs to be defined as an impact factor for patient recruitment in specific disease areas. In this case the patients are expected to be recruited in specific periods during the calendar year.

More tabs can be added at this stage, if more factors that will contribute to the monthly recruitment rate are identified by the research team.

The input information from all the tabs is used to calculate the expected cumulative monthly recruitment rate contributed from all centres and presented in the Main tab, thus defining the *lambda* parameter for the Poisson model to be used in R. This is done by multiplying the expected recruitment rate per month per centre with the values from each tab and then added for all centres to define the expected monthly recruitment rate; this calculation has been programmed and happens automatically. The user then hits the "Process" button and the recruitment graph is produced as shown in Figure 30 (the values used in the graph are for demonstration purpose). The X axis represents the trial recruitment duration in months and the Y axis represents the cumulative number of patients expected to be recruited. The recruitment graph includes the median recruitment curve, the 25% centile, 75% centile, as well as the additional user-defined centile, which is used in the monitoring stage to identify recruitment deficiency. The user has the option to activate or deactivate any of the recruitment curves, and the ones that have been deactivated appear with a grey label at the bottom of the recruitment graph.

The "Publish" button gives the user the option to save the result of this specific analysis, so that a trial History will be created hosting all the changes made during the trial conduct and can be explored at any stage of the trial or even later for the purpose

of informing future trials in the same disease area. When publishing the data, a window opens asking the user to provide an explanation about the changes they made.

Site	Expected Monthly Recruitment	Apr 2021	May 2021	Jun 2021	Jul 2021	Aug 2021	Sep 2021	Oct 2021	Nov 2021	Dec 2021	Jan 2022	Feb 2022	Mar 2022
Site 1	0.8	0.00	0.26	0.53	0.53	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Site 2	0.5	0.00	0.00	0.17	0.33	0.33	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Site 3	0.4	0.00	0.00	0.00	0.13	0.26	0.26	0.40	0.40	0.40	0.40	0.40	0.40
Site 4	0.8	0.00	0.00	0.00	0.00	0.26	0.53	0.53	0.80	0.80	0.80	0.80	0.80
Site 5	1	0.00	0.00	0.00	0.00	0.00	0.33	0.66	0.66	1.00	1.00	1.00	1.00
Site 6	0.6	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.40	0.40	0.60	0.60	0.60
Site 7	0.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.20	0.20	0.30	0.30
Site 8	0.8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	0.53	0.53	0.80
Site 9	0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.33
Site 10	0.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10
Site 11	0.6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Site 12	0.5	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Expected Initiated Sites		1	2	3	4	5	6	7	8	9	9	10	11
Expected lambda		0.50	0.76	1.19	1.49	2.16	2.92	3.59	4.16	4.86	5.33	5.59	6.13
Expected cumulative lambda		0.50	1.26	2.46	3.95	6.11	9.03	12.61	16.77	21.63	26.95	32.55	38.67

Figure 30: Recruitment graph based on the results from the input information

Ability to reach the recruitment target within the early stages of the trial are dependent on the ability to hit centre initiation targets. The graph in Figure 31 allows the comparison of centre initiation rates against the expected recruitment rates used to develop the recruitment curve.

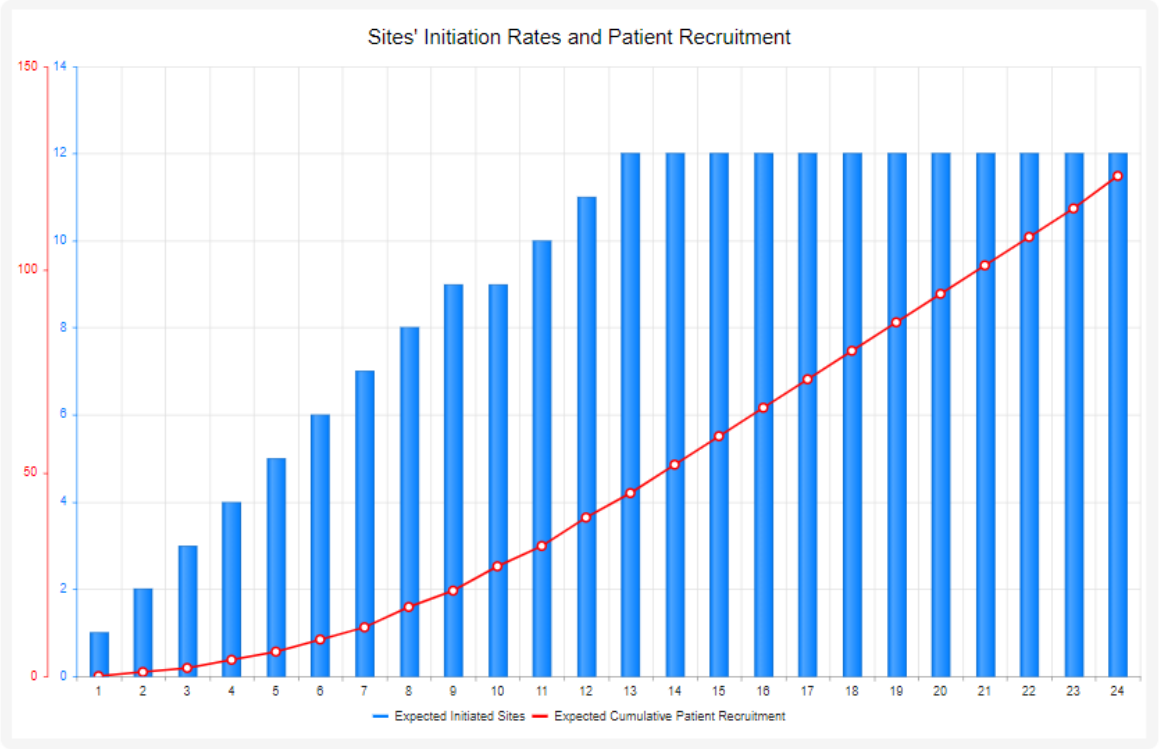


Figure 31: Recruitment Graph with the expected active centres per month and the expected cumulative number of patients to be recruited per month

8.3.4. Monitoring stage

At the monitoring stage, the user initially defines the date when the monitoring is done (domain = **Actuals' report date**, where actuals represent the actual recruitment figures observed), and this could be for example one year after the design stage, where the actual number of patients enrolled per month up to that date will be inserted. The importance of this domain is apparent in the case when an internal pilot study has been designed for the trial, and at the end of this period, researchers would like to evaluate recruitment performance and decide whether or not they will move to the main trial. Once this date has been defined, the cells for the actuals after that date will be inactive so that the users would not be able to make any changes. In addition, at the monitoring stage the user needs to provide the actual month when each centre was initiated by entering the dates into the column next to expected monthly recruitment target for each centre.

When this information is displayed on the recruitment graph (1st recruitment graph, Figure 32) as a new curve with a different colour (blue curve), a comparison is made with the curve representing the expected number of patients per month (black curve) and the user can then identify whether the recruitment is falling within green, amber

or red areas. The observed recruitment curve falling within the green area, means that the curve based on the actuals is placed somewhere between the median number of patients expected (black curve) and the 3rd quartile (green curve), and requires no corrective actions. The amber area is defined as that between the curve representing the median number of patients expected and the lowest acceptable threshold, e.g. 30% (red curve), denoting close monitoring and action is required, while red is the area under the lowest acceptable curve, denoting urgent action required or even abandoning the trial because of poor recruitment.

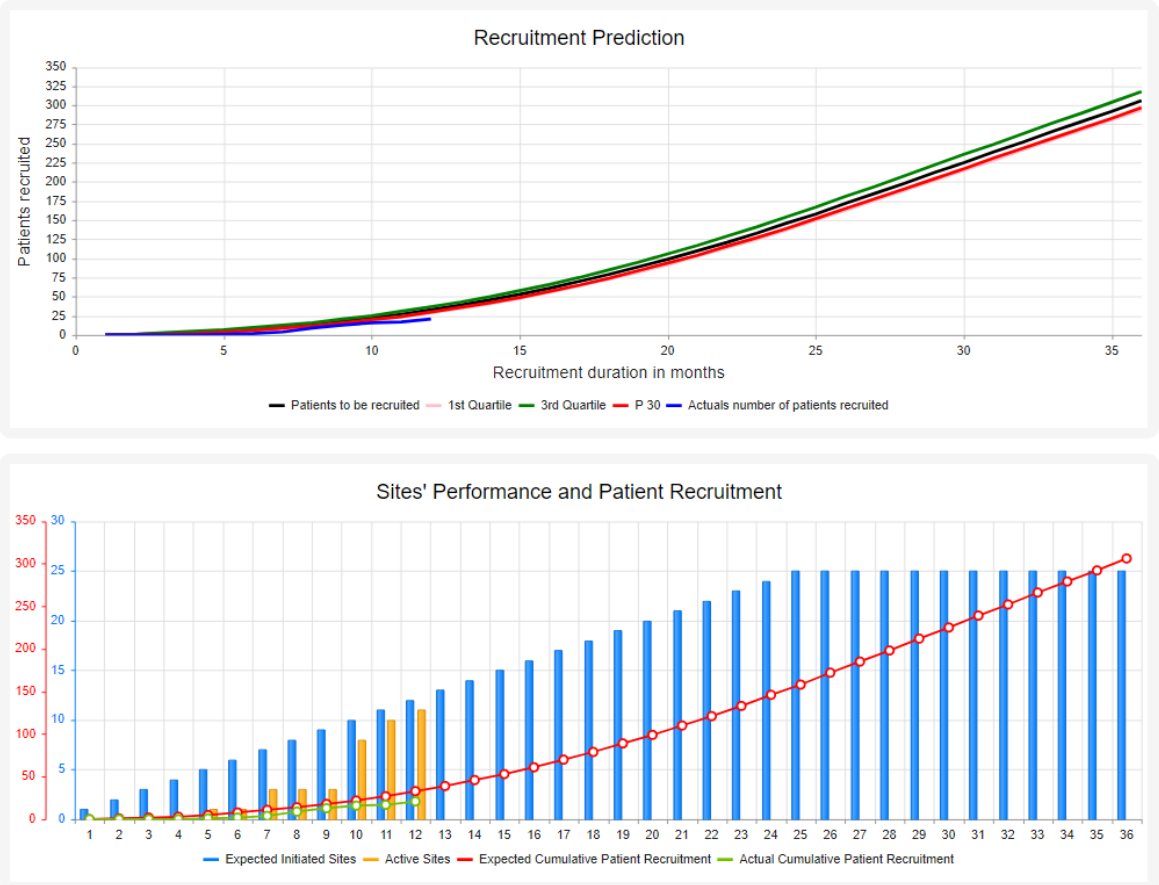


Figure 32: Graphs produced at the monitoring stage of the trial recruitment

The second graph in Figure 32 presents the number of centres expected to open (blue columns), the actual number of active centres (orange columns), the expected number of patients (red curve) and the actual number of enrolled patients (green curve).
As we mentioned previously, the number of patients recruited is closely related to the number of active centres. Therefore, an additional measure to be considered at the monitoring stage is the cumulative number of recruiting months across centres and

whether differences between that observed and predicted could explain the recruitment results. The recruitment figures leading to the calculation of this measure are presented below:

1) the observed number of recruitment months across centres
2) the predicted number of recruitment months across centres

and the centres' performance is then expressed as a proportion of the recruitment months observed versus those predicted.

$$Recruitment\ months\ realised = \frac{number\ of\ recruitment\ months\ the\ centres\ are\ open}{number\ of\ recruitment\ months\ the\ centres\ were\ expected\ to\ be\ open}$$

The investigators should be eager to examine what part of the recruitment shortfall can be explained by the number of active centres, because this could help in decision making about the remedial actions required when recruitment of patients is below that expected. The impact of centre initiation delays is displayed in the Study page Output labelled as "Recruitment months realised" when accrual monitoring is performed. This value can then be used to explain the results for the "Observed Recruitment total" by multiplying the expected recruitment rate by this value, and then a crude estimate of the number of participants expected to be recruited allowing for the lower centres initiation rates can be obtained. This new measure is presented under the label "Expected recruitment based on actual open sites".

The "Publish" option should be used at this stage so that the user can save the result of the monitoring and the study can move on to the re-profile stage. The History where the results from each stage have been saved is displayed at the bottom of the Study page and can be accessed at any time.

8.3.5. Re-profiling stage

After publishing the results of the monitoring, the study switches to the re-profile mode. The comparison of expected and actual recruitment figures defines whether corrective actions are required depending on where the actual recruitment curve falls into. Corrective actions include better training for the personnel involved in patient recruitment within centres, research team putting more effort into opening more centres when the number of centres already open is far behind the scheduled, increasing effort within each centre to encourage recruitment etc. Whether remedial actions are possible or not, the research team will need to re-profile the recruitment

curve. The date of the re-profiling needs to be defined, and it is the same as the date for the monitoring, when we first re-profile the study or at any other interim time during the study, which means that the user can monitor and re-profile the study more than once. As shown in Figure 33, moving from prediction to monitoring is a one-way operation, while it is possible to go from monitoring to re-profiling and back again.

Figure 33: Study stages

Re-profiling gives the user the opportunity to amend the cells given in the Velocity, the Seasonality and any other active tab, but only for the months after the Actualise to date. When re-profiling, the same Poisson model is used, but the user will need to update the input information depending on the different scenarios for the corrective actions required, such as

- if the research team decides to add new centres, then the monthly expected rate for all the new centres and the performance expected is to be defined by filling this information into the cells of the relevant tabs
- if additional training has been planned for the staff within the centres and the impact expected is better performance for some centres, this could also be communicated by changing the values in the cells of the Velocity tab regarding the period from the Actualise to date onwards
- if an extension of the recruitment period is inevitable, then the expected recruitment duration at the study page Input should be updated and this information will be incorporated in the different tabs, by adding more months, which needs to be filled with the relevant information.

After all the calculations are complete and displayed in the Main tab, the new expected monthly recruitment rates are ready to be used in the Poisson model implemented in R. The R script uses the input data in the same way as in the prediction stage; but then the actual accrual which are now available, are also incorporated in the recruitment graph.

The results about the updated recruitment plan at participant and centre level are presented in Figure 34, which includes the actual number of patients recruited until the monitoring date (green curve), and the new recruitment curve (red curve), which represents the updated expectations in relation to patient recruitment by taking into account all the corrective actions to be implemented.

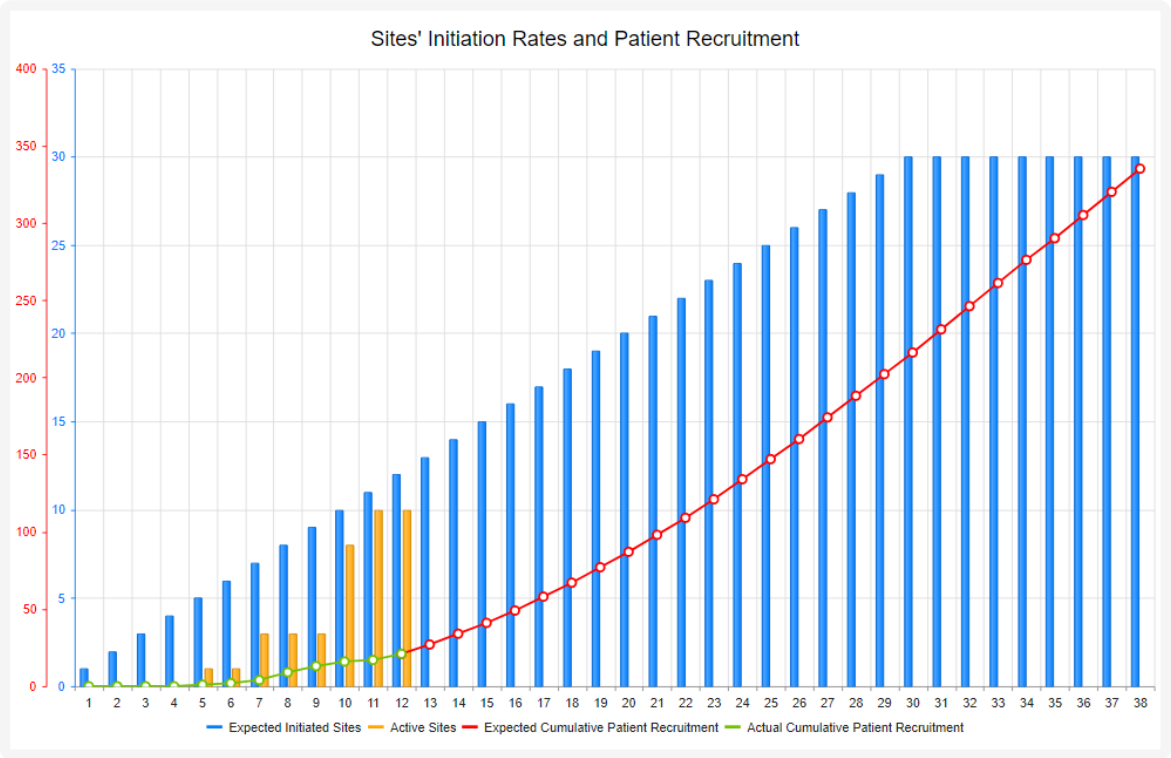


Figure 34: Graph produced as a result of the study re-profiling

8.3.6. Availability

The web-based tool based on the Poisson model is available at the following website https://ctrc.liv.ac.uk/InDevelopment/PRCT/Home (please make sure you refresh the webpage once you access it by pressing Ctrl+F5). In the longer term the website will be hosted in the main page of the Liverpool Clinical Trials Centre (LCTC) website http://www.lctc.org.uk/Home. The users will need to create an account where they provide information about their trial and consent to this information being stored in the website.

8.4. Case Studies

Recruitment data from two clinical trials, EcLiPSE and TOPS, have been used retrospectively for the model demonstration. Within these trials the original centre initiation schedule and impact of factors on recruitment capacity were available to be reconstructed within the website. The recruitment plan as designed at the planning

stage including all the parameters about the monthly recruitment rates and expected duration of the trial, as well as the actual accrual data have been used from each trial to help understanding how the model and the web application are working. The actual number of patients recruited in the end and the final recruitment duration have been compared with the relevant results from the model implementation in order to evaluate whether the variability around the average recruitment rate and the recruitment uncertainty have been captured from the new stochastic model.

8.4.1. EcLiPSE clinical trial

The EcLiPSE clinical trial [137] was introduced in chapter 7, where it was used as a case study for the demonstration of models implemented in the Shiny application. A short summary is provided here as a reminder of the study.

EcLiPSE planned to open approximately 25-30 Emergency Departments (EDs) in NHS secondary and tertiary hospitals in the UK. Eligible children were to be randomised to receive either intravenous levetiracetam 40mg/kg or intravenous phenytoin 20mg/kg, with the required sample size being 308 patients. An 18-month internal pilot study involving five centres was planned; however additional centres were to be opened during this period.

8.4.1.1. Design stage

The information required to implement the new web-based tool for the EcLiPSE trial was provided by the EcLiPSE team as described in chapter 7. The trial is expected to recruit 308 participants from 25 centres over a period of 36 months. The information provided in Table 14 of chapter 7 about the expected monthly recruitment target per centre and the staggered centre initiation times, was used to define the expected monthly rates from all centres.

Recruitment prediction for the EcLiPSE trial is displayed in Figure 35 and Figure 36 below, with the first graph presenting patient recruitment prediction and the second graph presenting centres' expected initiation rates in combination with expected patient recruitment. Based on the median recruitment curve in Figure 35 (black curve), 306 patients are expected to be recruited after the period of 36 months with the 1st and the 3rd quartile being 294 and 318 patients respectively.

Figure 35: Expected patient recruitment

In Figure 36 we can see that it is not until the 25th month when all the centres are expected to be open. This longer period scheduled to initiate the centres was necessary due to the conduct of the trial in an emergency department setting and challenge of arranging training visits supporting maximum attendance given high staff volumes.

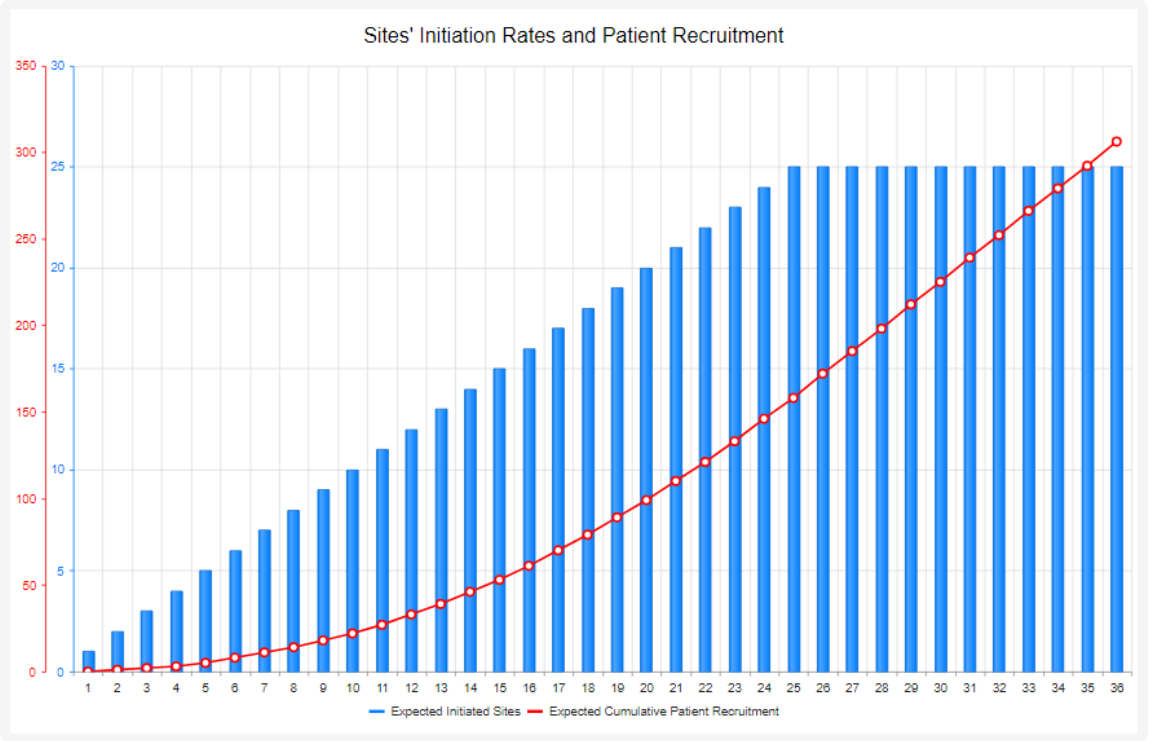


Figure 36: Expected Patient Recruitment and Centres' Performance

8.4.1.2. Monitoring stage

Once the trial is open to recruitment we need to compare the actual recruitment rate with that predicted. The latest point for which there are observed data is called the "Actuals' report date" as shown in Figure 37 below. Specification of this date allows input of the observed recruitment up to that time point. In the EcLiPSE trial for demonstration purposes this is defined as one year after the initiation of recruitment, the 1st of March 2016.

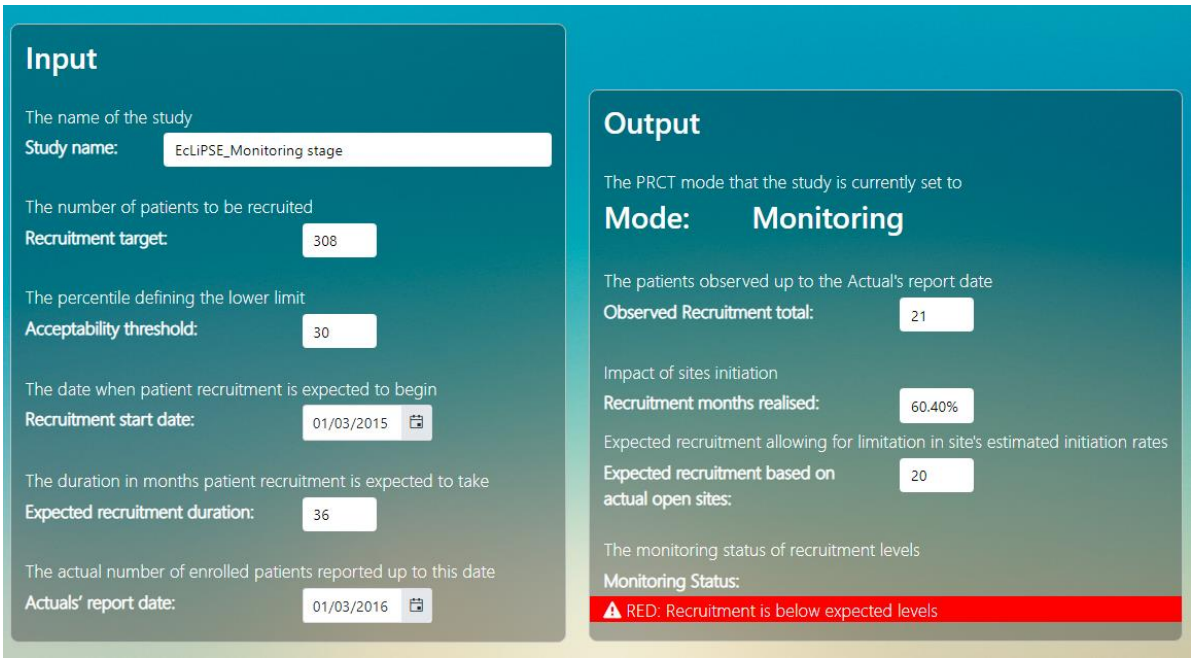


Figure 37: Input and Output parameters during the monitoring stage

In addition, at the monitoring stage the user needs to provide the actual month when each centre was initiated. This is done by entering the dates into the column next to expected monthly recruitment for each centre, while the actual number of patients recruited per month at each centre is added in the row below each centre's expected recruitment, called "Site's name – Actuals". After completing the actuals in the cells up to February 2016 in the website page, the graphs presented in Figure 38 and Figure 39 are produced.

Figure 37 above presents the input information used for the monitoring stage and the results as an output. Twenty-one patients have been recruited during the first year of the trial, which is below the expected 33 (median recruitment, black curve in Figure 38), and this is depicted in the figure above with the warning note in a red label stating that recruitment is below expected levels.

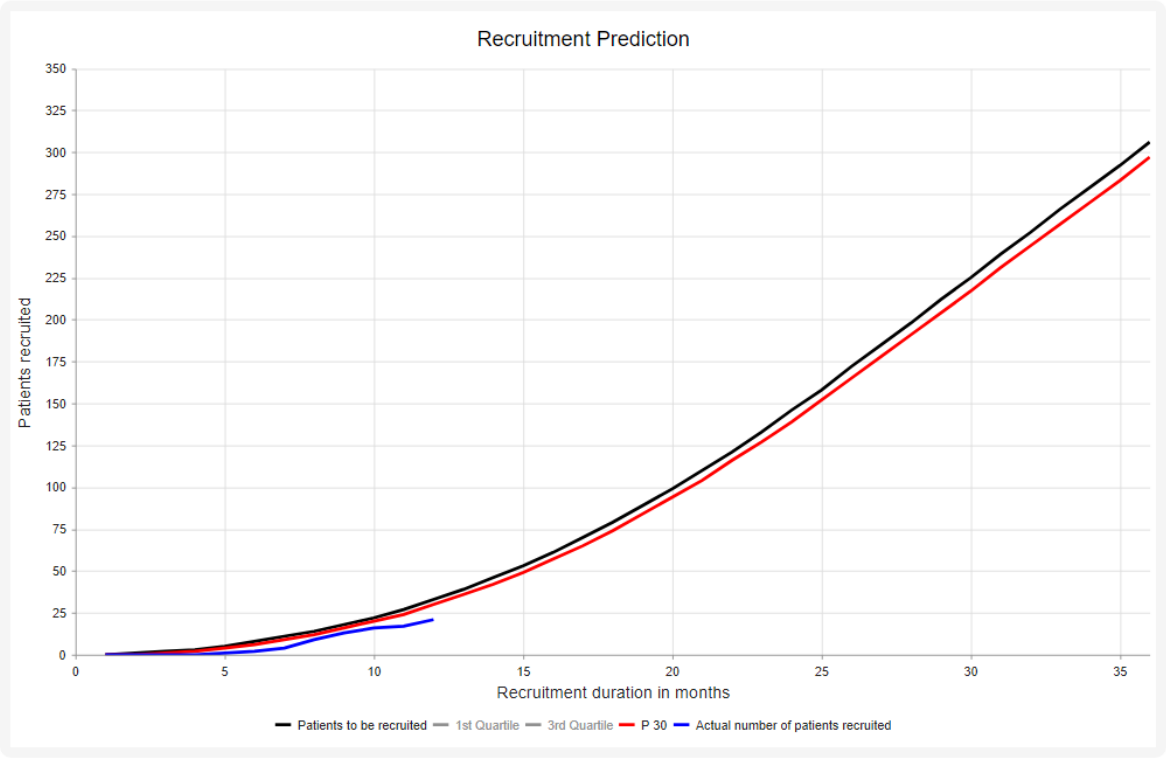


Figure 38: Expected Vs Observed number of patients recruited

In Figure 38 above, the number of patients to be recruited (black curve), actual number of patients recruited (blue curve) and the lowest acceptable threshold for each months (red curve) have been plotted (note the greyed out legend indicates that these curves have been switched off). It is clear that the actual number of patients recruited is below the median expected and even below the lowest acceptable limit which is defined as 30% for this trial.

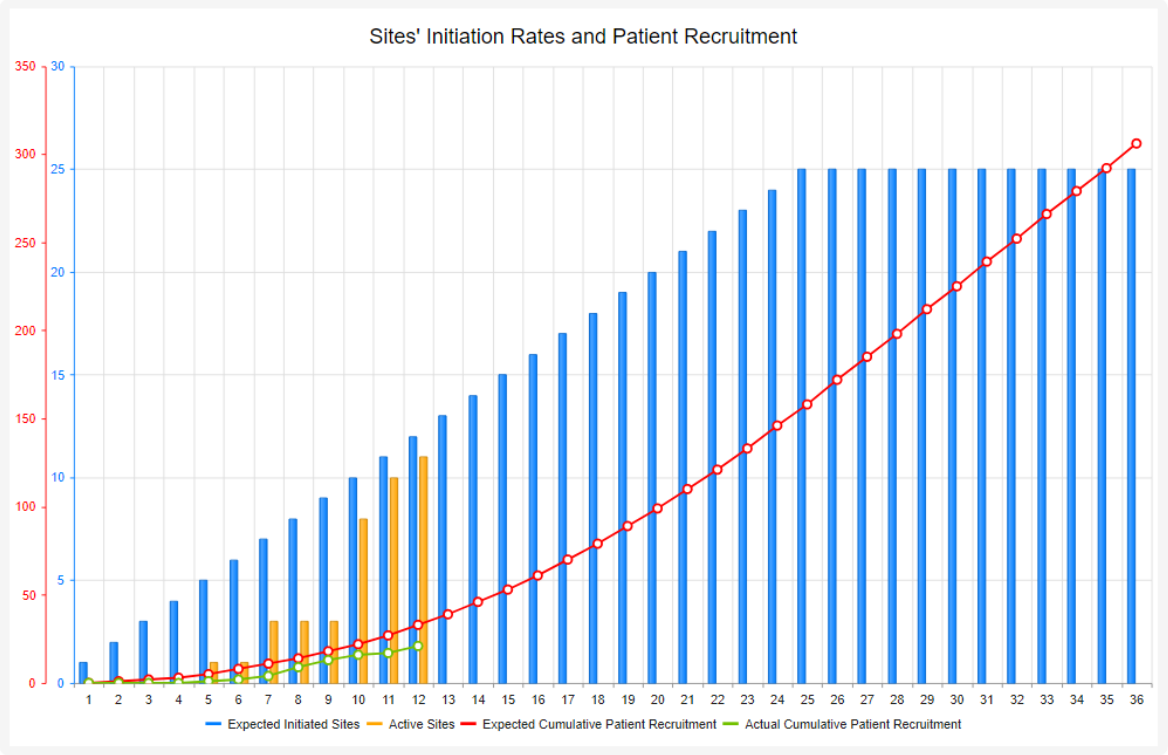


Figure 39: Expected Vs Observed centre initiations and patient recruitment

During the monitoring phase, another factor related to patient recruitment is the duration in months for which the centres have been open to recruitment, and this has been calculated and presented under the label "Recruitment months realised". As described earlier, this measure is evaluated with the following formula:

$$Recruitment\ months\ realised = \frac{number\ of\ recruitment\ months\ the\ centres\ are\ open}{number\ of\ recruitment\ months\ the\ centres\ were\ expected\ to\ be\ open}$$

In the ECLIPSE trial, because of staggered initiation times, the expected value is 66.22 recruitment months, while the number of actual recruitment months the 11 initiated centres have been opened during the first year is 40. Thus, the "Recruitment months realised" figure which is expressed as a proportion of the recruitment months expected is 40/66.22 ≈ 0.604, meaning that approximately 60% of the expected recruitment months has been observed, as shown in Figure 37. If we multiply this proportion by the expected cumulative number of patients in February 2016, which is 33, then the result will be 33*0.604 ≈ 19.93 meaning that approximately 20 participants are expected to be recruited based on the number of months the centres

are open to recruitment. The number of patients actually recruited at the end of February 2016 was 21, which is slightly different but bigger than the previous expected result. This suggests that lower than expected patient recruitment is almost entirely explained by the reduction in recruitment months across centres.

8.4.1.3. Re-profiling stage

In response to the delays in centre initiations an additional 5 centres were added at this stage with the first expected initiation in April 2017. One centre was added per month and staggered centre opening times were applied. The recruitment period was also extended for another two months. Therefore, from August 2017 until April 2018 we are expecting to have 30 centres in total to contribute to recruitment. The lowest monthly expected rate from all the centres used at the design stage, was defined as the expected monthly rate for the 5 new centres.

In the input framework we updated the expected recruitment duration to be 38 months, while in the Main tab we added another 5 centres and defined the expected monthly recruitment rate to be approximately 0.28 patients per month for each new centre. In the Velocity tab, which is active only for the period after February 2016, we defined the staggered centre initiation times for each new centre. The results are presented in Figure 40 and Figure 41. The median number of patients to be recruited after 38 months is 335 and if the lowest acceptable limit was to be defined at 30%, then the acceptable number of patients is 326, which is higher than the target sample size required (Figure 40). In addition, all centres were expected to be open not earlier than the 30th month from the initiation date, March 2015 (see Figure 41).

Figure 40: Re-profiling of patient recruitment after 12-month of accrual

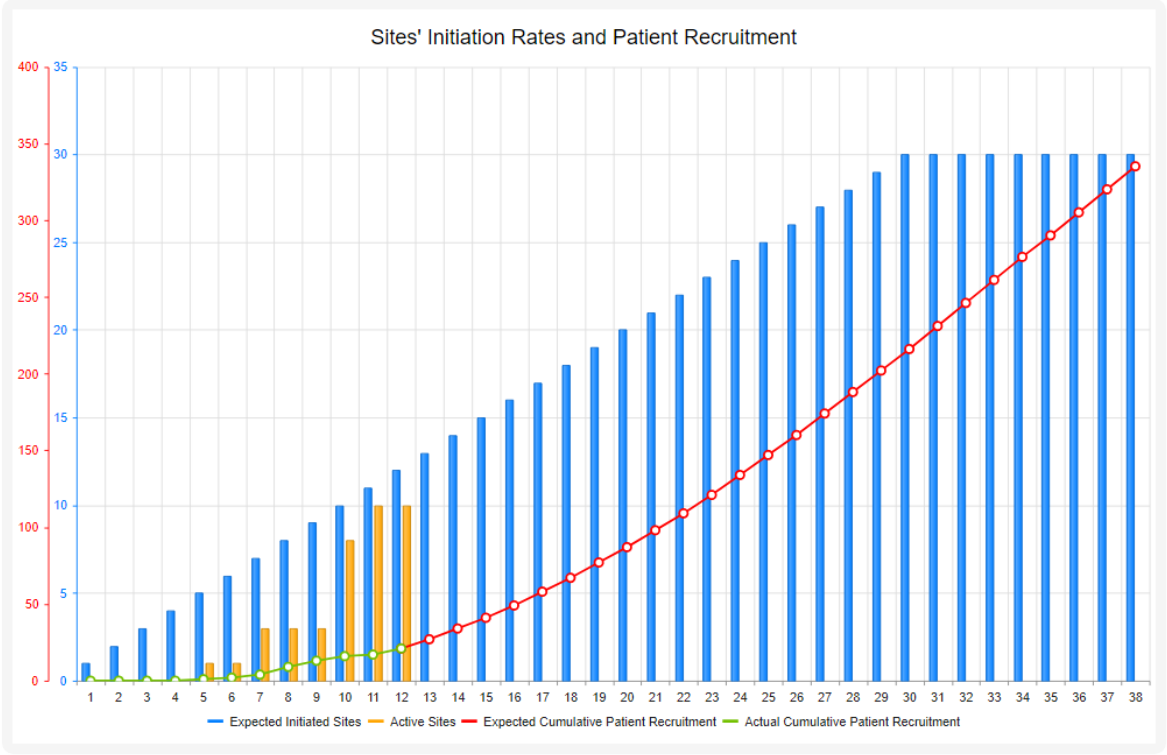


Figure 41: Re-profiling of EcLiPSE trial at patient and centre level

While the trial target was 308 participants, as we already know the trial was completed on time in April 2018 after 286 participants were randomised with consent. A total of 286 participants was considered an adequate amount because as already explained in chapter 7, the adjustment for loss to follow up of 10% used to inflate the sample size calculation at the design stage was not required due to the completeness of data collected and low attrition.

By April 2018, the Poisson model expected 335 patients to be recruited with probability 50% and the 1st and 3rd quartiles around the median are (323, 347). The expected median value was higher than the value required by 27 participants with the lower quartile being 15 higher. Clearly, there was no intention to over recruit and in setting a higher median, the achievability of the target should have had a higher probability.

Patient recruitment in this trial can be considered successful, since the updated target was reached within the timeframe expected and no extension was required. However, the numbers were lower than the median and indeed than the lower quartile. Centres' fatigue was considered as an explanation but this factor wasn't accounted for in the initial prediction.

8.4.2. TOPS clinical trial

TOPS was an international randomised control trial which aimed to investigate the impact of the timing of surgery for cleft palate repair on speech development [141]. Cleft palate is among the most common birth abnormalities. The success of primary surgery in the early months of life is crucial for successful feeding, speech, hearing, dental development and facial growth. Over recent decades, age at palatal surgery in infancy has reduced. This has led to palatal closure in one-stage procedures being carried out around the age of 12 months, but in some cases as early as 6 months.

Objectives

The primary objective of the Timing Of Primary Surgery for Cleft Palate (TOPS) trial was to determine whether surgery for cleft palate performed at 6 or 12 months of age was most beneficial for speech outcomes. This research investigated the effect of the timing of surgery by assessing and comparing speech development outcomes measured across 12 months, 3 years and 5 years of age. In addition, secondary

outcomes included growth, perioperative complications, dentofacial development, hearing level and middle ear function.

8.4.2.1. Design stage

The study information required to implement the new web-based model for the TOPS trial are listed below, as they were provided by the TOPS team.

- Required sample size = 648 patients to be randomised, which will allow for 10% drop out
- Expected recruitment duration: 37 months (July 2010 – July 2013)
- Number of centres to be open: 20
- Staggered initiation times and seasonality effects have been applied to each centre
- Recruitment to the trial to be commenced in July 2010

In summary, the research team initially was expecting to recruit 648 participants from 20 centres in a period of 37 months. The recruitment rates for centres were informed by the Scandcleft project [142].

Velocity tab

The expected monthly recruitment rate per centre as well as the staggered initiation times applied to all centres have been inputted in the website based on the information provided by the research team.

Seasonality tab

In this study, the research team considered that seasonality was an important factor to be added for some centres. Specifically, the Bauru centre was expected to be closed every December and January, so there are zeros placed in the cells for the relevant months, December 2011, January 2012, December 2012 and January 2013, but not for December 2010 and January 2011 because the centre was not expected to be open yet. While for the centres Copenhagen, Oslo, Bergen, Malmö, Göteborg, Stockholm, Linköping, Umeå, Uppsala and Helsinki, it was expected that during the summer months, July and August they will be closed, so there are zeros placed in the cells for the following months: July and August 2011, July and August 2012 and July 2013.

Using all the parameters defined above, the expected monthly rates from all centres were defined.

Patient recruitment prediction has been plotted in Figure 42 below, while centres' expected initiation rates in combination with expected patient recruitment have been plotted in Figure 43. Based on the median plotted in the first graph (black recruitment curve) 647 patients are expected to be recruited after the period of 37 months with the 1st and the 3rd quartile being 630 and 665 respectively. In the second graph, we can see that it is not until the 9th month when all twenty centres are expected to be open, as this was defined by the staggered initiation times applied to all centres.

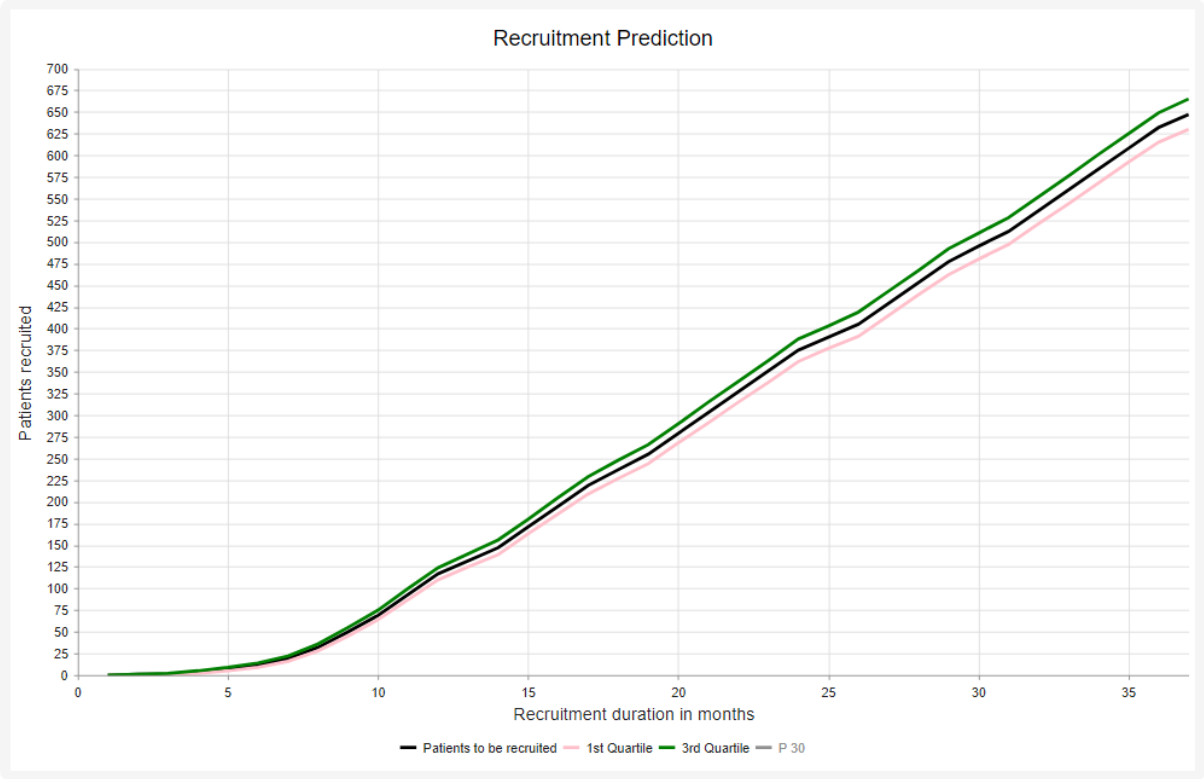


Figure 42: Expected Patient Recruitment

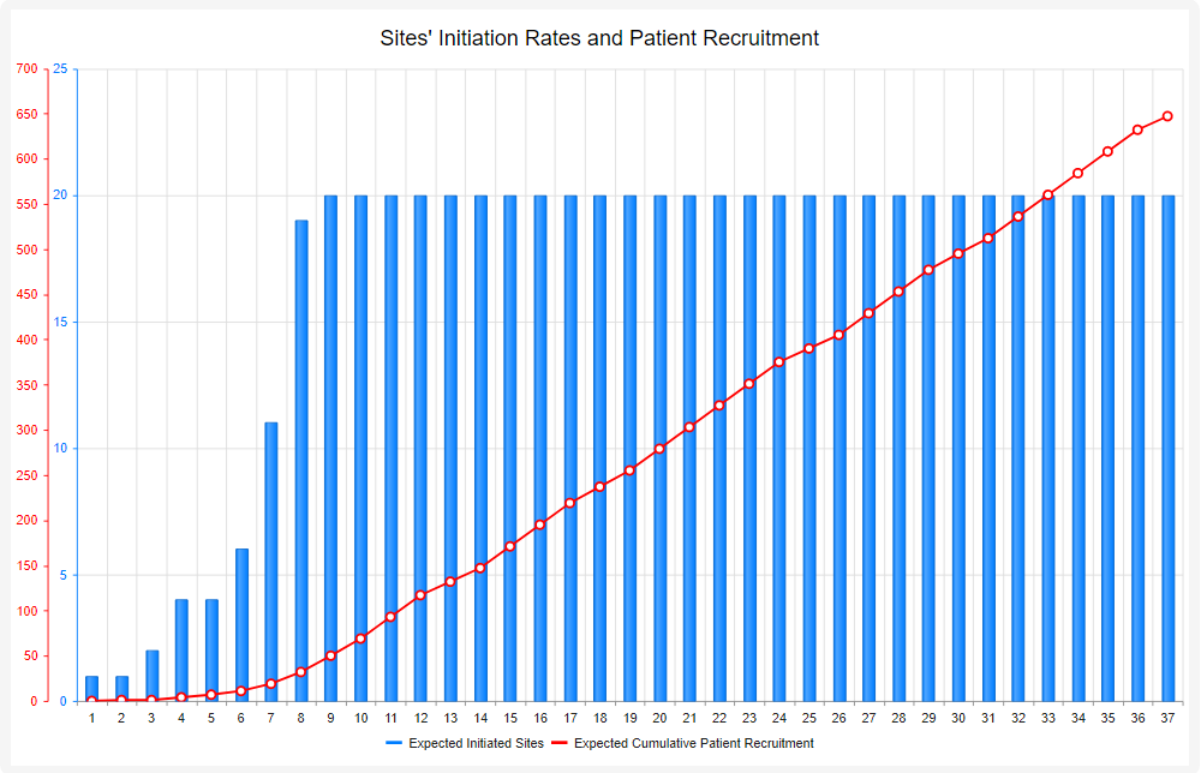


Figure 43: Expected Patient Recruitment and Centres' Performance

8.4.2.2 Monitoring stage

At this stage we need to define the "Actuals' report date" domain, which in this case is December 2012, and add the actual month when each centre was opened and the actual number of patients recruited per month at each centre for the period up to November 2012.

After completing the actuals in the cells up to November 2012 in the website page, the following output and graphs are produced.

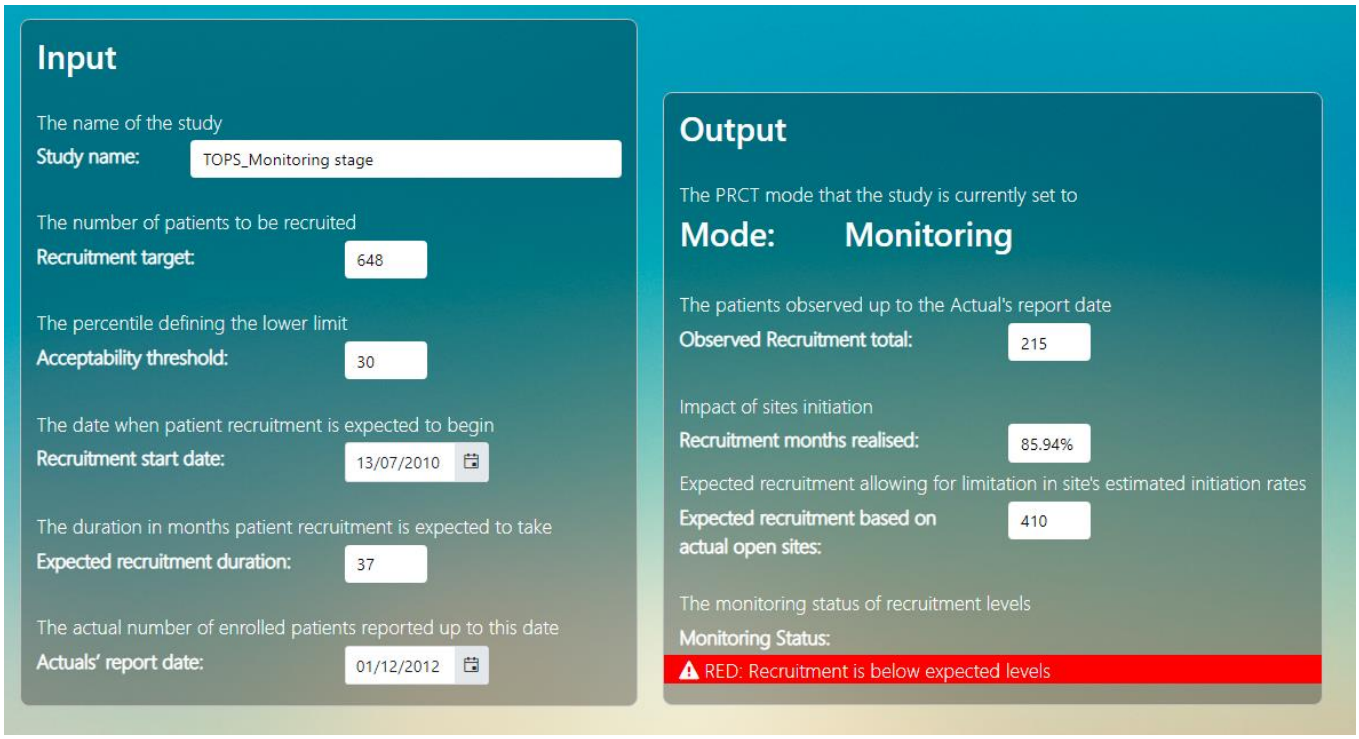


Figure 44: Output parameters displayed for the monitoring stage

Figure 44 presents the output results for the monitoring stage as they are illustrated in the graphs in Figure 45 and Figure 46 below. The number of patients recruited during the first 29 months of the trial is 215 patients which is much lower and less than half of that expected 477 (median), and this is depicted in the figure above with the warning in a red label stating that recruitment is below expected levels.

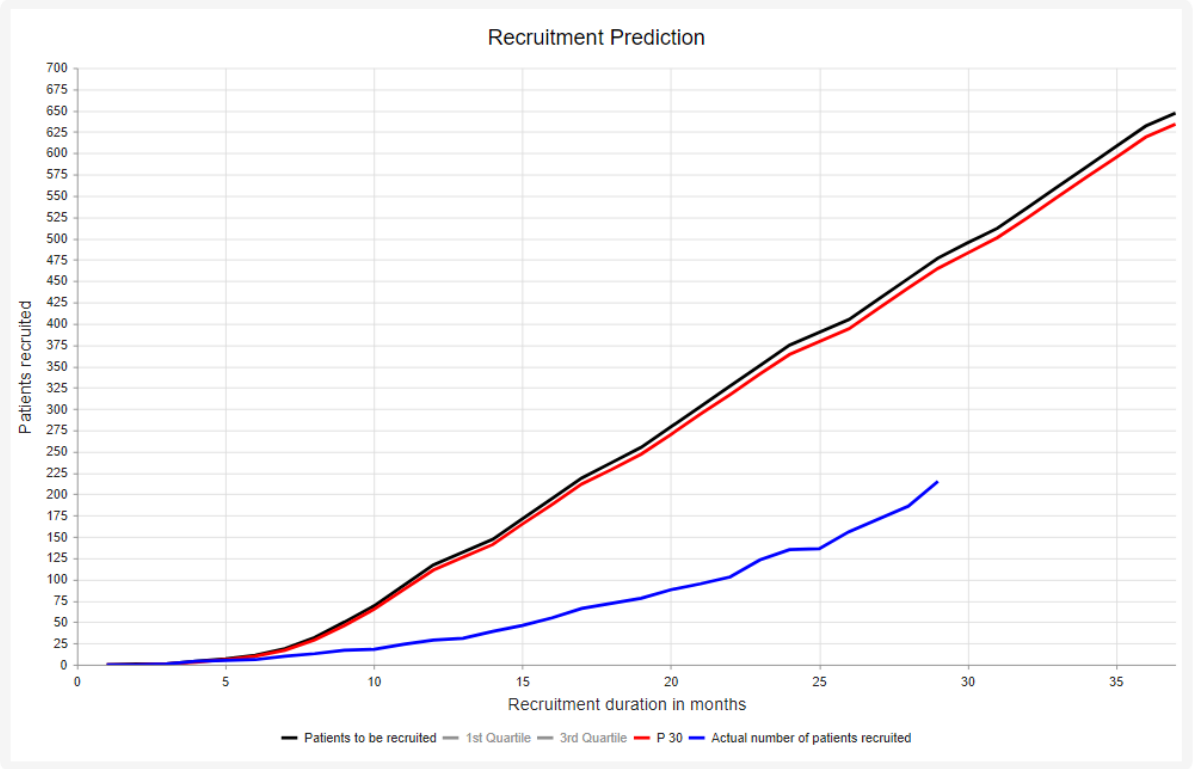


Figure 45: Expected Vs Observed number of patients recruited

During the monitoring phase, an essential factor relating to patient recruitment is the number of recruitment months the centres have been opened. Because of staggered initiation times, 441 recruitment months was the expected value for the centres, while the number of actual recruitment months the centres were opened during this 29-month period is 379. Thus, the "Recruitment months realised" figure which is expressed as a proportion of the recruitment months expected is 379/441 ≈ 0.859, meaning that approximately 86% of the expected recruitment months has been observed, as shown in Figure 44 above. If we multiply this proportion by the expected cumulative number of patients in November 2012, which is 477 then the result will be 477*0.859 ≈ 409.7 meaning that approximately 410 participants are expected to be recruited when allowing for delays in centres initiation. Comparing the expected recruitment based on actual initiated centres with the 215 patients actually recruited until November 2012, it is obvious that the inadequate patient recruitment observed should be attributed to additional factors beyond the limited recruitment months realised.

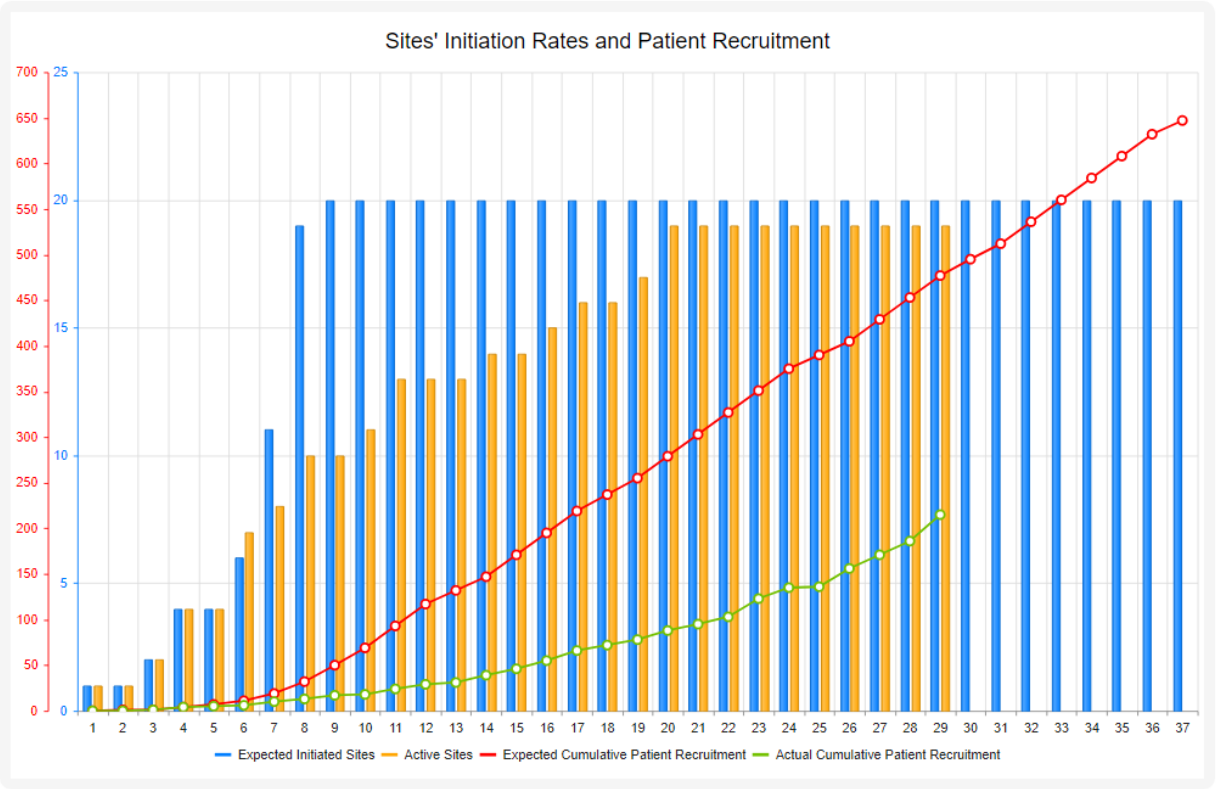


Figure 46: Expected Vs Observed centre initiations and patient recruitment

In Figure 45, the cumulative number of patients expected to be recruited, actual number of patients recruited and the lowest acceptable threshold for each month have been plotted. It is obvious that the actual number of patients recruited is much smaller than that expected.

The fact that, by implementing this model, the slow recruitment could be attributed to more reasons other than limited centres initiation times, would help the investigators to better understand the limitations of the study and properly define the corrective actions and the reprofiling stage required. In this example, the recruitment rates were impacted by parental preference to have a repair earlier as demonstrated in the screening logs.

8.4.2.3. Re-profiling stage

Based on the performance of centres so far, it was considered essential by the research team to update the monthly expected recruitment rates for all centres participating, as shown in Table 18 below. In addition, Helsinki centre was withdrawn and another 3 centres (Edinburgh, Salisbury and Oxford) were added at this stage starting from December 2012. One centre was expected to be added per month so staggered centre initiation times have been applied for all new centres, but no seasonality aspects were

applied. Seasonality has been applied to all centres participating, apart from the UK centres. Recruitment period has also been extended for another 23 months until June 2015 to allow the trial to reach its recruitment target. Therefore, from December 2012 until June 2015, all 22 centres are expected to contribute to patient recruitment.

Centre	**Initial expected monthly recruitment rate per centre**	**Number of patients recruited until November 2012**	**Revised expected monthly recruitment rate per centre**
Manchester	0.75	22	0.8
Liverpool	0.8	14	0.4
Belfast	0.4	3	0.1
Birmingham	1.76	11	0.4
Newcastle	0.94	20	1.3
Bristol	0.91	16	0.7
Swansea	0.48	3	0.2
Leeds	1.56	7	0.26
Glasgow	1.56	7	0.3
Bauru	6.08	51	5.58
Copenhagen	0.88	15	1.03
Oslo	1.26	8	0.86
Bergen	0.88	1	0.11
Malmö	0.76	12	0.57
Göteborg	0.85	3	0.11
Stockholm	1.21	8	0.57
Linköping	0.48	5	0.28
Umea	0.63	2	0.05
Uppsala	0.72	7	0.34
Helsinki	1.01	0	Helsinki centre was withdrawn
Edinburgh	This centre was added later	-	0.83
Salisbury	This centre was added later	-	0.58
Oxford	This centre was added later	-	0.6

Sum of patients recruited until November 2012	**215**	

Table 18: Expected monthly recruitment rate (initial & revised) and observed accrual date for each centre in the TOPS trial

All the changes described above were added to the website, with the expected recruitment duration revised to 60 months, Helsinki centre removed and the three new centres added and the expected monthly recruitment defined for each of them.

The results of these changes are presented in Figure 47 and Figure 48 below.

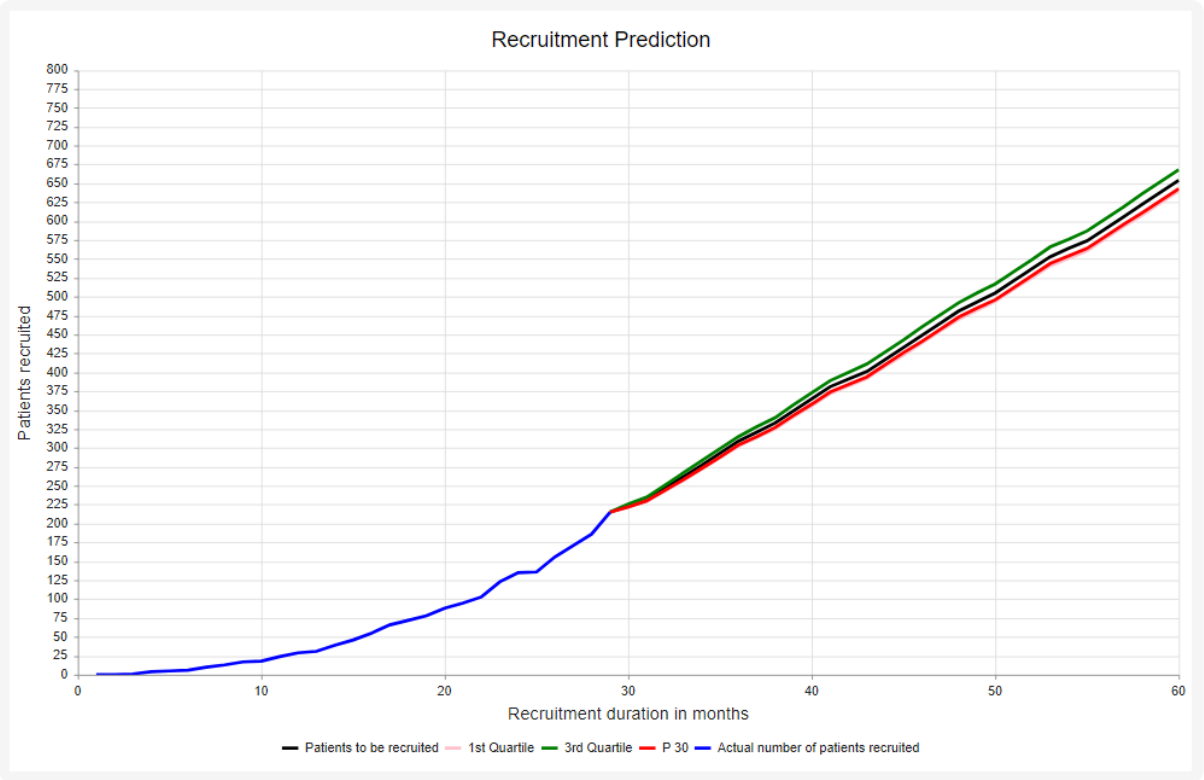


Figure 47: Re-profiling of patient recruitment after 29 months of accrual

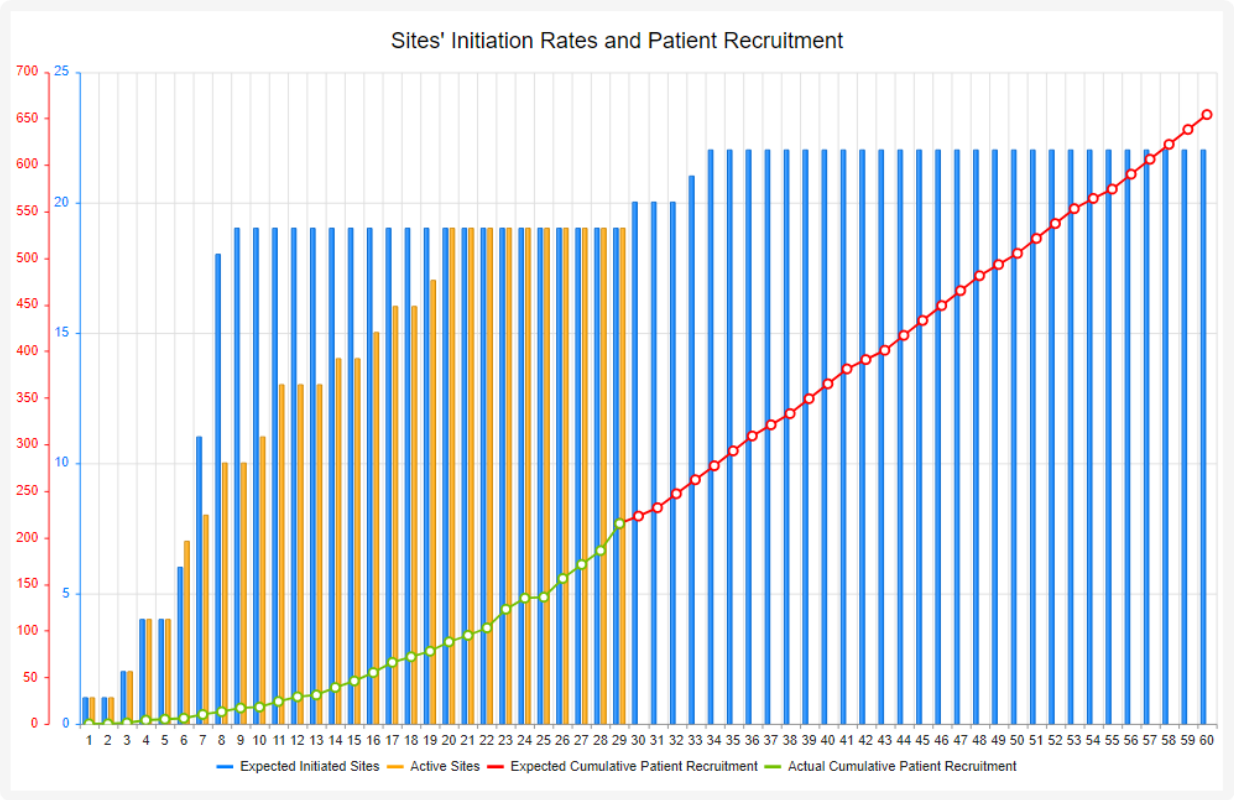


Figure 48: Re-profiling of TOPS trial at patient and centre level

The median number of patients expected to be recruited at the end of the revised 60-month period is 654 patients, with the lowest acceptable limit if that defined at 30%, being 643 patients. In the second graph we can see that all 22 centres are expected to contribute to recruitment.

As we already know by the end of June 2015, 558 infants with an isolated cleft palate were recruited from cleft palate centres in the UK, Scandinavia and Brazil. This is lower than the required sample size of 648 babies, but the decision to stop recruitment at this point was supported by the Oversight Committee after reviewing the impact on trial power and prolongation of the recruitment period for centres' fatigue and funder plausibility.

TOPS was a challenging clinical trial. At the reprofiling stage the revised expected monthly recruitment rates were reduced by more than 50% for half of the centres, while they were slightly higher for three of them. In addition, the recruitment period was extended by 23 months but the trial did not reach its recruitment target on time.

8.5. Discussion

8.5.1. Main findings

In this chapter, I introduce an approach for modelling the number of patients to be recruited in a specific time period. I used an extension of the non-homogeneous Poisson model and incorporated monitoring tools and a re-profiling tool. The user interface is simple and the way the user will need to input the information required is clear. The rational for implementing this approach was to build on but improve the approach already familiar to many researchers based on answers I received from the statisticians' survey [140]. I avoided statistical complexity and focused on ensuring the parameters required were intuitive. A very important aspect of this model at the design stage is that it motivates the investigators to think about all the parameters, which will have an impact on patient recruitment in the study. Acknowledging the presence of those factors and including them in the calculations for the definition of the monthly expected rates, will help in producing more accurate recruitment rates per month, and cumulative rates overall.

The non-homogeneous Poisson model proposed in this chapter offers the option of an independent recruitment rate per month, which is defined by the contribution of the different parameters that are expected to have an impact on patient recruitment. The results from the survey (chapter 6) revealed that the majority of researchers use deterministic approached for recruitment prediction. This new model uses the same approach to define the monthly recruitment rates, but it builds on this by using the Poisson model to define the average number of patients to be recruited and any other quantile, which can be used as the lowest acceptable threshold for the number of patients to be expected.

Despite acknowledging the importance of treating recruitment as a stochastic process, we have specified the monthly recruitment rate (*lambda*) in a deterministic way. This helps to keep the focus of the method on the monthly recruitment rate itself and avoid the introduction of complexity with difficult to define parameter estimates. This could result in overly precise estimates, however the method allows the user to define the lower limit of acceptability. While increasing the uncertainty could be viewed as beneficial, there is a point where the intervals become too wide to be of use to those planning the recruitment for the trial. In a Bayesian model for example, when the investigators are not sure about the progress of recruitment, they define a lower value

for the prior certainty *P* as described in chapter 7, which leads to wider prediction intervals about the average number of patients expected to be recruited.

A desirable feature of the Bayesian models is their ability to include the recruitment rates observed to date during the trial. The limitation was the inability to allow for known future changes, for example introduction of more centres or the end of a learning curve. In the approach developed here, we re-profile the recruitment curve at specific time points allowing the user to incorporate data observed and impact of upcoming changes into the ongoing prediction. This is implemented in a similar way to the original prediction ensuring it builds on user experience.

At the monitoring stage of the trial, the benefit of using a statistical model is the prespecification of a quantile to act as a trigger when the observed recruitment rate is inconsistent with that prespecified. Lee [27] used two interim recruitment goals, the expected interim goal and the minimum acceptable interim goal. The lowest acceptable threshold is defined as the minimum number of participants that will assure with a reasonable probability that the number of patients agreed between the stakeholders and the funder when designing the study, will be reached. The comparison of this threshold with the actual number of patients recruited prompts the investigators to take actions in case patient recruitment is behind schedule. The difficulty in using this method is knowing when to apply these recruitment goals. In the monitoring approach applied here, I use a lower stochastic bound of acceptability. The advantage is that this is continuous across time and the trajectory demonstrates the number of patients expected to be recruited by the end of the trial, if the same trend continues, similarly highlighting the need for action.

When remedial actions are required, researchers will need to define the impact of these actions in the future, meaning that the re-profiling of patient recruitment curve should follow. Here, the research team will need to acknowledge the recruitment performance of the study so far and combine it with the initial estimates defined at the design stage, in order to update the prediction for the future patient recruitment. The impact of any corrective actions required, such as more centres or different expected monthly rates for each centre, can be included at this stage to update the recruitment prediction. After this stage, the user can go back to the monitoring stage and again to re-profiling, as many times as needed during the recruitment phase of the trial.

8.5.2. Strengths and Limitations

This model adds to a deterministic approach by taking into account variability for the number of patients to be recruited when using the Poisson distribution and calculating the probability with which the specific number of patients will be reached.

The model allows the user to easily define the parameters such as the number of centres, the average expected rate per centre, seasonality and any other factor that will have an impact on patient recruitment.

The evaluation of recruitment performance for the study during the monitoring phase, by plotting the expected and the actual figures for both centres and number of patients is very useful in evaluating the progress and informing decision making in relation to any actions required.

The limitation of this model is that the *lambda* parameter of the Poisson distribution is defined in a deterministic way and there is no stochasticity considered around the expected rate. This could be expanded and a distribution could be assigned for the parameter *lambda* as with other methods [38, 62]. However, the model has been developed in a way that can be easily understood by the research team and allow them to incorporate all the factors they believe will have an impact on patient recruitment. Adding a level of complexity to the model implementation should be carefully considered and compared to the benefit this may offer. For example, a point is reached when the level of uncertainty expressed is too wide to make the model helpful.

8.5.3. Summary

As we known from the survey presented in chapter 6, there is a level of scepticism around the benefits of the more complex statistical approaches presented in chapters 2 and 4. Additional barriers are the time required to understand and implement the methods and the lack of software and tools for their implementation. In chapter 7, we provided a Shiny application to make the methods more accessible, however limitations remain. In this chapter, we proposed an alternative method, which builds on the deterministic approach implemented by many, without decreasing flexibility. It provides the users with a familiar framework, such as the use of an excel spreadsheet to calculate the average recruitment rate monthly, but also the use of the Poisson distribution to add uncertainty around the number of patients expected to be recruited in a monthly basis.

The model can also be used for the monitoring and re-profiling of patient recruitment when corrective actions are required, thus offering a complete tool that can be used at the different stages of patient recruitment. The website where the model is hosted provides a user-friendly environment that allows the user to explore its functions.

Chapter 9: Overall Discussion, Future work and Conclusion

9.1. Overview

Clinical trials are designed to answer questions of importance about patient treatments. Without adequate recruitment, clinical trials may not answer the question they were designed to address and therefore patient recruitment is a key determinant of success. However, in most trials enrolment is insufficient in comparison to what was expected, with time and financial extensions requested for 45% of publicly-funded trials in the UK [5], while 26% of the RCTs funded by the Swiss National Science Foundation were prematurely discontinued [6].

A contributing factor in the difference between expected and observed recruitment is the initial prediction, which is frequently based on wrong assumptions, unreliable data sources and overly simplistic methods. The ability to learn from experiences across trials is prevented as the assumptions, data sources, and methods used are not reported. Likewise, methods used for monitoring recruitment during the trial are seldom reported. However, if difficulties with patient recruitment are detected early enough, remedial interventions can then be implemented as necessary, including reprofiling of the remaining recruitment period. Therefore, improving recruitment prediction and monitoring may reduce resource waste.

Statistical methodology has been developed targeting recruitment prediction, however these complex models require potentially unrealistic assumptions and parameter estimation that is less than intuitive, with a call for user-friendly tools to be developed [13].

The central aim of this thesis was to improve recruitment prediction and monitoring by systematically reviewing the methodology available, determining methods used in practice and reducing the gap between model development and implementation.

9.2. Principal findings

The research was guided by three main objectives as they were described in chapter 1. The first objective focused on mapping the statistical methods described in the literature about recruitment prediction and monitoring.

The first systematic review (chapter 2) was conducted to identify research articles describing statistical methods that can be used for recruitment prediction of patients at

the design stage of a clinical trial. The models described varied considerably in their flexibility and assumptions but also in their complexity.

Monitoring of patient accrual to ensure that the trial will reach the recruitment target within the predefined time is crucial and could help investigators to act on time. In the second systematic review (chapter 3), research articles describing methods to compare predicted against actual patient recruitment, including graphical and tabular approaches or simple metrics, were included.

Early detection of inadequate recruitment optimises the ability of researchers to develop rescue strategies or in the absence of potential solutions, recommendations may need to be made for the trial to close to support redistribution of resources to more promising clinical trials.

When corrective actions are not considered sufficient in bringing patient recruitment back on track, then an updated recruitment prediction followed by reprofiling of the trial is required. Predictions made during the trial recruitment period, using observed accrual data, may be considered more reliable than those made at the design stage of the study. The purpose of the third review (chapter 4) was to identify statistical models, which can be used to predict recruitment during trial conduct utilising available accrual data; this approach includes revised predictions. The models described, if broadly implemented, could help investigators and funders evaluate the present recruitment situation and make informed decisions about the future of the trial.

The second objective focused on investigating the level of information provided in the publications about predicted and observed recruitment, and identifying the current practice for recruitment prediction and monitoring. The 25 latest publications from five high impact factor journals were explored to evaluate recruitment reporting (chapter 5), while the current practice was determined by surveying the statisticians and the chief investigators from the National Institute for Health Research, the UK Clinical Research Collaboration registered Clinical Trial Units Network and the European Clinical Research Infrastructure Network (chapter 6).

The limited reporting of recruitment prediction makes it impossible to evaluate the recruitment performance of the trial, since no comparison can be made between the expected and the actual recruitment figures (chapter 5). Researchers should be clear about factors considered at the design stage of the trial and data sources used to

inform their prediction as well as describing their trial experience in the final publications, since this information can be used to inform future studies.

The results of the surveys indicate that recruitment is generally not recognised as a stochastic process in the approaches used and that those involved in recruitment prediction prefer simple approaches (chapter 6). Barriers to uptake of the statistical models include complexity of their implementation and an absence of evidence that the time taken to implement them will result in improving the accuracy of recruitment prediction.

The third objective focused on developing guidance supported by software with a web-based interface to facilitate models' implementation. This was achieved by developing a Shiny application for the implementation of already known models (chapter 7) and by developing a new web-based tool based on the Poisson model to support recruitment prediction, monitoring and re-profiling in a clinical trial (chapter 8).

Shiny application provides an easy to use interface, where the user can implement a range of statistical models by defining the parameters required. The user then can easily observe the impact of parameter changes on the recruitment results and the uncertainty around them.

The results from the two surveys indicated that there are many factors that the investigators need to take into account when designing the trial. Thus, a new model was developed where the user could define all the parameters expected to have an impact on patient recruitment and be able to construct a different recruitment rate per month as needed. The new approach is implemented in a web-based tool, which extends specification of the simple approach used so far to incorporate variation via the Poisson model. The model can be used for the prediction, monitoring and re-profiling of patient recruitment. The website where the PRCT application is hosted, provides a user-friendly environment that allows the user to explore its functions.

9.3. What does this thesis add?

The work of this thesis has provided a detailed insight into the patient recruitment prediction and monitoring in clinical trials. A thorough description of the models for recruitment prediction at the design stage (chapter 2) and during trial conduct (chapter

4) in combination with the list of parameters required for each, could be used as a guide to select the right model depending on the requirements of the trial. Methods to monitor recruitment such as tables and graphs, and metrics such as the R statistic and the Accrual Index provided in chapter 3 can be used to evaluate recruitment efficiency.

In addition, investigating current practice within the research team about recruitment prediction and monitoring, contributed to our understanding of their time constraints and needs. As a result, the Shiny application (chapter 7) and the PRCT web-based method based on the Poisson model (chapter 8) were developed. These are two useful statistical tools, which can contribute to model implementation, thus filling the gap highlighted in the statisticians' survey about the lack of user-friendly applications.

The trials used as case studies to present the possibilities of the Shiny application, underline the advantages and disadvantages of the models. The PRCT application is based on a simple model that places the emphasis on allowing for factors that reduce recruitment capacity and can be used in prediction and monitoring of patient recruitment as well as in reprofiling of future recruitment.

9.4. Implications of the thesis

Patient recruitment has been acknowledged as a challenging issue in clinical trials and it is considered successful only when the recruitment target is achieved. However, recruitment target and the time length required to reach it, are defined when designing the study, making prediction of recruitment a key determinant of whether participant enrolment will be considered adequate or inadequate during the trial conduct when compared with the expected.

While it is clear that modelling recruitment represents a statistical challenge, until the models described in this thesis are implemented within the mainstream, the solutions proposed will be unattainable for many and any resulting improvements will not be observed. Getting the prediction right at the beginning of the study will contribute to better planning. The statistical models described for recruitment prediction at the design stage and during trial conduct allow for the stochasticity and uncertainty around the recruitment process to be incorporated. The discussion in chapter 2 indicates when the models could be used depending on how the expected recruitment rate is defined, the availability of data to be used at the design stage to inform the models, whether the study is a multicentre clinical trial etc. In addition to that, the

flexibility of the research team and whether they are familiar with using statistical models should be considered. As pointed out in the statisticians' survey, they prefer using simple methods, because the time pressure does not allow them to explore more options. Recruitment prediction is usually undertaken during the unfunded preparation time of a grant application, and the time spent on this is limited. However, since there will always be uncertainty around patient recruitment, this should be incorporated and the non-homogeneous Poisson model offered in the PRCT method can be used to account for that. I believe that by providing the proper training, the research team will be able to easily use this method given that this is an extension of the excel spreadsheet the majority of them are already using.

When the trial is ongoing, the description of different approaches that can be used for recruitment monitoring will help the research team to evaluate recruitment performance at centre level and overall and help them plan future recruitment and consider corrective actions when recruitment is slower than expected. Ideally, a recruitment graph would include the number of expected and actual centres and the number of expected and actual patients. When possible the monthly rates of screening compared to actual screen rates could be presented to evaluate the amount of patients moving from the eligibility status to those who gave consent to participate and when reasons for lack of consent are provided, the evaluation and communication of those reasons could be used to inform future practice.

As for the statistical models about recruitment prediction during trial conduct, an extended discussion in chapter 4 suggests whether the models can be used depending on the amount of observed recruitment, the optimal start time for monitoring, centres observed performance etc. Yet, Bayesian models can be used at any time to make ongoing predictions, but when limited observed recruitment data is used, the future prediction could be considered poor since the prediction interval is quite wide, representing a lot of uncertainty about the prediction, which is not useful for decision making during the trial conduct.

As identified in the statisticians' survey, the use of statistical models to predict recruitment depends on the availability of software and tools for their implementation. Thus, the Shiny application was developed and provides an easy to use interface. The user can implement a range of statistical models by defining the parameters required and observe the impact of parameter changes on the recruitment results and the

uncertainty around them. The models can be used at the design stage of the trial or during trial conduct.

Following the feedback of statisticians about the preference of using simplistic approaches for recruitment prediction and monitoring, the PRCT method was developed, which extends specification of the simple approach used so far to incorporate variation via the Poisson model. The PRCT method is hosted in a website that provides a user-friendly interface and allows the user to explore its functions. This simple model will help the research team to account for all the parameters expected to have an impact on patient recruitment when designing the study, monitor recruitment by inputting the observed data and compare them with what was expected, and re-profile the future recruitment depending on the corrective actions required when recruitment is trailing behind schedule.

Implementation of statistical methods for recruitment prediction and monitoring by using web-based statistical tools would help in better planning, early detection of inadequate recruitment with subsequent corrective actions and well-informed future predictions, so that resources are carefully used and waste in research is reduced.

Coronavirus Pandemic

Patient recruitment planning and monitoring can be very challenging under normal circumstances, let alone during a pandemic. Yet, not all the trials were impacted by the pandemic in terms of recruitment and each trial needs to be assessed individually in terms of whether it was at the design stage or at the monitoring stage. The pandemic is unprecedented and there is no data to inform estimates on the impact of recruitment. However, the PRCT method may be used to re-profile and produce alternative scenarios considering a best-case scenario where the trial is not affected by the pandemic and a worst-case scenario where the trial is being halted.

9.5. Strengths and Limitations

This thesis provides a detailed description of the available statistical models and the parameters required for their implementation. Different approaches were used to identify the relevant articles for the three systematic reviews and the strengths and limitations for each have been discussed in the relevant chapters. In the first review, the ORRCA database, a previous systematic review, and an additional Google search were used to identify the eligible papers published until December 2016. It is worth

mentioning that no additional eligible papers were identified with the Google search and this was an indication that the ORRCA database was inclusive. Thus, for the second and the third review, which were conducted in a later time, the ORRCA database was used as the main source of the search for the period up to December 2016 (at the time of the search the ORRCA database contained articles up to December 2016) and we complemented this search by conducting citation tracking of the eligible references. The focus of the citation tracking was mainly on identifying eligible articles that were published after December 2016 (January 2017 to September 2019), so it was deemed appropriate that with citation tracking through Web of Science we could identify these references. As mentioned in chapter 3, it is highly likely that new papers proposing new approaches would reference previous relevant research.

The methods included can be used for recruitment prediction at the design stage, for recruitment monitoring and recruitment prediction during trial conduct.

In addition, the results from both surveys contributed to understanding how the recruitment prediction and monitoring is done within the research team. Survey participants also provided important insight about their needs and preferences in relation to statistical models and web-based applications. This feedback was taken into account when developing the Shiny application and the PRCT method.

The mapping of methodology about recruitment prediction and monitoring in combination with the Shiny application and the new PRCT method could be very useful tools but only if researchers use them in practice. However, the statistical models will be broadly used only if evidence is provided demonstrating their benefit in comparison to the simple approaches used so far. Barriers to uptake of the statistical models include complexity of their implementation and an absence of evidence that the time taken to implement them will result in improving the accuracy of recruitment prediction.

In addition to the publication of the Shiny application and the PRCT method, which are in preparation for submission, workshops could also be organised to let the researchers involved in the patient recruitment process know that there are some tools they could use at the different stages of recruitment. Yet, this should be done once there is evidence that the models included in Shiny and the PRCT website are working

well. This evidence could be obtained by inviting key users to provide initial feedback on their experience of the Shiny and PRCT tools.

For the statistical models to be implemented, data sources are needed to define their parameters. Investigators would use their experience and relevant published data, when available, to inform the parameters. However, whether the data used to inform the model parameters are good enough to provide accurate prediction should be further explored. A score system could be implemented to evaluate model's performance prospectively after the initial prediction at the design stage, based on the data sources used to inform recruitment modelling (e.g. audit data, feasibility surveys, centres' questionnaire, published literature, research team experience, previous studies etc.). When different data sources are used, then a comparison of the expected and observed recruitment could define which approach captures best the observed recruitment.

There are many factors that could have an impact on patient recruitment. Some of them could be considered at the design stage of the study and incorporated with an appropriate definition of the model parameters, but there are other factors for which we cannot account at the design stage. This could be handled with continuous monitoring of recruitment and implementation of corrective actions when required.

Recruitment data from clinical trials were used retrospectively to demonstrate the Poisson and the Bayesian models developed in Shiny, as well as the PRCT model. However, this needs to be done for studies prospectively in real time and in a bigger scale, to gather the proof required to evaluate the performance of the different models.

9.6. Future work arising from this thesis

Recruitment prediction is highly dependent on the data sources used by the research team when designing the study. In chapter 5 we presented the results from a cohort of RCTs regarding the level of information reported about predicted and observed recruitment of patients in clinical trials. A complete comparison of what was expected, which is usually reported in the earliest version of the study protocol, with what was observed in relation to the number of patients, centres and recruitment duration could provide more rich information. However, in chapter 5 we focused only on the final publications and how prediction of recruitment and observed figures were reported. For future work, we will look at how the recruitment prediction is described within protocols and within grant applications for the RCTs included in this cohort.

While research focusing on recruitment challenges is frequently published, the need for more research related to participant retention and evaluation of available methods used has been underlined [143-145]. Clinical trials often struggle to recruit the required number of patients, but there are also many challenges in retaining the number of participants recruited. Retention strategies and digital tools have been investigated and despite the frequency of their use, the potential benefits are still relatively unknown [144]. Further studies are required to evaluate costs, accuracy and efficiency alongside rates of retention, and should also capture key process measures, such as the satisfaction of end-users of the digital tools [143].

Finally, the PRCT method and the models included in the Shiny application will be used to design new studies, monitor patient recruitment and re-profile the recruitment curve when required. Accuracy and efficiency of the new models alongside rates of recruitment need to be assessed. Thus, the results from the different models could be used to evaluate models' performance at the different stages of recruitment. A portfolio of trials will be created including for each trial the prediction, monitoring and reprofiling of recruitment, as a result of the different models. These data will be analysed with the aim of demonstrating evidence of the benefit of the new web-based models. This evidence is required to convince investigators that the time spent learning to use these tools will result in improving the accuracy of prediction and facilitating monitoring.

Part of the future work is also the training of the research staff on how to use the models described in chapters 7 and 8. Whether the level of explanation provided in the website and/or relevant documentation is adequate will be evaluated and updated accordingly. Their feedback can be used to improve the user interface and understand their preferences about the different models provided, which could be based on the requirements of each study.

9.7. Conclusion

The work of this thesis has provided a detailed insight into the challenges regarding recruitment prediction and monitoring of patients in clinical trials. Statistical methodology has been developed to support recruitment prediction at the design stage and during trial conduct. However, lack of time, funding, capacity and the absence of demonstration of model benefits in comparison to simple approaches, are preventing

investigators from implementing them. This is compounded by the absence of web-based interface or software to facilitate models' implementation.

Therefore, with this PhD thesis we contribute to the knowledge enhancement of statistical models for recruitment prediction and methods for recruitment monitoring, and develop an interface to facilitate the implementation of different models. This work will assist investigators with choosing the right model/approach for their trial leading to improvements in the accuracy of recruitment prediction and reducing waste in research.

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Appendix A

Appendix A notes the first author publications arising from this thesis.

Chapter 2

Journal of Clinical Epidemiology 2019 July; doi:10.1016/j.jclinepi.2019.07.002 ; **Title**: A systematic review describes models for recruitment prediction at the design stage of a clinical trial. Authors: **Efstathia Gkioni**, Roser Rius, Susanna Dodd, Carrol Gamble

Chapter 6

Journal of Clinical Epidemiology 2020 March; doi:10.1016/j.jclinepi.2020.03.012 ; **Title**: Statistical models to predict recruitment in clinical trials were rarely used by statisticians in UK and European networks. Authors: **Efstathia Gkioni**, Susanna Dodd, Roser Rius, Carrol Gamble

Appendix B

Appendix B includes supporting information related to Chapter 2.
Some of the articles we considered for inclusion in the systematic in chapter 2, provided the code they used for the implementation of the models they described in the publications. For some of them it was possible to find the relevant code/programme but not for all. Please see below all the information we were able to get from the publications.

1. **Carter *et al, 2005***

Publication: Practical considerations for estimating clinical trial accrual periods: application to a multi-center effectiveness study
https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-5-11

To facilitate implementation of the models in practice, a spreadsheet template for the calculation of the conditional model and SAS programs for the Poisson process are posted on the first author's website http://people.musc.edu/~carterre/manuscripts
We were unable to access this additional material because the link provided in the paper is not working.

2. **Gajewski *et al*, 2008**

Publication: Predicting accrual in clinical trials with Bayesian posterior predictive distributions
https://onlinelibrary.wiley.com/doi/epdf/10.1002/sim.3128

In this paper the authors by using a Bayesian framework, they combine the prior information about the expectations related to recruitment and the information up to date to obtain a prediction. Thus, they provide posterior predictive distribution of the accrual.
The link to the **accrual R package** and all the documentation needed can be found in the link below:
https://cran.r-project.org/web/packages/accrual/index.html

3. Moussa, 1984

Publication: Planning a clinical trial with allowance for cost and patient recruitment rate
https://www.sciencedirect.com/science/article/pii/0010468X84900497

Moussa describes the model introduced by Lee, which has been explained in chapter 2, and provides the code for its implementation and an extension to include cost implications. The programme used has been described in the paper of Moussa and an example of the output has been included as Appendix (please see next page).
The source listing of the program is available from the author on request. We were not able to obtain the source for the Programme.

APPENDIX

Sample input–output

PLANNING A CLINICAL TRIAL

THE CASE OF EQUAL SAMPLE SIZES
(P1 = 0.25, P2 = 0.40, Alpha = 0.010, Power = 0.950, R = 1.000)
SAMPLE SIZE, FIRST GROUP = 318
SAMPLE SIZE, SECOND GROUP = 318
THE 99% CONFIDENCE LIMITS FOR THE DIFFERENCE BETWEEN THE TWO PROPORTIONS

THE LOWER LIMIT = 0.052
THE UPPER LIMIT = 0.248

SAMPLE SIZE REQUIREMENTS FOR MINIMIZING TOTAL COST C, ASSUMING ONE-SIDED TEST
(α = 0.01, Power = 0.95, P1 = 0.25, P2 = 0.40 C1 = 1, C2 = 5)

Ratio of sample sizes ($N2/N1 = R$)	$N1$	$N2$	Required total sample size	Total cost
0.50	484	242	726	1694.004
0.40	567	227	794	1701.581
0.60	429	257	686	1714.137
0.70	389	272	661	1750.102
0.30	706	212	918	1764.588
0.80	359	287	647	1795.958
0.90	336	302	639	1848.407
1.00	318	318	635	1905.470
1.10	302	333	635	1965.888
1.20	290	348	638	2028.821
1.30	279	363	642	2093.688
1.40	270	378	648	2160.074
1.50	262	393	655	2227.676
1.60	255	408	663	2296.265
1.70	249	423	672	2365.666
1.80	244	438	682	2435.745
1.90	239	453	692	2506.394
2.00	234	469	703	2577.526
2.10	230	484	714	2649.074
2.20	227	499	726	2720.981
2.30	223	514	737	2793.199
2.40	220	529	749	2865.689
2.50	218	544	762	2938.420
2.60	215	559	774	3011.362
2.70	213	574	787	3084.493
2.80	211	589	800	3157.792
2.90	208	605	813	3231.242
3.00	206	620	826	3304.828

SAMPLE SIZE REQUIREMENTS FOR MINIMUM TOTAL COST

Ratio of sample sizes (N2/N1 = R)	N1	N2	Required total sample size	Minimum cost
0.50	484	242	726	1694.004

SUMMARY OF THE FIXED COST SAMPLE SIZE ANALYSIS (Total allowed cost = 1500.000)

Sample size		Normal deviate		
Group 1	Group 2	R	Z	Power
429	214	0.50	−0.116	0.454

THE OPERATING CHARACTERISTIC CURVE OF THE CLINICAL TRIAL WITH FIXED COST = 1500

Delta (P2 − P1)	Beta
0.00	0.990
0.01	0.988
0.02	0.981
0.03	0.973
0.04	0.963
0.05	0.948
0.06	0.930
0.07	0.908
0.08	0.880
0.09	0.848
0.10	0.809
0.11	0.765
0.12	0.716
0.13	0.663
0.14	0.606
0.15	0.546
0.16	0.486
0.17	0.425
0.18	0.366
0.19	0.310
0.20	0.258
0.21	0.211
0.22	0.169
0.23	0.133
0.24	0.103
0.25	0.078
0.26	0.057
0.27	0.042
0.28	0.029
0.29	0.020
0.30	0.014
0.31	0.009
0.32	0.006
0.33	0.004
0.34	0.002
0.35	0.001
0.36	0.001
0.37	0.000
0.38	0.000
0.39	0.000
0.40	0.000
0.41	0.000
0.42	0.000
0.43	0.000
0.44	0.000
0.45	0.000

0.46	0.000
0.47	0.000
0.48	0.000
0.49	0.000
0.50	0.000

The operating character is a curve diagram

INTERIM RECRUITMENT GOALS FOR ESTIMATED CONSTANT MONTHLY RECRUITMENT RATES

Interim point (months)	Group 1			Group 2		
	Rate	MAIG+	EIRG*	Rate	MAIG+	EIRG*
	18.914			9.685		
3		50	56.741		25	29.054
6		105	113.483		52	58.108
12		214	226.965		107	116.216
Final		429	453.930		214	232.432

Rate = Estimated monthly recruitment rate
MAIG+ = Minimum Acceptable Interim Goals
EIRG* = Expected Interim Recruitment goal

INTERIM RECRUITMENT GOALS FOR NON-CONSTANT RECRUITMENT RATES

Interim point (months)	Group 1			Group 2		
	Rate	MAIG	EIRG	Rate	MAIG	EIRG
	20.553			10.891		
3		55	61.658		28	32.672
6		108	123.317		55	65.345
12		245	246.633		108	130.690
Final		429	493.266		214	261.380

RECRUITMENT PROJECTION BASED ON ACTUAL ENROLLMENT TO DATE

Group	Contracted goal	Actual enrollment to date	Final projected intake	Standard deviation	Final deficit
1	429	40	320	56.4	−109
2	214	20	160	40.3	−54

PROBABILITY OF ACHIEVING GOAL BASED ON ACTUAL ENROLLMENT TO DATE

Group	Projected probability of achieving		
	Goal	95% goal	90% of goal
1	0.878	0.939	0.973
2	0.792	0.860	0.911

DETERMINATION OF EXTENSION OF RECRUITMENT DURATION BASED ON PROJECTED PROBABILITY OF ACHIEVING THE CONTRACTED GOAL

Group	Planned duration (months)	Recommended extension	
		months	%
1	24	13	54%
2	24	15	63%

THE PROGRAM HAS BEEN SUCCESSFULLY COMPLETED

Appendix C

Appendix C includes supporting information related to chapter 6. More specifically, Ethical Approval for both surveys is provided in C.1, email invitation and the list of questions for the Chief Investigators' survey are given in C.2 and email invitation and the list of questions for the Statisticians' survey are given in C.3.

C.1. Ethical approval

UNIVERSITY OF LIVERPOOL

Health and Life Sciences Research Ethics Committee (Human participants, tissues and databases)

5 September 2018

Dear Prof Gamble

I am pleased to inform you that your application for research ethics approval has been approved. Application details and conditions of approval can be found below. Appendix A contains a list of documents approved by the Committee.

Application Details

Reference:	2282
Project Title:	Survey on statistical methods used for recruitment prediction and monitoring of patients in clinical trials.
Principal Investigator/Supervisor:	Prof Carrol Gamble
Co-Investigator(s):	Miss Efstathia Gkioni, Dr Susanna Dodd
Lead Student Investigator:	-
Department:	Biostatistics
Approval Date:	05/09/2018
Approval Expiry Date:	Five years from the approval date listed above

The application was **APPROVED** subject to the following conditions:

Conditions of approval

- All serious adverse events must be reported to the Committee (ethics@liverpool.ac.uk) in accordance with the procedure for reporting adverse events.
- If you wish to extend the duration of the study beyond the research ethics approval expiry date listed above, a new application should be submitted.
- If you wish to make an amendment to the study, please create and submit an amendment form using the research ethics system.
- If the named Principal Investigator or Supervisor leaves the employment of the University during the course of this approval, the approval will lapse. Therefore it will be necessary to create and submit an amendment form within the research ethics system.
- It is the responsibility of the Principal Investigator/Supervisor to inform all the investigators of the terms of the approval.

Kind regards,

Health and Life Sciences Research Ethics Committee (Human participants, tissues and databases)

edreseth@liverpool.ac.uk

0151 795 4358

Appendix - Approved Documents

(Relevant only to amendments involving changes to the study documentation)

The final document set reviewed and approved by the committee is listed below:

Document Type	File Name	Date	Version
Study Proposal/Protocol	Survey Protocol	22/06/2018	V1.1
Questionnaire	Questions_Chief Investigators survey	27/07/2018	V1.2
Questionnaire	Questions_Statisticians survey	27/07/2018	V1.2
Advertisement	Email invitation_Chief Investigators survey	31/07/2018	V1.2
Advertisement	Email invitation_Statisticians survey	31/07/2018	V1.2

C.2. Chief Investigators' survey: email invitation and list of questions

Email invitation

The email invitation targeting UK respondents is slightly different from the email invitation sent to the ECRIN Chief Investigators as shown in the different sections below.

Subject: Investigating recruitment prediction at the pre-trial planning stage in recently funded clinical trials

Dear Sir/Madam,

My name is Efstathia Gkioni and I am a PhD student at the Department of Biostatistics, University of Liverpool.

My PhD relates to the recruitment prediction of patients in clinical trials and it is funded by Marie Skłodowska-Curie Actions (MiRoR Project: http://miror-ejd.eu/).

……

……..

UK Chief Investigators

The difficulties of predicting recruitment at the trial design or grant application stage are widely acknowledged but little is known about the approaches used. I would like to determine current practice within a cohort of newly funded clinical trials and identified your trial as being potentially eligible.

I obtained your details following a search of the NIHR Journals Library website in relation to this trial:

TRIAL project title and co-investigators

……

……

ECRIN Chief Investigators

The difficulties of predicting recruitment at the trial deign or grant application stage are widely acknowledged but little is known about the approaches used. I would like to determine current practice within a cohort of newly funded clinical trials.

……

……

The following text was the same in both groups (UK & ECRIN Chief Investigators)

I have attached a word document with eight short questions, which I would be grateful if you can answer. As a thank you for taking time to complete the survey all responders will be entered in to a prize draw for £75.

If there is another member of your team who I should contact who led on this aspect then I would be grateful if you could forward this email to them and cc me in or reply to me with their contact details.

Your participation in the survey is voluntary and your decision to respond is taken as evidence of your consent. The data provided will be held securely and treated confidentially. Care will be taken to ensure that neither your trial or yourself are identifiable in any reports. At the end of my PhD an anonymised data set will be created and stored for the purposes of data sharing with identifiers destroyed.

Thank you very much for your time.

Efstathia Gkioni
Marie Curie Research Fellow (MiRoR Project)
Institute of Translational Medicine
Department of Biostatistics
Block F/Waterhouse Building,
University of Liverpool
1-5 Brownlow Street, Liverpool
L69 3GL

Tel: (0151)794 9743
Email: e.gkioni@liverpool.ac.uk

List of questions

The aim of this short survey is to figure out the challenges in predicting recruitment at the pre-trial planning stage. We would like to understand more about how this is currently done in a range of newly funded clinical trials.

Details of Chief Investigators or their Representatives:

Name: _____
Email: _____
Country: _____

We ask for the above details for the sole reason of keeping a record of who has responded. We will not use any of the details for any analyses or reporting.
Any responses will be anonymised in relation to the identity of yourself and your trial.

1. In determining the disease or condition prevalence, what sources of data were available to you to use? *Please select all that apply.*

    a) Population based data on Geographical areas covered by sites
    b) Disease/condition incidence data
    c) Audit data from a single site
    d) Audit data from multiple sites
    e) Estimates obtained from sites based on their experience/perceptions rather than available data
    f) Feasibility or pilot study
    g) Previous RCTs in similar populations
    h) Other - Please specify

Answer:
……
……
……
……

2. In considering the translation of these data sources to your trial population which of the following adjustments did you make within your grant application to predict recruitment in to your study? *Please select all that apply.*

    a) Estimated impact of specific eligibility criteria
    b) Ethnic minorities (e.g. being of an ethnic minority appears to be barrier to participation in RCTs)
    c) Seasonal effects
    d) Consent rate
    e) Other - Please specify
    f) None

Answer:
……
……

……
……

3. Within your trial's recruitment period, did you assume that all sites would be open for the same length of time?

    a) Yes
    b) No - Please specify

Answer:
……
……
……
……

4. Within your trial's recruitment period, did you assume that all sites would have the same average recruitment rate?

    a) Yes
    b) No - Please specify

Answer:
……
……
……
……

5) In considering recruitment to your trial, were you aware of any trials recruiting at the same time that would compete for the same patient population?

    a) Yes - please specify any strategy employed to allow for the impact on your recruitment
    b) No

Answer:
……
……
……
……

6) Did you search a trial registry for competing trials?

    a) Yes
    b) No

Answer:

……
……
……
……

7) Is your trial open to co-enrollment (e.g. patient enrolment to more than one trial)?

   a) No
   b) If yes, what restrictions apply?

Answer:
……
……
……
……

8) In estimating your recruitment rate, there may be a need to be optimistic about your recruitment rate for the trial to be attractive to the funder. Do you feel that this issue impacted the recruitment rate used?

   a) No
   b) Yes

Answer:
……
……
……
……

Thank you for your participation. A summary of the study findings will be sent to you at your request when the study is completed.

C.3. Statisticians' survey: email invitation and list of questions

Email invitation

Subject: Exploring the methods used for the prediction and monitoring of patient recruitment in clinical trials - a survey across UKCRC registered trials units and members of the ECRIN Organisation

I would like to ask you to participate in a brief survey to determine current practice in predicting participant recruitment in clinical trials.

Your responses to this survey will help us determine current practice and the role of statistical models identified in the literature.

The survey is brief and will take about 10 minutes to complete. As a thank you for taking time to complete the survey all responders will be entered in to a prize draw for £75.

Please click the link below to go to the survey Web site or copy and paste the link into your Internet browser.

Survey link: https://survey.liv.ac.uk/Recruitment-Prediction-Methods/

Your participation in the survey is voluntary and your decision to respond is taken as evidence of your consent. The data provided will be held securely and treated confidentially. Care will be taken to ensure that neither your clinical trials unit or yourself are identifiable in any reports. This survey will contribute to my PhD. At the end of my PhD an anonymised data set will be created and stored for the purposes of data sharing with identifiers destroyed.

Thank you very much for your time and cooperation.

Efstathia Gkioni
Marie Curie Research Fellow (MiRoR Project)
Institute of Translational Medicine
Department of Biostatistics
Block F/Waterhouse Building,
University of Liverpool
1-5 Brownlow Street, Liverpool
L69 3GL

Tel: (0151)794 9743
Email: e.gkioni@liverpool.ac.uk

List of questions

Subject: Exploring the methods used for the prediction and monitoring of patient recruitment in clinical trials - a survey across UKCRC registered trials units and members of the ECRIN Organisation
ECRIN: *European Clinical Research Infrastructure Network*

CTU/ Individual Institution name:
_____

Details of Stats Representative:
Name: _____
Email: _____
Country: _____

We ask for the above details for the sole reason of keeping a record of who has responded. We will not use any of the details for any analyses or reporting.

The following questions have been designed to investigate the practices used within your CTU for the recruitment prediction of patients in clinical trials. The aim of this survey is to identify which methods/practices investigators routinely use, whether they consider these methods to be effective and whether they are aware of the statistical models identified in the literature, which could be used for recruitment prediction.

Your participation in the survey is voluntary and all of your responses will be kept confidential. No personally identifiable information will be associated with your responses to any reports of these data and subsequently, your responses will be destroyed.

A. Introductory questions

1. Who usually leads recruitment prediction for a clinical trial within your unit?
   Please select all that apply.
   a) Chief Investigator
   b) Trial Coordinator
   c) Statistician
   d) Other (e.g. IT team, Senior staff, Please specify)

2. Do you believe a statistician should be involved in the recruitment prediction process?
   a) Yes
   b) No

   Please give reasons

3. When predicting the recruitment rate at the **pre-trial planning stage**, where do you find the information about the prevalence of the condition being studied, the eligibility of patients, the consent rate of participants etc.?
   Please provide information.

4. In considering recruitment to trials in your CTU, are you usually confident that you are aware of other trials recruiting at the same time that would compete for the same patient population?

    c) Not confident at all
    d) Not very confident
    e) Neither
    f) Fairly confident
    g) Very confident

B. Recruitment prediction

5. In addition to the number of patients and the number and size of sites, what factors would you routinely consider when predicting rates of recruitment? *Please select all that apply.*
    a) Staggered site openings
    b) Seasonal variation
    c) Holiday periods
    d) Other (Please give details)

6. Do you use any statistical model for recruitment prediction?
    a) Yes

    Please specify

    b) No

7. Are you aware of any of the statistical approaches listed below for use in recruitment prediction? *Please select all that apply.*
    a) Poisson model- assumes a constant average rate of recruitment
    b) Poisson Gamma model- which models variability in centre recruitment rates using a gamma distribution
    c) Bayesian approaches requiring a prior for recruitment to be specified
    d) Other (Please give details)
    e) None

8. Have you ever simulated recruitment data to support your pre-trial planning?
    a) Yes, routinely
    b) Sometimes
    c) Never

9. If you do not use any of the approaches mentioned above for recruitment prediction, what is the reason for this? *Please select all that apply.*
    a) I prefer using a simple approach (e.g. using Excel) rather than assuming statistical distributions for recruitment prediction
    b) I am not familiar with these models for recruitment prediction
    c) I am familiar with some/all of these models but I don´t know how to implement them for recruitment prediction

d) I am not convinced of the value of implementing these models
e) Other (Please give details)

C. Recruitment Monitoring and implementation of statistical models via web application

10. How do you routinely monitor recruitment during the course of a trial? *Please select all that apply.*
    a) Tables showing the expected and actual recruitment rates
    b) Recruitment Graphs showing the expected and actual recruitment rates
    c) Individual recruitment targets for each site
    d) Common recruitment target for all sites
    e) Comparison of overall recruitment rates for each site with recruitment rate over recent months
    f) Other (Please give details)

11. Are you aware of any software/web platforms for planning and monitoring patient recruitment?
    (a) Yes
    Please give details
    (b) No

12. If a user-friendly web application implementing some of the aforementioned models became freely available, would you be interested in using it for predicting and/or monitoring of the trial recruitment? *Please select all that apply.*
    a) No, I don't believe it is a statistical issue and it is best handled by the trial team.
    b) Not for prediction but I would be interested in using it for monitoring
    c) Yes, I want to improve prediction of recruitment
    d) Yes, I want to use it for both initial prediction and monitoring of recruitment
    e) Other (Please give details)

13. Please give details of any further practices or tools/resources that you think could influence your future practice, in terms of prediction accuracy in patient recruitment.

14. Do you have any comments or suggestions on how funders/trial teams monitor recruitment progress/milestones?

Thank you for your participation. A summary of the study findings will be sent to you at your request when the study is completed.

Appendix D

Appendix D includes supporting information related to Chapter 7. The R code developed for the Shiny application is provided below.

```
# This is the user-interface definition of a Shiny web application.
# Find out more about building applications with Shiny here:
http://shiny.rstudio.com/

library(shiny)
if(!"poisson" %in% installed.packages()) install.packages("poisson")

library(poisson)

if(!"accrual" %in% installed.packages()) install.packages("accrual")

library(accrual)

if(!"DT" %in% installed.packages()) install.packages("DT")

library(DT)

library(shinyjs)

## Define UI
ui<-fluidPage(
  useShinyjs(),

## Application title
  titlePanel("Patient Recruitment"),
##
  sidebarLayout(position="left",
                sidebarPanel(width=3,
                             #Merge HPP, NHPP and Bayesian models
```

```
                selectInput("model", "Statistical Model",
                            c("HPP"=1, "NHPP"=2, "Bayesian1_Patients"=3,
"Bayesian1_Time"=4, "Bayesian2"=5)),
                ## HPP Model
                conditionalPanel(
                  condition="input.model==1",

                  sliderInput(inputId="HPPlambda",
                              label="The rate at which events occur in the Poisson
process:",
                              min = 0.1, max = 20, value =5.6, step =0.1),

                  sliderInput(inputId="HPPnum.events",
                              label="Number of patients:",
                              min = 1, max = 800, value =152, step = 1),

                  sliderInput(inputId="HPPt1",
                              label="End time:",
                              min = 1, max = 80, value =24, step = 1),

                  sliderInput(inputId="HPPnum.sims",
                              label="Number of simulated paths to plot:",
                              min = 1, max = 1000, value=500, step = 1),

                  sliderInput(inputId="HPPnum.points",
                              label="Number of points to use in estimating mean and
                              quantile processes:",
                              min = 1, max = 200, value =100, step = 1)

                ),
                ## NHPP Model
                conditionalPanel(
                  condition="input.model==2",
```

```
  sliderInput(inputId="NHPPlambda",
              label="The rate at which events occur in the Poisson
process:",
              min = 0.1, max = 20, value =6, step =0.1),

  sliderInput(inputId="NHPPnum.events",
              label="Number of patients:",
              min = 1, max = 800, value =152, step = 1),

  sliderInput(inputId="NHPPt1",
              label="End time:",
              min = 1, max = 80, value =24, step = 1),

  sliderInput(inputId="NHPPmonth",
              label="Non-homogeneous recruitment time:",
              min = 1, max = 36, value =6, step = 1),

  sliderInput(inputId="NHPPnum.sims",
              label="Number of simulated paths to plot:",
              min = 1, max = 1000, value=500, step = 1),

  sliderInput(inputId="NHPPnum.points",
              label="Number of points to use in estimating mean and
              quantile processes:",
              min = 1, max = 200, value =100, step = 1)
 ),

 ## Bayesian Model with three different options for the prior
 conditionalPanel(
  condition="input.model==3",

  sliderInput(inputId="B1P_n",
              label="Target sample size:",
```

```
                min = 1, max = 800, value =190, step = 1),

              sliderInput(inputId="B1P_T",
                label="Target completion time:",
                min = 1, max = 80, value =45, step = 1),


              sliderInput(inputId="B1P_P",
                label="Prior Certainty:",
                min = 0, max = 1, value=0.1, step = 0.01),

              sliderInput(inputId="B1P_m",
                label="Sample observed to date:",
                min = 0, max = 500, value =100, step = 1),

              sliderInput(inputId="B1P_tm",
                label="Time to date:",
                min = 0, max = 50, value =24, step = 1),

              sliderInput(inputId="B1P_Tp",
                label="Specific time that want to predict the recruitment:",
                min = 1, max = 80, value =45, step = 1),


              selectInput(inputId="B1P_Prior", label = "Method:",
                choices = c("Informative Prior", "Accelerated Prior", "Hedging
Prior"),
                selected = "Informative Prior")
            ),

            ## Bayesian Model with three different options for the prior
            conditionalPanel(
              condition="input.model==4",
```

```
                sliderInput(inputId="B1T_n",
                            label="Target sample size:",
                            min = 1, max = 800, value =190, step = 1),

                sliderInput(inputId="B1T_T",
                            label="Target completion time:",
                            min = 1, max = 80, value =45, step = 1),



                sliderInput(inputId="B1T_P",
                            label="Prior Certainty:",
                            min = 0, max = 1, value=0.5, step = 0.01),

                sliderInput(inputId="B1T_m",
                            label="Sample observed to date:",
                            min = 0, max = 500, value =100, step = 1),

                sliderInput(inputId="B1T_tm",
                            label="Time to date:",
                            min = 0, max = 50, value =24, step = 1),

                sliderInput(inputId="B1T_Np",
                            label="The specific number of subjects want to be
predicted:",
                            min = 1, max = 800, value =190, step = 1),

                selectInput(inputId="B1T_Prior", label = "Method:",
                  choices = c("Informative Prior", "Accelerated Prior", "Hedging
Prior"),
                            selected = "Informative Prior")
              ),

              ## Bayesian Model where we can upload a csv file
              ## with the enrolment data we have up to date
```

```
                    conditionalPanel(
                     condition="input.model==5",

                     fileInput("data", "Choose CSV File",
                               multiple = FALSE,
                               accept = c("text/csv","text/comma-separated-
values,text/plain",
                                          ".csv")
                     ),
                     checkboxInput("header", "Header", TRUE),

                     sliderInput(inputId="B2n",
                                 label="Target sample size:",
                                 min = 1, max = 800, value =190, step = 1),

                     sliderInput(inputId="B2T",
                                 label="Target completion time:",
                                 min = 1, max = 80, value =48, step = 1),

                     sliderInput(inputId="B2P",
                                 label="Prior Certainty:",
                                 min = 0, max = 1, value=0.1, step = 0.1)
                    )


                   ),# close the sidebarPanel
            # Show a plot of the generated distribution
            mainPanel(
              tabsetPanel(id="menu",
                          tabPanel("Model Description",
                                   br(),
                                   br(),
                                   conditionalPanel(
                                    condition="input.model==1",
```

```
                p("HPP: Homogeneous Poisson Process"),
                br(),
                p("In HPP the average accrual rate is considered constant."),
                br(),
                p("Patient arrival times in a clinical trial are considered
random and there are examples such as single centre trials where the gap between
patient enrolments is expected to be the same, on average, throughout the trial."),
                br(),
                p("When these assumptions apply, patient recruitment can
be modelled as a homogeneous poisson process.")
                ),
               conditionalPanel(
                condition="input.model==2",
                br(),
                p("NHPP: Non-Homogeneous Poisson Process"),
                p("Based on the NHPP approach, patient accrual initially is
anticipated to increase linearly and after a predefined time point is assumed to be
constant."),
                br(),
                p("In multi-centre clinical trials, for example, the gap
between patient enrolments is expected to be large at the beginning of the trial
                  but it reduces as more centres are open to recruitment."),
                br(),
                p("Patient recruitment in these trials can be modelled by
using non-homogeneous Poisson processes,
                  where the recruitment rate is expected to increase linearly
as more centres are open until the time when all centres are open,
                  and the recruitment rate is expected to reach its full
capacity and remains constant after that.")
                ),

               conditionalPanel(
                condition="input.model==3",
                br(),
```

p("Bayesian Accrual Prediction"),
br(),
p("A Bayesian method has been developed to integrate researcher's experience on previous trial and data from the current study in order to provide reliable prediction on patient accrual rate for clinical trials. In this approach assumes that the waiting time between the recruitment of two consecutive subjects are i.i.d. exponential random variables. A conjugate prior distribution is used for the underlying enrollment rate "),

br(),
p("Parameter description"),
br(),
p("1. Target sample size is the number of patients expected to be recruited in a fixed time frame."),

br(),
p("2. Target completion time is the predifined duration of the trial."),
br(),
p("3. Prior certainty is a parameter P (0<P<1) which defines the confidence of investigators about their anticipation for the time needed to enroll all patients in the trial."),
br(),
p("4. Sample observed to date is the number of patients already enrolled in the clinical trial."),
br(),
p("5. Time to date is the number of months since the trial initiation date."),
br(),
p("6. This time parameter is for the duration the users want to define the number of patients to be expected."),
br(),
p("The Method parameter defines the Prior option."),
br(),

```
                p("'Informative Prior' is defined after investigators answer to
two questions:
                  (1) How long will it take to enroll n patients and
                  (2) How confident they are in their answer to (1)"),
                br(),

                p("'Accelerated Prior' means that the value for P is
calculated as follows: P=1-m/n. This is a combination of accrual data where m is the
number of patients enrolled up to date and n is the overall number of participants
expected to be enrolled."),
                br(),
                p("'Hedging Prior' specify the prior distibution for P as
uniform(0,1) instead of fixing investigator's confidence (P) as a single value." )
                ),

               conditionalPanel(
                 condition="input.model==4",
                 br(),
                 p("Bayesian Accrual Prediction"),
                 br(),
                 p("A Bayesian method has been developed to integrate
researcher's experience on previous trial and data from the current study in order to
provide reliable prediction on patient accrual rate for clinical trials. In this approach
assumes that the waiting time between the recruitment of two consecutive subjects are
i.i.d. exponential random variables.  A conjugate prior distribution is used for the
underlying enrollment rate "),

                 br(),
                 p("Parameter description"),
                 br(),
                 p("1. Target sample size is the number of patients expected
to be recruited in a fixed time frame."),

                 br(),
```

```
                p("2. Target completion time is the predifined duration of
the trial."),
                br(),
                p("3. Prior certainty is a parameter P (0<P<1) which defines
the confidence of investigators about their anticipation for the time needed to enroll all
patients in the trial."),
                br(),
                p("4. Sample observed to date is the number of patients
already enrolled in the clinical trial."),
                br(),
                p("5. Time to date is the number of months since the trial
initiation date."),
                br(),
                p("6. This parameter defines the number of patients for
which the users want to define the recruitmetn duration to be expected."),
                br(),
                p("The Method parameter defines the Prior option."),
                br(),
                p("'Informative Prior' is defined after investigators answer to
two questions:
                  (1) How long will it take to enroll n patients and
                  (2) How confident they are in their answer to (1)"),
                br(),

                p("'Accelerated Prior' means that the value for P is
calculated as follows: P=1-m/n. This is a
                  combination of accrual data where m is the number of
patients enrolled up to date
                  and n is the overall number of participants expected to be
enrolled."),
                br(),
                p("'Hedging Prior' specify the prior distribution for P as
uniform(0,1) instead
                  of fixing investigator's confidence (P) as a single value." )
```

```
                ),


                conditionalPanel(
                  condition="input.model==5",
                  br(),
                  p("Bayesian model with Informative Prior in a multicentre
study "),
                  br(),
                  p("In a multicentre clinical trial, the contribution of centres
in overall patient recruitment is very important
                    and could define whether or not patient recruitment will be
succesful."),
                  p("In this Bayesian model the user has the option to upload a
csv file with the following information:"),
                  br(),
                  p("1. number of centres"),
                  br(),
                  p("2. the duration in months for which each centre has been
active, and "),
                  br(),
                  p("3. the number of patients recruited so far from each
centre "),
                  br(),
                  p("Each row in this file represents one centre."),
                  br(),
                  br(),
                  p("Additionally, the target sample size and the target
completion time need to be defined, as well as the prior certainty,
                    which represents investigators prior beliefs about the
progress of recruitment in the formula of the informative prior")
                  )
                  ),
```

```
                ##  At this point we want to provide information in a table format
for the number of patients recruited based on the model.
                tabPanel("Patient Enrolment Times",
                        br(),

                        actionButton("actionTable",label = "Update"),
                        br(),
                        br(),
                        br(),
                        dataTableOutput("EventTimes"),
                        br()

                ),
                ## Provide the recruitment graph for each model
                tabPanel("Recruitment graph",
                        br(),
                        br(),
                        br(),
                        br(),

                        plotOutput(
                          "mainplot", width = 800, height = 500),
                        conditionalPanel(
                          condition="input.menu==\'Recruitment graph\'",
                          actionButton("action", label = "Display Graph")
                          )

                ),
                ## Provide supplementary material for the better understanding of
the models
                tabPanel("Useful Information",verbatimTextOutput('),
                        br(),
```

```
                p("The documentation for the Poisson R Package and the
available Poster can be accessed below:"),
                br(),
                p("Poisson: Simulating Homogenous & Non-Homogenous
Poisson Processes"),
                br(),
                p("https://cran.r-
project.org/web/packages/poisson/index.html"),
                br(),
                p("doi:10.1186/1745-6215-16-S2-P85"),
                p("Brock et al:  Modelling clinical trial recruitment using
poisson processes. Trials 2015 16(Suppl 2):P85"),

                br(),

p("##################################################################
###############"),
                br(),
                br(),
                p("The documentation for the Accrual R package and two
relevant publications can be accessed below:"),
                br(),
                p("https://cran.r-
project.org/web/packages/accrual/index.html"),
                br(),
                p("Gajewski et al:  Predicting accrual in clinical trials with
Bayesian posterior predictive distributions"),
                p("doi/abs/10.1002/sim.3128"),
                br(),
                p("And"),
                p("Jiang et al: Modeling and validating Bayesian accrual
models on clinical data and simulations using adaptive priors"),
                p("doi: 10.1002/sim.6359.")
            )
```

```
                              )#close the tabsetPanel
                              )#close the mainPanel
                              )#close the sidebarLayout
  )#close the fluidPage

#########################################################################
#####
server<-function(input, output) {

  output$EventTimes <- renderDataTable({
    set.seed(1234)
    input$actionTable

####
observe({
      if (input$model==1)
        shinyjs::show(id ="EventTimes" )

      else if (input$model==2)
        shinyjs::show(id ="EventTimes" )

      else
        shinyjs::hide(id ="EventTimes")
    })
     ##The hpp.sim produces the n consecutive event times of the HPP with given rate.
      if(input$model==1)
      results<-hpp.plot(input$HPPlambda, input$HPPnum.events,
                        input$HPPnum.sims, t0=0,
                       input$HPPt1, input$HPPnum.points)$x[-1,]

      results2<-hpp.plot(input$HPPlambda, input$HPPnum.events,
                        input$HPPnum.sims, t0=0,
                        input$HPPt1, input$HPPnum.points)$x.q[-1,]
```

```
    #The table with the rowMeans for each event time is presented,
    # where each row represent the simulated times for one patient.

    ##NHPP model
    if(input$model==2){
      set.seed(1234)
      intensity <- function(t) pmin(t/input$NHPPmonth, 1)

      results<-nhpp.plot(input$NHPPlambda, input$NHPPnum.events,
prob.func=intensity,
                  input$NHPPnum.sims, t0=0, input$NHPPt1,
input$NHPPnum.points)$x[-1,]

      results2<-nhpp.plot(input$NHPPlambda, input$NHPPnum.events,
prob.func=intensity,
                input$NHPPnum.sims, t0=0, input$NHPPt1,
input$NHPPnum.points)$x.q[-1,]
    }


table <-
data.frame(Patients=1:nrow(results),TimeRecruited=round(rowMeans(results), digits
= 2), Quantile=round(results2, digits=2))
   #The variable TimeRecruited is defined as the mean of each row, where each row
#represents one patient

   datatable(table, filter="top", rownames = FALSE)

   table2 <-
data.frame(Patients=1:nrow(results),TimeRecruited=round(rowMeans(results),digits =
2), Quantile=round(results2, digits=2))

 })
```

```
###########
  observe({
    if (input$B1P_Prior=="Informative Prior")
      shinyjs::show(id ="B1P_P" )
    else
      shinyjs::hide(id ="B1P_P")
  })

  observe({
    if (input$B1T_Prior=="Informative Prior")
      shinyjs::show(id ="B1T_P" )
    else
      shinyjs::hide(id ="B1T_P")
  })

  output$mainplot <- renderPlot({
    set.seed(1234)
    input$action
    isolate({
      if(input$model==1)

        hpp.plot(input$HPPlambda, input$HPPnum.events,
                 input$HPPnum.sims, t0=0,
                 input$HPPt1, input$HPPnum.points, xlab = "t (months)", ylab = "Number
of patients")



      if(input$model==2){

        intensity <- function(t) pmin(t/input$NHPPmonth, 1)
        nhpp.plot(input$NHPPlambda, input$NHPPnum.events, prob.func=intensity,
                  input$NHPPnum.sims, t0=0,
                  input$NHPPt1, input$NHPPnum.points, xlab = "t (months)", ylab =
"Number of patients")
```

```
    }

    # Produce a plot and output for prediction of the number of subjects can be
recruited in a #fixed time frame.
    if(input$model==3)

      accrual.n.plot(input$B1P_n, input$B1P_T,
                     input$B1P_P, input$B1P_m, input$B1P_tm, input$B1P_Tp,
input$B1P_Prior)

    # Produce a plot and output for prediction of time frame for a certain number of
#subjects.
    if(input$model==4)
      accrual.T.plot(input$B1T_n, input$B1T_T,
                     input$B1T_P, input$B1T_m, input$B1T_tm, input$B1T_Np,
input$B1T_Prior)

    # Produce a plot and output for prediction of the number of subjects for a
multicenter #trial can be recruited in a fixed time frame.
    if(input$model==5){

      req(input$data)
      data<-read.csv(input$data$datapath,
                     header =TRUE,
                     sep =',')
      dimdata<-dim(data)[1]

      set.seed(123)

      accrual.plot.multicenter(input$B2n, input$B2T,
                               input$B2P, dimdata, max(data[,2]), data[,2], data[,3], all=TRUE)

    }
```

```
    #title(paste("Statistical Model", input$model))
  })})

}
shinyApp(ui = ui, server = server)

#The end
```

Appendix E

Appendix E includes supporting material related to Chapter 8. An example of the R code developed for the Poisson model at the design stage (E.1) and an example for the Poisson model at the re-profiling stage (E.2) are provided below.

E.1. Design stage

```
#Poisson model

#The inverse CDF at q is the smallest integer x, such that CDF[dist,x]>=q

#In R there is the quantile function for the Poisson

#qpois(p, lambda, lower.tail = TRUE, log.p = FALSE)

prct <- function(recruitmentTarget, recruitmentDuration, CumulativeRates_exp,

add_percentile)

{


X<-matrix(NA, nrow=length(recruitmentDuration), ncol=3)

for(i in 1: length(recruitmentDuration)){

X[i,]<-qpois(c(0.25, 0.75, add_percentile=0.30), lambda=CumulativeRates_exp[i])

}

print(X)


##Print the median for the expected number of patients per month

Cum_medians<-vector()

for (i in 1: length(recruitmentDuration)){

Cum_medians[i]<-qpois(0.5, lambda=CumulativeRates_exp[i])

}

print(Cum_medians)
```

```
##Print all the results together in one table
table<-

data.frame(Month=1:length(recruitmentDuration),Expected_Patients=Cum_medians,

Quantile=X)

print(table)


}

prct (recruitmentTarget, recruitmentDuration, CumulativeRates_exp, 0.30)
```

The following is an example describing the data used for the model implementation. In the PRCT tool, the data will be extracted from the information inputted by the user at the design stage.

```
setwd("Define the path where to find the data")


## Read data in  R
mydata<- read.csv(file="EcLiPSE_design(2).csv", header=TRUE)

head(mydata)

#the following parameters to be defined:

#the monthly rates

#the expected recruitment target

#the expected recruitment duration


#Define recruitment duration in months

recruitmentDuration<- c(1:mydata$rec.duration[1])

print(recruitmentDuration)


#Define recruitment target

recruitmentTarget = mydata$rec.target[1]

print(recruitmentTarget)
```

```
#Define the monthly rates

for (i in 1:length(recruitmentDuration)){

  monthlyRates<-mydata$rate

}
print(monthlyRates)

#Define the cumulative expected recruitment rates

for (i in 1:length(recruitmentDuration)){
  CumulativeRates_exp<-c(0.2343, 0.8679, 2.0267,3.5667, 5.5129, 7.8645,
10.7004,14.0019, 17.8563,22.2605, 27.2649, 32.8287, 39.0164, 45.78, 53.1445,
61.1117, 69.7116, 78.9752, 88.8259, 99.2211, 110.0929, 121.4515, 133.3064,
145.6712, 158.5594, 171.7958, 185.2158, 198.6358, 212.0558, 225.4758, 238.8958,
252.3158, 265.7358, 279.1558, 292.5758,305.9958)
}
print(CumulativeRates_exp)

##The end
```

E.2. Re-Profiling stage

```
#This R code version is for the re-profiling phase
#We need to extract the cumulative number of patients recruited up to date and define
the remaining expected number of patients and the remaining time

#Data extracted should contain:
#(1) the expected recruitment at the design stage
#(2) the actual patient recruitment up to date and
#(3) the revised expected recruitment for the remaining months based on recruitment
up to date

prct <- function(recruitmentTarget, recruitmentDuration, New_CumulativeRates_exp,

add_percentile)

{

#At this point we need to produce data based on the new recruitment rate after the first

#accrual data we had


  Y<-matrix(NA, nrow=length(new_recruitmentDuration), ncol=3)
```

```
 for(i in 1:length(new_recruitmentDuration)){
   Y[i,]<-qpois(c(0.25, 0.75,
add_percentile=0.30),lambda=New_CumulativeRates_exp[i])
 }
 print(Y)

 #Print the median for the expected number of patients per month
 Cum_medians<-vector()
 for (i in 1: length(new_recruitmentDuration)){
  Cum_medians[i]<-qpois(0.5, lambda=New_CumulativeRates_exp[i])
 }
 print(Cum_medians)


 #Print all the results together in one table
 table<-
data.frame(Month=1:length(new_recruitmentDuration),Expected_Patients=Cum_med
ians, Quantile=Y)
 print(table)
}
prct(recruitmentTarget, recruitmentDuration,New_CumulativeRates_exp, 0.30)
```

The following is an example describing the data used for the model implementationIn the PRCT tool, the data will be extracted from the information inputted by the user at the monitoring and re-profiling stages.

```
setwd("Define the path where to find the data ")
#Read the new csv file in R
mydata<- read.csv(file="EcLiPSE_reprofile(4).csv", header=TRUE)
head(mydata)
```

```
########### Original and updated duration for the trial
#Define recruitment duration in months

recruitmentDuration<- c(1:mydata$recruitment.duration[1])

print(recruitmentDuration)


#Define the time up to date

time_uptodate<-c(1:mydata$time_up.to.date[1])

print(time_uptodate)


###########Original and updated patient target for the trial

#Define recruitment target

recruitmentTarget = mydata$recruitment.target[1]

print(recruitmentTarget)


#Define the number of patients up to date

patients_uptodate<-mydata$patients_up.to.date[1]

print(patients_uptodate)


#Define the new target about the number of patients

new_recruitmentTarget = recruitmentTarget-patients_uptodate

print(new_recruitmentTarget)


#Define the new recruitment duration

new_recruitmentDuration<-c(length(time_uptodate)+1:(length(recruitmentDuration)-

length(time_uptodate)))

print(new_recruitmentDuration)


#Define the actual monthly rates for the time up to date
```

```
#We can use just a vector which stores the actual number of patients recruited up to
date
for (i in 1:length(time_uptodate)){
  monthlyRates_actual<-c(0,0,0,0,1,1,2,5,4,3,1,4)
}
print(monthlyRates_actual)

#Print the cumulative number of patients recruited
for (i in 1:length(time_uptodate)){
  monthlyRates_cumulative<-cumsum(monthlyRates_actual)
}
print(monthlyRates_cumulative)

#Define the new expected monthly rates
for (i in 1:length(new_recruitmentDuration)){
new_monthlyRates_exp<-
c(6.1877,6.7636,7.3645,7.9672,8.5999,9.2636,9.8507,10.3952,10.8718,11.3586,
11.8549,12.3648,12.8882,13.3264,13.69,13.97,14.25,14.53,14.72,14.82,14.82, 14.82,
14.82,14.82, 14.82,14.82)
}
print(new_monthlyRates_exp)
#Print the new cumulative expected monthly rates
for (i in 1:length(recruitmentDuration)){
New_CumulativeRates_exp<-c(6.1877, 12.9513, 20.3158, 28.283, 36.8829, 46.1465,
55.9972, 66.3924, 77.2642, 88.6228, 100.4777, 112.8425, 125.7307, 139.0571,
```

152.7471, 166.7171, 180.9671, 195.4971, 210.2171, 225.0371, 239.8571, 254.6771,

269.4971, 284.3171, 299.1371,313.9571)

}
print(New_CumulativeRates_exp)

##The end