Estimating Site Performance 2 (ESP2) Study Protocol

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STUDY SUMMARY

Question asked – Can a guided trial prediction form for trial mangers be used as a way of predicting which trial sites will recruit to target?

Considered for entry – Trial managers anywhere in the world who are working on randomised or non-randomised trials of interventions.

Populations – Trial managers (or other individuals) responsible for recruitment site set-up and carrying out site initiation training.

Outcome assessment – a) Can trial managers predict if local recruitment sites will recruit to the predicted target b) what are the most important factors (from eight alternatives) of the prediction.

Co-ordination – CHaRT, University of Aberdeen

INTRODUCTION

Background

A large investment of public money is made by the UK each year to fund large multicentre clinical trials. 'Treatment evaluation', largely trials, represents 8.5% of total spending by the 12 main public and charitable funders of health research in the UK, or £140 million (UK Clinical Research Collaboration 2012). 'Treatment evaluation' represents over a third of NIHR funding and nearly half of MRC funding. The UK pharmaceutical industry spends nearly £5 billion on research and development every year (Department for Business 2011). Reviews have found that many (around half) of these studies will not recruit to target and need extensions, revisions to the sample size (power of the study) or need to be closed, which essentially leaves the clinical question unanswered (McDonald et al 2006; Bower et al 2007; Sully et al 2013). The NIHR would ideally like to see a greater participation in health research from patients and health care professionals (Department of Health 2006). However, money to increase the amount of research will be directed away from additional research if trials fail or have to be extended to achieve the required outcome targets. Trials have had to become more pragmatic to fit in with patients and health care professionals (Campbell et al 2007). Business models for running clinical trials have been shown to be good strategies for running more effective trials (Francis et al 2007; McDonald et al 2011). However, hold ups in obtaining local hospital R&D approval are still being observed (Kearney et al 2014; Treweek et al 2013) as are the efficient recruitment of participants (Bower et al 2014). These are just some of the many reasons that contribute to the high failure rates of trials.

One potential reason for failure that has had little consideration is that some local sites just fail to perform as recruitment centres and never fulfil their predicted potential. This was explored by our pilot work– the ESP study (Bruhn et al 2019). Ten trial managers working across eight trials made predictions for 56 site visits. Trial managers' sensitivity was 82% and their specificity was 32%, correctly identifying 65% of sites that would hit their recruitment target and 54% of those that did not. Eight 'red flags' for recruitment failure were identified: previous poor site performance; slow approvals process; strong staff/patient preferences; the site recruitment target; the trial protocol and its implementation at the site; lack of staff engagement; lack of research experience among site staff; busy site staff. We used these red flags to develop a guided prediction form.

ESP2 will test the guided prediction form in a much larger study involving trial managers from across the UK and the world. ESP2 is a collaboration with the UK Trial Managers' Network (https://www.tmn.ac.uk/) of over 1200 trial managers.

Rationale for study

A great amount of time, effort and cost is taken in setting up local recruitment sites for clinical trials. Many of the local sites will have been identified by a trial's chief investigator because of eminent individuals working in the clinical area at the site, or through personal acquaintances. Alternatively,

local sites may have been put forward by the hospital's Research & Development departments, sometimes without prior contact with the local consultant who is expected to act as principal investigator. Another route for attracting local sites is promoting the trial and then interested clinical staff approach the trial office. Regardless of how a site is identified as a potential recruiter, it would be ideal to have a way to potentially predict whether the site would be a "good" site to have involved in the trial (in this context, to determine "good", we are focusing on recruitment).

In other words, is there a good way of making decisions about which sites are worth investing energy in, and which are not? ESP2 focuses on looking at this issue at the site set-up stage, once the site initiation training has been done.

OBJECTIVES

Is there a good way of making decisions about which local recruitment sites are worth investing energy in when setting up a clinical trial?

ESP2 hypotheses that trial managers who use the guided prediction form will be able to predict whether a site will be a 'good' site and recruit to target. If confirmed, such knowledge would enable energy and resources to be targeted more effectively using a simple form together with trial managers' experience.

OUTCOME MEASURES

Primary outcome measure

- The primary outcome is the proportion of correct predictions made by trial managers of sites that fail to recruit .

Secondary outcomes

- The impact each of the eight red flags has on recruitment predictions.

RESEARCH METHODS

The dedicated trial managers who handle local site set-up are deeply involved in this process and will (we speculate) have a good sense of whether a site will go on to recruit to its target. ESP2 asks trial managers to use our guided prediction form to predict site recruitment, which we will then compare to actual recruitment performance. If the form helps prediction, it could be rolled out as a trial management tool to enable time and energy to be directed to sites with a good chance of recruitment success, and prevent it being wasted on sites that are highly unlikely to meet their targets. It could also be a useful tool to help less experienced trial managers.

STUDY DESIGN

Inclusion criteria

- The people providing predictions must be trial managers responsible for setting up trial recruitment sites and carrying out site initiation training with site staff. Some people undertaking this activity may have a different job title; they will be eligible to take part on the basis of undertaking this activity.
- The recruitment prediction is for a site in a randomised or non-randomised trial. The site and the individual making the prediction can be anywhere in the world.
- The trial must be testing one or more interventions.
- The trial must be opening new recruitment sites.
- Individuals should be willing to make at least one prediction. These predictions can be for different sites within the same trial, sites across many trials, or a combination of both. There is no limit to the number of predictions a trial manager can make.

Exclusion criterion

- Cluster randomised trials.

Proposed start date and end date

Start: Autumn 2019.

End: Once we have around 1000 predictions. We expect that this may take up to two years, plus a further six months to allow the sites involved in the last predictions to do some recruitment.

Recruitment

Trial managers will be recruited by a variety of approaches: through UK Trial Managers' Network (e.g. we will ask trial managers to take part via email correspondence, and via flyer/presentation at the UKTMN Annual Meeting. We will also run a UKTMN webinar to raise awareness and support recruitmet), within the Aberdeen Trials Unit, by word of mouth at meetings with staff at other Trials Units, through the five Trial Forge Centres (Aberdeen, Bristol and Cardiff in the UK; Basel in Switzerland; Brisbane in Australia) and by twitter. We will also use study flyers to promote the study, based on the template in Appendix 1 and incorporating study updates as the study progresses. All of these approaches will be used regularly until we reach 1000 trial manager recruitment predictions (see *'Sample size'*).

Information about ESP2 will be provided on a dedicated website (https://w3.abdn.ac.uk/hsru/ESP2/Public/Public/index.cshtml, managed by the Centre for

Healthcare Randomised Trials, CHaRT) for trial managers who consider taking part. Trial managers who do want to take part need to register their interest through the website and this registration will be taken as their consent to take part. Each trial manager will be given a unique identifier and will remain anonymous in all our reporting.

WHEN SHOULD TRIAL MANAGERS MAKE THEIR PREDICTIONS?

Trial managers should make predictions soon after completing the site initiation training. The site does not need to be open for recruitment when the prediction is made, so long as the site initiation training has been done.

DATA COLLECTION

Brief demographic information about the trial manager will be collected through the study website at registration. In addition, brief details about the trials the trial manager wishes to make predictions for will also be collected through the study website.

Trial managers will then be asked to fill in a short, online questionnaire for each site they carry out site initiation training for, and give a prediction as to whether that site is likely to meet its recruitment target. Trial managers will also be asked to pick the three red flags on our prediction questionnaire that were most important for their prediction. Trial managers may not wish to make predictions for all sites; they are not required to do so. However, there is no limit to the number of predictions a trial manager can make (although they should not make multiple predictions for the same recruitment site for the same trial).

Follow-up

Trial managers will be asked to tell us the total recruitment at each site for which they made a prediction 6 months after their prediction and again at 12 months after the prediction. This request will be sent automatically to trial managers via the study website.

This will give us actual site recruitment, which we can then compare to the target recruitment that the trial manager gave when making his or her prediction. For example, a trial manager may say that the recruitment target for a site is 80 participants at 12-months. She predicts recruitment failure at this site. At 6 months the trial manager tells us actual recruitment is 34 and at 12-months actual recruitment is 67. Her prediction of recruitment failure was correct.

At each timepoint we will also include an update option in case the site has been closed or the recruitment timeline amended.

Withdrawal

Trial managers are free to withdraw from taking part in ESP2 at any point during the study. Trial managers are encouraged to complete a prediction form for every site they complete site initiation training for but are able to participate to whatever extent they wish – for example, they may complete prediction forms for some but not all sites that they carry out site initiation training for.

If a trial manager withdraws because he or she is moving to a new post, we will encourage the replacement trial manager to register if he or she wishes to, in order to provide predictions and/or recruitment updates. This will help to reduce missing data.

Sample size

Our sample size decisions have been guided by Prof Graeme MacLennan, statistician and Director of CHaRT.

We are interested in the ability of trial managers to correctly identify a site that will fail to recruit. For a diagnostic test this is called specificity, the proportion of correct negatives. Our pilot work found a specificity of 32% (Bruhn et al 2019). We expect the eight red flags to improve this substantially because they were identified through qualitative work in our pilot as markers of poor recruitment.

The sample size is dependent on assumptions about prevalence (the proportion of sites that fail to recruit), sensitivity and specificity. The specificity of 32% seen in the pilot *without* the use of the red flags is too low for trial management decision-making. Instead we believe a 75% specificity is what we should target– it is high enough that the prediction cannot be ignored – and we want to be certain that the 95% confidence interval around a result of 75% has a lower bound above 65% (i.e. we want some certainty that our specificity is not actually much lower than 75%).

Our pilot (Bruhn et al 2019) had a recruitment failure prevalence of 40% of sites. The sensitivity in the pilot was 82%.

Therefore, if we take a recruitment failure rate of 40%, a sensitivity of 90% (a bit higher than the pilot because we expect the red flags to help here too) and the measured specificity of 75% that we want, a sample size of 1000 predictions would give us 80% power to rule out specificity of below 70%. Halving the sample size to 500 and with 40% prevalence, 90% sensitivity and a measured specificity of 73%, we'll still have adequate power to rule out a lower bound to of 65%.

Therefore, we will aim for 1000 predictions. However we would still have acceptable power, based on reasonable assumptions, providing we reach 500 predictions. In our pilot we got 56 predictions from one trials unit, ten trial managers and eight trials. In the UK as a whole there are 51 registered trials units and well over 1200 trial managers. Each trials unit is likely to have a portfolio of at least ten trials. Clearly, our web-based study is open to trial managers well beyond the UK. The pool of potential predictions is therefore very large. A target of 1000 predictions is not at all implausible.

ANALYSIS

Demographic information for trial managers and trials will be reported in frequencies and percentages. Site recruitment will be recalculated to be *pro rata* to the duration given for the target (i.e. if recruitment runs for two years but we measure at one year, we will halve the recruitment target we judge the prediction against). This does make the assumption that recruitment is constant across the period but we think one year should be long enough for recruitment to have settled to its steady-state. Sites will be deemed to have met their recruitment target if they hit or exceeded that target. We will calculate specificity and sensitivity as well as positive and negative predictive values.

If data allow, we will do three pre-planned subgroup analyses:

1. Explore the effect of trial manager experience on prediction accuracy.
2. Explore whether prediction accuracy for randomised trials differs from that for non-randomised trials.
3. Explore whether prediction accuracy varies by disease area.

Our earlier study (Bruhn et al 2019) found some suggestion of a link between experience and prediction accuracy and whether a trial was randomised or not and prediction accuracy. As ESP2 is much bigger, we may be able to draw more certain conclusions as to whether relationships do exist.

RESEARCH GOVERNANCE

The University of Aberdeen Research Governance Manager has confirmed that this study does not require NHS REC or NHS R&D management approval. The University of Aberdeen Research Governance Manager has indicated that formal Sponsorship of the study is not required. The study will be submitted to the University of Aberdeen College of Life Sciences and Medicine Ethics Review Board (CERB) review. The study is very low risk.

FINANCE

Web-development was funded by the University of Aberdeen Development Trust. Website maintenance was funded from the Health Research Board (Ireland) grant HRB-TMRN-2017-2. ESP2 incurs only minor costs in terms of trial manager time but this will be borne by the institutions for which the trial managers work. Funding for dissemination will either be sought from internal department funds or from external sources as necessary.

DATA HANDLING

The website has been developed by data management staff at CHaRT and complies with GDPR. Staff taking part in the study will be assured that all predictions will be kept confidential. It will not be possible to identify individual recruitment sites or trials in reports from the study. Data will be kept for 3 years after publication and will be available form the project team on reasonable request and taking care to avoid identifying trials and trial managers.

STUDY MANAGEMENT

The study will be managed by the investigators listed above. Participating trial managers will be able to contact any of the investigators for information about the study, or if they have queries via an ESP2 mailbox.

END OF THE STUDY

The study will run until we have 1000 predictions, which we expect to take no more than two years. If at two years, we have more than 500 predictions but fewer than 1000, we will stop the study for new predictions. An additional six months beyond this point will allow some recruitment at sites involved in predictions made at the end of the prediction period. Analysis will occur after this time.

AUTHORSHIP AND PUBLICATION

We will follow International Committee of Medical Journal Editors (ICMJE) guidelines on authorship (see http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

This work will be disseminated at meetings and conferences such as the UK Trial Managers' Network Annual Meeting, Society of Clinical Trials Conference and the International Clinical Trials Methodology Conference. The results will also be published in a peer reviewed journal. In any publication resulting from this work, it will not be possible to identify individual trial managers, trials or sites. Trial managers who contribute predictions and recruitment data to the ESP2 study will be appropriately acknowledged. A summary of results will be sent to all participating trial managers by email.

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Appendix 1

Flyer template

[Template - used for recruitment and updates]

[**Start of recruitment/update text**]

[example text]

Setting up trial sites takes up time, effort and cost. Not all of this is worth it because not all of those sites will recruit as planned. This is a shame because those sites that do not recruit as planned are likely to take up just as much, or perhaps more, trial manager time as sites that do recruit. What would help would be some way to predict whether a site would be a "good" site to have involved in the trial as far as recruitment is concerned. In other words, is there a good way of making decisions about which sites are worth investing energy in, and which are not?

The Estimating Site Performance–2 project (ESP2) project aims to test a tool that just might help. The project is led by trial managers based at the University of Aberdeen, UK and asks trial managers to make predictions about site recruitment after carefully considering eight 'red flags' for poor recruitment. These flags (e.g. lack of site staff engagement, or previous poor performance) were developed in the original ESP project, which was published in 2019 in *Trials* (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3287-6).

The UK Trial Managers' Network (UKTMN; http://www.tmn.ac.uk) has partnered with Trial Forge (https://www.trialforge.org) to support ESP2. The project needs 1000 recruitment predictions from trial managers so it is likely that trial managers across the world can play a role. Predictions will be made online and the web-based system is due to be launched in early autumn 2019. After a prediction has been

made, the ESP2 team will contact you six months later and then again at 12 months to see how recruitment is going.

We all know that sites that don't recruit are a problem. ESP2 aims for a tool that supports trial managers' hunches about site recruitment that is backed up by a 1000 predictions, from hundreds of trial managers, in dozens of trials and which makes those hunches too compelling for anyone to ignore.

You can find out more about ESP2, and sign up to take part at:

bit.ly/Recruitment_ESP2

For more information, please contact the ESP2 study team via esp2@abdn.ac.uk.

[**End of recruitment/update text**]