Blinding of the trial statistician in clinical trials

Acronym:
BOTS

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ABBREVIATIONS

CI	Chief Investigator
PIS	Participant Information Sheet
UoN	University of Nottingham
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
NIHR	National Institute for Health Research
UKCRC	UK Clinical Research Collaboration
UKTMN	UK Trial Managers' Network
HTA	Health Technology Assessment
EME	Efficacy and Mechanism Evaluation
MHRA	Medicines and Healthcare Products Regulatory Agency

STUDY BACKGROUND INFORMATION AND RATIONALE

There is good empirical evidence of risk of bias in clinical trials associated with key aspects of design and conduct such as allocation concealment and blinding. For example, the merits of blinding trial participants, treating clinicians, and outcome assessors are well established, particularly for trials that use subjective outcomes (Wood L et al. 2008). However, more recent evidence has challenged the notion that blinding is always necessary to protect against bias (Moustgaard H et al. 2020).

By contrast, there is little empirical evidence to guide Clinical Trials Units (CTUs) and trial teams about the practice of blinding statisticians. Existing guidelines recommend that the trial statisticians, or the statisticians that work most closely with a given trial, remain blinded to treatment allocation prior to the final analysis. In particular, guidelines state that any interim analyses are conducted by a separate team of statisticians and/or programmers to those that will be involved in the final analysis (Pocock 2004 & MHRA 2012). While these guidelines are not based on empirical evidence, there are clearly benefits to taking such an approach.

Firstly, ensuring the trial statisticians remain blinded to treatment allocation prior to the final analysis reduces the risk that the statisticians could introduce any bias through their conduct and reporting. In particular, blinding the statisticians that are responsible for developing the statistical analysis plan ensures that the approach to the analysis is not influenced by this knowledge.

Moreover, the trial statistician will typically contribute to decisions made by the trial management team, and their advice or recommendations could be influenced by knowledge of treatment allocation. Keeping the trial statisticians blind to treatment allocation throughout the trial also reduces the risk of the wider trial management team becoming unblinded. This potential for knowledge of treatment allocation to influence decisions made by the trial management team is primarily a risk for trials with subjective outcomes or where a per-protocol analysis is planned, but presents less risk for trials with objective outcome determination and an intention to treat analysis.

The recommendations could be considered as gold-standard, but for effective implementation it requires multiple teams to be fully immersed in a study. In academic CTUs, particularly smaller units, it may be impractical to blind trial statisticians in the way suggested by the guidelines. In units that do use a second statistician for any examination of data separated by trial arm, this comes with a substantial additional resource cost, and can present logistical challenges. For example, an unintended consequence is that interim analyses are prepared and presented by a statistician with less insight and in-depth knowledge of the trial (DeMets D 2018 & Wittes J 2004), leading to suboptimal presentation of interim trial data to the Data Monitoring Committee (DMC), and potentially less effective oversight of the trial. Within a DMC meeting, discussions may be limited if the second statistician is not as immersed in the research question as the primary statistician and was not involved in the trial design.

There is variation in practice between CTUs when it comes to blinding trial statisticians. We surveyed registered CTUs about whether the trial statisticians were able to access disaggregate data prior to the final analysis. Of the 20 respondents, at 7/20 units this was always the case, at 3/20 units this was never the case, while 10/20 had different approaches depending on the type of trial.

Since existing guidelines do not make any distinction between different types of trial design they are not risk proportionate. This aim of this research is to identify evidence and develop guidance document for a risk proportionate strategy for blinding statisticians in clinical trials.

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STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to inform the development of a guidance document to advise CTUs on a risk proportionate approach to blinding statisticians within clinical trials.

PRIMARY OBJECTIVE

To identify and provide evidence for a risk proportionate strategy for blinding statisticians in clinical trials.

SECONDARY OBJECTIVES

- To investigate the experiences, opinions and ideas of key stakeholders on blinding of trial statisticians who work in the delivery and oversight of clinical trials.
- To compare the outcomes of recently published randomised trials where the statistician was blinded prior to the final analysis versus those where the statistician was not.
- To develop a consensus group of key stakeholders to review the study results and provide recommendations for the development of the guidance.

STUDY DESIGN

STUDY CONFIGURATION

This is a mixed-methods research which involves three parts:

Part I: A qualitative study using focus groups and interviews as data sources to determine the views and opinions of key stakeholders on blinding of trial statisticians who work in the delivery and oversight of clinical trials.
Part II: A quantitative study to assess the impact of blinding on the proportion of trials demonstrating significance for the primary outcome.
Part III: Combining the results of part I and part II along with a consensus workshop with a consensus group to produce guidance for CTUs.

STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Data collection, analysis and the study output are planned to be completed within 12 months. The timescale below gives a brief overview of the project plan.

0 – 2 months: Qualitative and quantitative study set-up

During this period, the research team will design a topic guide for focus groups and interviews, develop supporting documents e.g., participant information sheet, invitation letter and consent form, obtain relevant approvals, identify and send invitations for potential participants in focus groups, interviews and consensus group. During this period, the research team will also design the data extraction form for the quantitative data collection.

3 – 7 months: Conduct of qualitative and quantitative study
During this period, focus groups, interviews and extraction of quantitative data, will be conducted. Data analysis and the writing-up findings will also be completed.

8 – 9 months: Consensus meeting
A first draft of the guidance document will be developed and circulated to the consensus group to independently rate the statements included in the guidance and provide feedback.

10 – 12 months: Development and dissemination of guidance documents
A workshop with the consensus group, will be conducted to discuss the groups' ratings and recommendations. After the workshop, the final version of the guidance document will be finalised.

STUDY MEYHODS

PART I: QUALITATIVE STUDY

This part of the study will investigate the experiences, opinions and ideas of key stakeholders on blinding of trial statisticians who work in the delivery and oversight of clinical trials. We will explore the following perspectives:

- Role of independent statisticians (e.g. if, when, why and how this is appropriate).
- Expectations (e.g. funders, sponsors, industry, other stakeholders).
- Resources (e.g. cost, recruitment, skills, funding sources, local partner support).
- Impact (e.g. producing and publishing outputs, reputation).

Sample

For focus groups, we aim to recruit a purposive sample of Statisticians, Trial Managers and Data Managers via (UK Clinical Research Collaboration (UKCRC) working groups, MRC-NIHR Trials Methodology Research Partnership (TMRP) working groups, National Institute for Health Research (NIHR) statistics group, and UK Trial Managers' Network (UKTMN) We also aim to include other stakeholders including CTU directors, DMC chairs and Unit Managers.

We are targeting 5-7 participants in each focus group to ensure the session is manageable, but also representative of stakeholders. The aim is to conduct focus groups with various stakeholders, however, if this is not feasible, then the research team may ask participants to join individual interviews.

Recruitment and informed consent

The research team will identify potential participants for focus groups and interviews by sending them an invitation email including a participant information sheet (see attached) outlining the purpose of the study and a consent form (see attached).

For focus groups, we will contact the relevant organisation administrators to share our invitation email with their members. The research team will try to organise focus groups to utilise existing meeting dates where possible.

Other stakeholders who might not be able to join focus groups due to time restraints, will be contacted for individual interviews. If the response rate is poor after seven days following the invitation email, the research team will send a reminder email.

On the day of the focus group or interview and prior to the session, the researcher(s) will explain the study to the participants again, allow time for any questions they may have about the study and take informed consent. Due to current COVID restrictions consent will be accepted as a return of email (to the invitation email) stating the participant has read and understood the consent form and agrees to participate. This correspondence will be filed as the record of consent.

The researcher(s) will explain to potential participants that entry into the study is entirely voluntary and that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and will be used in the final analyses where appropriate.

Data collection

The researcher(s) will conduct focus groups and interviews through the Microsoft Teams platform. Focus groups and interviews will be video and audio recorded with consent. A topic guide (see attached Topic Guide) will be developed to help guide discussion at both focus groups and individual interviews (Stewart DW et al. 2007). Field notes will also be used to record discussions and agreement during focus groups.

Analysis

The research team will transcribe the audio-recorded data for both focus groups and interviews. At least two researchers will analyse the transcripts. An inductive/deductive thematic approach (Fereday J et al. 2006) will be used to identify participants' perspectives regarding statistician blinding in clinical trials.

Two researchers will independently conduct initial open coding and categorisation with the aid of NVivo12, a qualitative data management software. The researchers will anonymise participant's information by using non-identifiable codes and removing identifiable information. Differences in interpretation will be resolved through discussion between coders and then if required, a third person (someone from the research team) will be involved. This is an established method to increase the trustworthiness of research (Cascio MA et al. 2019). Categories and themes will be developed by constantly refining the coding scheme and master themes will be identified.

Themes developed from both data sources (focus groups and interviews) will then be triangulated for inter-method convergence, discrepancy or complementary information (O'Cathain A et al. 2010). Triangulation enables comparison of concurrently collected data obtained via different methods and from different researchers to be explored for interaction thereby adding validity to research findings (Farmer T et al. 2006). The triangulation will help the research team to develop a comprehensive understanding on how statistician blinding is perceived from different perspectives. It will also help in exploring the reasons why

researchers choose to do blinding in a certain way and their thoughts and opinions on alternative methods.

PART II: QUANTITATIVE STUDY

This part of the study will retrospectively compare the outcomes of recently published NIHR Health Technology Assessment (HTA) and NIHR Efficacy and Mechanism Evaluation (EME) funded randomised trials where the statistician was blinded prior to the final analysis versus those where the statistician was not. This will help us to identify the blinding methods used in clinical trials and whether it impacted the findings.

Sample

NIHR HTA and EME funded trials, published between 2016 and 2020, will be included. This cohort contains at least 200 high quality randomised trials and it is expected that they will be less prone to other methodological deficiencies that could confound the comparison of interest.

Data collection

The studies will be collected from the NIHR Journals Library, hosted by NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC). The research team will identify the blinding-status of the trial statistician either from the published HTA or EME recent journal articles, by direct contact with the study authors, or direct contact with the collaborating CTU (where applicable).

A data extraction form (see attached Data Extraction Form) will be used to extract data about trial characteristics associated with risk of bias, adopted from the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne JAC et al. 2019). Other key study characteristics, such as trial design, single or co-primary outcome, number and type of interventions and comparators, will also be extracted from the published monograph. Extraction of these data was successfully piloted by a previous study. (Raftery J et al. 2015).

Data extraction will be carried out by two researchers independently and any discrepancies will be resolved via agreement between the researchers. Any subsequent disagreement will be resolved by a third researcher.

Analysis

Descriptive statistics describing the study characteristics will be presented by blinding status of the statistician. Continuous data will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical data will be summarised in terms of frequency counts and percentages. No formal statistical comparisons will be made.

The proportion of statistically significant findings for the primary outcome will be compared between groups of studies where the trial statistician was blinded versus not blinded, using a logistic regression model, adjusting for potentially confounding study characteristics. The between group effect will be reported using an adjusted odds ratio along with a p-value and a corresponding 95% confidence intervals.

For trials with a single primary comparison the reported p-value will be compared between groups by using a linear regression model or a non-parametric alternative, as appropriate.

PART III: GUIDANCE DEVELOPMENT

The analysed data from part I and part II will be used to develop a guidance document to advise CTUs on a risk proportionate approach to blinding statisticians within trials.

Sample

Key stakeholders, including Statisticians, Trial Managers and Data Managers, CTU Directors, Unit Managers and DMC chairs as well as a representative for the Medicines and Healthcare Products Regulatory Agency (MHRA), will be invited to join a consensus group. We are aiming for 10-20 participants covering all key stakeholders with a particular emphasis on statisticians.

Data collection and analysis

The research team will send an invitation letter (to potential members of the consensus group via email.

In this part of the research, we applied a modified formal consensus method to derive a set of recommendations for blinding statisticians in clinical trials. The results from part I & II will be used to provide the empirical evidence on which to base the development of guidance for CTUs, which will then be discussed and rated by the consensus group.

Our modified formal consensus method is based on the RAND/UCLA appropriateness method, a formal consensus method that is commonly used in healthcare research (Fitch et al., 2001). In this research, a first draft of the guidance document will be developed by the research team informed by the findings from the qualitative and quantitative studies. The research team will share the first draft document along with a questionnaire to help the consensus group to rate the guidance statements and to give feedback on each statement before the workshop. Ratings will be made on Likert scales from 1 (strong disagreement with the statement) to 5 (strong agreement).

The research team will arrange for a workshop meeting via the Microsoft Teams platform with breakout sessions for particular groups or tasks as required. In the workshop, the researchers along with the consensus group will review the guidance, the member's ratings and feedback in order to provide recommendations for the development of the guidance. Following this, the research team will share any subsequent revisions with the chair of the consensus group to provide input on behalf of the group, before approving the guidance document. Figure 1 illustrates a summary of the consensus method intended to be used to develop a guidance document.

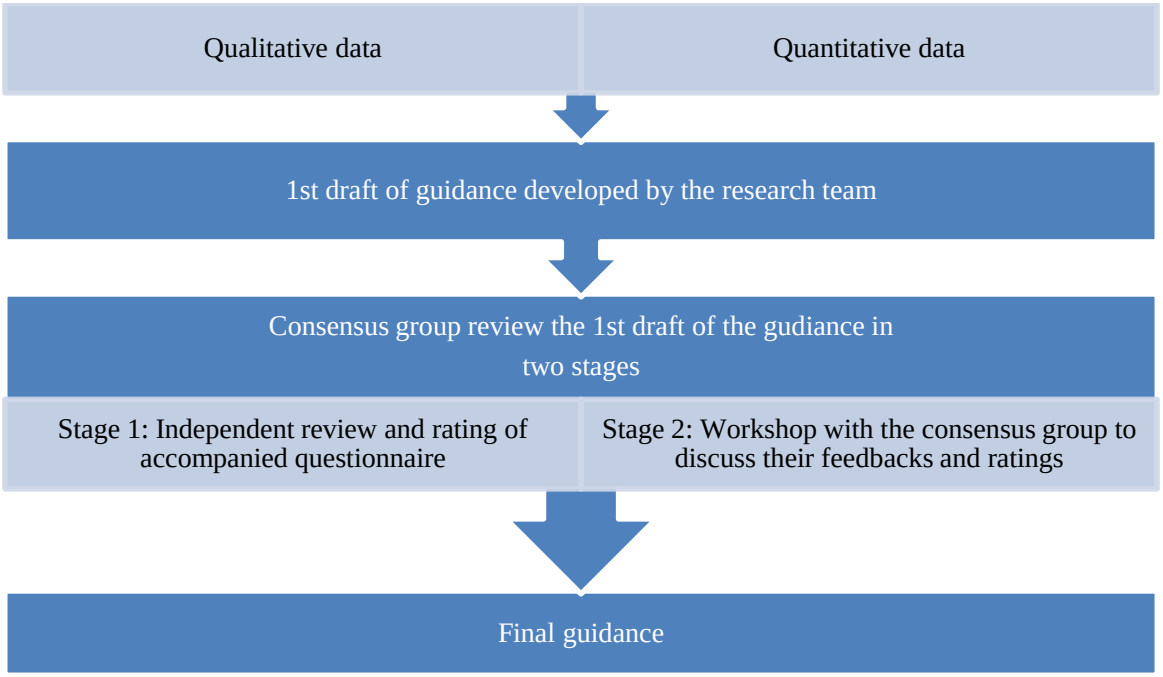

Figure 1: summary of the consensus method to develop a guidance document.

ETHICAL AND REGULATORY ASPECTS

ETHICS AND APPROVALS

The qualitative study will not be initiated before the protocol, consent forms and participant information sheets have received relevant approval.

All focus group and interview participants will be provided with a consent form and information sheet (which includes a detailed description of the nature of the study, why the research is being conducted, why they have been chosen to participate, and the nature of the questions that will be asked), and the researcher(s) will answer any questions before consenting. All participants will have time to decide if they wish to participate in the study.

Participants will be asked for their permission to video and audio record the focus groups and interviews. Focus group and interview transcripts will not contain names or other details that might identify the participant. Instead, non-identifiable codes will be used, and other identifiable information will be removed. To avoid identification of participants through quotes in published research, all participants will be assigned non-identifiable codes.

RECORDS

Source documents

Source documents will be filed at the Nottingham Clinical Trials Unit and may include but are not limited to, consent forms, study records, field notes, focus group and interview transcriptions and audio and video records. Only the research team will have access to the study documentation.

DATA PROTECTION

The research team will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. All source documents will be held securely on the University of Nottingham secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

Confidentiality and privacy will be ensured for all participants. The information gathered will only be used for scientific purposes for example presentations, research purposes, publications and using anonymous direct quotes, phrases and terminology in the analysis and report.

The research team will video and audio record focus groups and individual interviews. Recordings will be transferred to the secured project shared drive as soon as possible by the research team.

The research team will de-identify transcripts of focus groups and interviews. These transcripts will be assigned a code. An encrypted document showing the link between the code and the corresponding transcript will be kept separately and preserved until the end of the study.

Complete anonymity of participants amongst other members cannot be guaranteed in focus groups. To address this, the participant information sheet states that participation is voluntary and reminds participants to respect the privacy of their colleagues and not repeat what is said in the discussions to others. Participants will be asked to sign a statement in the consent form that states they will not reveal any information that is shared in confidence in the focus groups. The researcher(s) will also remind participants about confidentiality of participants and information shared in the focus groups.

RECORD RETENTION AND ARCHIVING

In accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator will be finally archived at the Nottingham Clinical Trials Unit at the University of Nottingham. This archive will include all anonymised video and audio recordings, transcripts, study databases and associated data encryption codes.

STATEMENT OF CONFIDENTIALITY

Individual participant information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

PUBLICATION AND DISSEMINATION POLICY

The full study report can be accessed through the University of Nottingham hosted webpage. To ensure that the findings from the research inform practice, the findings will be disseminated by presenting the results at national and international conferences and seminars, holding workshops with key stakeholders, publishing in a peer reviewed journals and sharing the results with key groups, e.g. Trial Managers network to share it with relevant people.

Study participants will receive a thank you email from the Chief Investigator. The guidance document along with a final report of key study findings will also be provided.

The final study dataset and data that directly underpin research findings which will be published or will be used for research will be used in anonymised form.

STUDY FINANCES

Funding source

This study is funded by NIHR CTU Support Funding Supporting efficient innovative delivery of NIHR research.

Participant stipends and payments

Participants will not be paid to participate in the study. No travel expenses will be offered as focus groups, interviews and consensus workshop will be conducted virtually.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Dr Christopher Partlett _____

Signature: _____

Date: _____

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