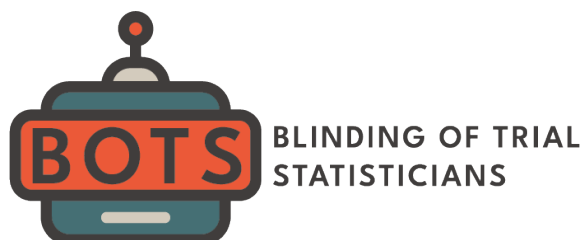


# ANNUAL EFFICIENT STUDIES FUNDING CALLS FOR CTU PROJECTS FINAL REPORT



## Section 1: Title of Project

Blinding of Trial Statisticians in clinical trials (BOTS)

## Section 2: Abstract

**Background:** Existing guidelines recommend statisticians remain blinded to treatment allocation prior to the final analysis, and that any interim analyses should be conducted by a separate team from the one undertaking the final analysis. However, there remains substantial variation in practice between Clinical Trial Units (CTUs) when it comes to blinding statisticians. Therefore, the aim of this study was to develop guidance to advise CTUs on a risk-proportionate approach to blinding statisticians within clinical trials.

**Methods:** This study employed a mixed-methods approach involving three stages: (I) a quantitative study using a cohort of studies (from a major UK funder published between 2016 and 2020) to assess the impact of blinding on the proportion of trials reporting a statistically significant finding for the primary outcome(s); (II) a qualitative study using focus groups to determine the perspectives of key stakeholders on the practice of blinding trial statisticians; and (III) Combining the results of stages I and II to develop a first draft of provisional guidance statements, then discussing this within a stakeholder meeting, before finalising guidance for CTUs.

**Results:** A total of 179 trials were included for review. The results of the primary analysis showed no evidence that the blinding status of the statistician was associated with the likelihood of trials reporting a statistically significant result, odds ratio (OR)

0.98 (95% confidence interval (CI) 0.47 to 2.05). Thirty-seven participants from 19 CTUs participated in one of six focus groups. Four main themes were identified: statistical models of work; factors affecting the decision to blind statisticians; benefits of blinding/not blinding statisticians and practicalities. Factors influencing the decision to blind the statistician included: available resources; study design and types of intervention; outcomes and analysis. The triangulation between stages I and II resulted in developing 40 provisional statements rated independently by the stakeholder meeting's participants. Ten statements reached agreement with no agreement on 30 statements. At the meeting, various factors were identified that could influence the decision of blinding the statistician, including timing, study design, types of intervention, and practicalities. Guidance including 21 statements was developed alongside a Risk Assessment Tool to provide CTUs with a framework for assessing the risks associated with blinding/not blinding statisticians and for identifying appropriate mitigation strategies.

**Conclusions:** This is the first study to develop a guidance document to enhance the understanding of blinding statisticians and to provide a framework for the decision-making process. The key finding was that the decision to blind statisticians should be based on the benefits and risks associated with a particular trial.

### SECTION 3: INTRODUCTION

Blinding (also called masking) of group allocation from individuals involved in a research study is an established methodology that is considered important in the conduct of randomised controlled trials (RCTs) (1). The rationale for keeping clinicians, participants and outcome assessors blinded to treatment allocation has been extensively studied and focuses on minimising the likelihood of differential treatment or assessments of outcomes (2, 3). Studies aiming to quantify the impact of lack of blinding have reported exaggeration of treatment effects of up to 68% (4, 5). However, there is literature that has challenged the dogma that blinding is always necessary and highlighted some challenges that might arise from using it (4, 6, 7).

The Medicines and Healthcare products Regulatory Agency's (MHRA) Good Clinical Practice (GCP) definition of blinding is given as:

“A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s)” (8).

Notably, this definition implies that blinding applies less frequently to data analysts or statisticians. The potential for the risk of bias arising from the statistician performing the analysis of the interim data and the final analysis has received little attention.

Bias may be introduced by statisticians through various routes e.g., when determining membership of analysis populations, influencing decisions related to the trial protocol, or through the selective use and reporting of statistical tests. Blinding the statistician until the analysis has been specified fully is one way to mitigate against this (1, 9). Existing guidelines recommend blinding the statisticians before the final database lock, (10) but these guidelines do not consider the trial-specific risk of blinding or not blinding the statistician.

Given that there is no available guidance for a risk-proportionate approach to blind trial statisticians (TSs) in RCTs, it makes sense to attempt to understand current practice (Work as Done) within context (11). To enable this, the objectives of this research were to:

- 1) Compare the outcomes of recently published randomised controlled trials where the statistician was blinded prior to the final analysis versus those where the statistician was not
- 2) Further explore current practice in academic CTUs, and the rationale
- 3) Understand stakeholder views on important risks and benefits to consider when deciding on whether to blind the trial statistician
- 4) Provide recommendations and a practical tool to enable CTUs to utilise a risk-based approach when considering blinding of the trial statistician

## SECTION 4: METHODS

BOTS employed a mixed methods approach conducted in three stages.

**Stage I:** Data were obtained from RCTs funded by the UK National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA), and the Medical Research Council (MRC)-NIHR Efficacy and Mechanism Evaluation (EME) programmes. This cohort was chosen as it comprised well-reported, high quality randomised trials with minimal potential for publication bias or other methodological deficiencies that could confound the comparison of interest.

A data extraction form was developed, including elements from the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) (12), used to extract data about trial characteristics associated with risk of bias. Data extracted included trial design, number and type of interventions, number of study arms, the type of assessed outcomes, the percentage of outcomes that were missing, the blinding status of TSs, and whether a statistically significant finding was reported.

Descriptive statistics describing the study characteristics were presented by blinding status of TSs. Continuous data were summarised by the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical data were summarised by frequency counts and percentages. The proportion of statistically significant findings for the primary outcome was compared where TSs were blinded versus not blinded, using a logistic regression model and adjusting for potentially confounding factors.

**Stage II:** To explore their perspectives on when and how to blind TSs, qualitative data was collected by conducting focus groups with key stakeholders who work in the delivery and oversight of clinical trials. With consent, focus groups were video and audio-recorded, for later transcription and analysis. The audio-recorded data were transcribed, and an inductive/deductive thematic approach (13) was used to identify participants' perspectives regarding statisticians' blinding in RCTs.

**Stage III:** A draft of the provisional guidance statements was developed by analysing and comparing the findings of stages I and II. To develop a guidance document for

blinding TSs in clinical trials, a triangulation design was used (14). Triangulation enables comparison of concurrently collected data obtained via different methods to be explored for interaction, thereby adding validity to research findings (15). A stakeholder meeting was then held to review the provisional guidance statements for agreement.

## SECTION 5: RESULTS AND CONCLUSION

After screening the abstracts of the 200 studies identified, 21 studies were excluded leaving a total of 179 trials appropriate for inclusion in the review. Following data extraction, the blinding status of the statistician remained unclear for 106 (59%) of the included studies. After contacting study authors, blinding status of the statistician was determined in 152 (85%) of included studies. Including only those trials where the blinding status of the statistician could be confirmed (n=152), there was no evidence that the blinding status of the statistician was associated with the likelihood of a trial reporting a statistically significant result, OR 0.98 (95% CI 0.47 to 2.05). However, there was strong evidence that blinding any of clinicians, participants and outcome assessors reduced the likelihood of statistically significant findings being reported, OR 0.33 (95% CI 0.13 to 0.86). Findings were consistent for a sensitivity analysis that assumed that the statistician was not blinded whenever the blinding status was unclear. Further, the sensitivity of the findings to alternative model specification were also explored and conclusions were found to be consistent with the primary analysis.

Six focus groups were conducted. Thirty-seven participants volunteered to participate, from 19 out of 52 CTUs in England, Wales and Scotland. Four themes were identified from the analysis of the focus groups' transcripts: 'Statistical models of work', 'Factors affecting the decision to blind or not blind statisticians', 'Benefits of blinding or not blinding statisticians', and 'Practicalities'.

The triangulation between stage I and II findings resulted in the identification of two main themes: (1) the association between the statisticians' blinding status and trial characteristics, and (2) the influence of statisticians' blinding status on trial findings. Interestingly, there was convergence between the quantitative and qualitative findings for the latter where the statistician's blinding status had no significant impact on trial

outcomes. Almost all participants in the focus groups agreed that they did not feel statisticians would knowingly introduce bias into the clinical trial. With respect to trial characteristics, participants in focus groups felt that having a blinded TS was more important for Clinical Trials of Investigational Medicinal Products (CTIMPs) where blinding of the intervention (e.g., using a placebo) was more likely. This result is somewhat contradictory to the quantitative data, which found that the proportion of trials with a blinded trial statistician was higher (42%) in non-CTIMPs compared to CTIMPs (33%). This could be explained through more frequent safety monitoring in CTIMPs, either causing or necessitating unblinding of the trial statistician. The non-CTIMPs were seen as more complex trials with more subjective outcomes.

The triangulation method resulted in the development of 40 provisional statements, which were sent to the stakeholder meeting participants for them to independently rate prior to the meeting day. During the stakeholder meeting, almost all participants agreed that it was crucial to avoid statements that gave instructions which must be followed, and instead provide items for consideration and flexibility depending on specific circumstances. The revision of the provisional statements, in line with the stakeholders meeting output, resulted in developing a guidance document for achieving a risk-proportionate approach to blinding statisticians within clinical trials. The guidance document consisted of 21 statements categorised under seven sections. The overall recommendation was ‘The decision to blind or not blind the statistician should be based on the benefits and risks associated with a particular trial.’ Based on the participants’ recommendation, the research team developed the BOTS Risk Assessment Tool (BRAT). This provides CTUs with a framework for assessing risks associated with blinding or not blinding the statisticians, and for identifying appropriate mitigation strategies.

In conclusion, no evidence was found to support the assertion that the blinding status of the statistician was associated with the likelihood of statistically significant findings being reported. However, the risk of bias certainly appeared lower compared with not blinding participants, clinicians, or outcome assessors, who perhaps have a greater opportunity to influence the findings. The guidance and the BRAT lays the groundwork for clinical trialists to apply evidence-based decision-making regarding blinding of statisticians.

## SECTION 6: DISSEMINATION

The principal outputs from this study are the guidance document and the BRAT.

Alongside these practical deliverables, the project resulted in two journal publications submitted to *Trials* (16, 17). These publications covered the findings of the three stages of the study, which will have relevance to the wider clinical research community.

The research team also disseminated the project through various seminars and conferences including the UKCRC Statistics Operations Group and NIHR statistics group meetings. Three abstracts for oral presentations were submitted to the International Clinical Trials Methodology Conference (ICTMC) 2022. A further presentation of the final guidance and risk assessment tool to the UKCRC Statistics Operations Group is planned.

Finally, the guidance, BRAT and study protocol are now freely available on the BOTS study webpage on the NCTU website (<https://www.nctu.ac.uk/other-research/bots-blinding-of-trial-statisticians.aspx>). The team will also make the open access journal publications available on the study webpage once published.

## SECTION 7: ACKNOWLEDGEMENTS

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*All authors contributed to designing the study. Christopher Partlett, Mais Iflaifel and Kirsty Sprange collected qualitative and quantitative data, analysed it, prepared the survey, the provisional statements for the guidance document and the BRAT. All authors contributed to interpretation of the data. All authors reviewed and edited drafts of the guidance document, the BRAT and the two manuscripts for publications.*

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## SECTION 9: APPENDICES

Supporting documents are available on the BOTS webpage on the NCTU website <https://www.nctu.ac.uk/other-research/bots-blinding-of-trial-statisticians.aspx> .

## SECTION 10: CONFLICT OF INTEREST DECLARATION

The authors all declared no conflicts of interest with relevance to this project.