|  |  |
| --- | --- |
| https://lh5.googleusercontent.com/jF9EgCAkSXFWy7K4bDDaBLnz8EzLdFU0iZJl5m2JTpK1S2T-zCk4Je1vDNGBDqYtHTQjC87DMCYlOxqDf4hidHCsqfHiocpay1yMZfJKw8KqaS7EyOOfz8hmzHkq5Ty1bvWeqBn-=s1600 | **C:\Users\cm1sahk\Downloads\Logo edited (1).png** |
|  | **Recording Harms in Behavioural change Intervention Trials** |
|  |  |
|  |  |
|  | **RESEARCH PROTOCOL****(Version 2) \*02\*November \*2022****Final Protocol at NRES Submission** |
|  | **REC Reference: 044669** |

**Table of Contents**

[**Abbreviations** 3](#_Toc118185348)

[**1 General information** 4](#_Toc118185349)

[**1.1 Investigator details** 4](#_Toc118185350)

[**1.2 Sponsor Details** 5](#_Toc118185351)

[**1.3 Protocol amendments** 5](#_Toc118185352)

[**Plain English summary** 6](#_Toc118185353)

[**Project Summary** 7](#_Toc118185354)

[**2 Introduction** 7](#_Toc118185355)

[**2.1 Background** 7](#_Toc118185356)

[**2.2 Why is this important?** 9](#_Toc118185357)

[**2.2.1 Aims and objectives** 10](#_Toc118185358)

[**2.2.2 Scope of interventions covered** 10](#_Toc118185359)

[**3 Study management and membership** 10](#_Toc118185360)

[**4 Methodology** 10](#_Toc118185361)

[**4.1 Scoping review of methods** 11](#_Toc118185362)

[**4.2. Qualitative interviews** 13](#_Toc118185363)

[**4.3 Workshop(s)** 16](#_Toc118185364)

[**4.3.1 Participants selection** 17](#_Toc118185365)

[**4.3.2 Consent and withdrawal** 17](#_Toc118185366)

[**4.3.3 Procedure** 18](#_Toc118185367)

[**5 Principles and recommendations for harms recording** 18](#_Toc118185368)

[**6 Outputs and Dissemination plan** 18](#_Toc118185369)

[**7 Ethics approval** 19](#_Toc118185370)

[**8 PPI Support** 19](#_Toc118185371)

[**9 Funding and any additional support** 19](#_Toc118185372)

[**10 Declaration of Conflict of Interest** 19](#_Toc118185373)

[**11 References** 19](#_Toc118185374)

# **Abbreviations**

AEAdverse Event

BCI Behavioural Change Intervention

CONSORT Consolidated Standards of Reporting Trials

CTU Clinical Trials Unit

HRA Health Research Authority

HTMR Hubs for Trials Methodology Research

ICH International Conference on Harmonisation

GCP Good Clinical Practice

ICMJE International Committee of Medical Journal Editors

ICTMC International Clinical Trials Methodology Conference

MHRA Medicines and Healthcare products Regulatory Agency

MRC Medical Research Council

NHS National Health Service

NIHR National Institute for Health Research

RCT Randomised Controlled Trials

REC Research Ethics Committee

ScHARR School of Health and Related Research

SMG Study Management Group

UK CRC UK Clinical Research Collaboration

PSC Project Steering Committee

# **1 General information**

## **1.1 Investigator details**

**Principal Investigator:**

Diana Papaioannou

CTRU, ScHARR

University of Sheffield

Regent Court

30 Regent Street

Sheffield, S1 4DA

d.papaioannou@sheffield.ac.uk

Senior Research Fellow/Assistant Director

Clinical Trials Research Unit (CTRU)

**Co-investigators:**

**Cara Mooney**

Project Manager/Oversight

CTRU, ScHARR

 University of Sheffield

c.d.mooney@sheffield.ac.uk

+44 114 222 4308

Study Manager

**Sienna Hamer-Kiwacz**

CTRU, ScHARR

University of Sheffield

s.a.hamer-kiwacz@sheffield.ac.uk

+44 114 222 0343

Research Assistant

**Louise Turner**

CTRU, ScHARR

University of Sheffield

Louise.turner@sheffield.ac.uk

+44 114 222 0737

Project Support Officer

**Professor Alicia O’Cathain**

Collaborator/Consensus study oversight

ScHARR

University of Sheffield

a.ocathain@sheffield.ac.uk

+44 114 222 0770

NIHR Senior Investigator and Professor

in Health Services Research at The University

of Sheffield and mixed methods expert

**Kirsty Sprange**

Collaborator- Qualitative study oversight

Nottingham Clinical Trials Unit (NCTU)

University of Nottingham

kirsty.sprange@nottingham.ac.uk

Assistant Professor at Nottingham

Clinical Trials Unit (NCTU); expertise

in complex behavioural trial design and

implementation and experienced in

qualitative research

**Professor Cindy Cooper**

Project Steering Committee member

CTRU, ScHARR

University of Sheffield

c.l.cooper@sheffield.ac.uk

+44 114 222 0743

Director of the Clinical Trials

Research Unit

**Professor Mike Robling**

Project Steering Committee member

Centre for Trials Research

Cardiff University

roblingmr@cardiff.ac.uk

Director of Population Health

Trials; expert in complex and

Behavioural trials

Project Steering Committee member

Centre for Trials Research

Cardiff University

moodyg@cardiff.ac.uk

**Dr Gwenllian Moody**

Trial Manager with expertise

in complex and behavioural trial

implementation

**Dr Victoria Cornelius**

Project Steering Committee member

Imperial Clinical Trials Unit

Imperial College London

v.cornelius@imperial.ac.uk

Reader in Medical Statistics

and Head of Statistics and

Trial Methodology; interest/

expertise in AE recording in trials

# **1.2 Sponsor Details**

The University of Sheffield

Sheffield

S10 2TN

## **1.3 Protocol amendments**

State “none” if no amendments. List and number amendments made since last HRA and REC approved version with dates and give the reason for the amendment. State which sections of the protocol were replaced added or deleted.

Version 1: Approved 28/01/2022

Version 2 (amendment 1): Approved 7/11/2022

# **Plain English summary**

**Background:** In drug trials, researchers will record and report the medical harms that patients may experience, for example, if they become very unwell or have to go to hospital. In trials of interventions which aim to change behaviours (like stopping smoking or eating more healthily), it is much less clear which harms should be recorded and how to report them. Researchers may miss harms that are important to patients or spend time measuring what is not important.

We have found trials which aim to change behaviour record harms in different ways or not all. It is hard for researchers to identify where participants may be being harmed and what they should record.

**Aims:** This study aims to write guidance on how to record harms in behavioural change intervention trials. This will hopefully improve the efficiency of harms recording, as well as consistency and transparency.

**Methods:** We will look at the literature to find types of harms that might occur in behavioural change interventions. We will interview people who run trials to find out problems they have experienced when recording harms, and what they have done to solve them. The information we find from the literature and interviews will be brought together to suggest guidance. We will ask experts in clinical trials to see if they agree with these suggestions and write some recommendationsor principlesto consider for harms recording and reporting.

**Patient and public involvement (PPI):** Although a PPI group will not be set up for this project, clinical trial participants or PPI representatives will be asked for their views on how harms should be recorded in behavioural change intervention trials.

**Dissemination.** The results will be published in academic journals and conferences. The guidance document will be made freely available. We will also make a short video of the study findings.

# **Project Summary**

|  |  |
| --- | --- |
| **Study title** | Recording Harms in Behaviour change Intervention Trials |
| **Funder** | National Institute for Health Research (NIHR) |
| **Sponsor** | University of Sheffield |
| **Project start date** | 1st October 2021 |
| **Project end date** | 31st December 2022 |
| **Hypothesis, aims and objectives** | ***Aim:*** To collaborate across several CTUs to determine appropriate practice for the collection and recording of harms in BCI trials to develop principles, considerations, and recommendations.***Objectives:***1. To scope and map the literature to identify definitions, typologies, instruments, and suggested principles for recording harms in BCI trials.2. To elicit perspectives and experiences of CTU and NIHR investigators involved in designing and delivering BCI trials.3. To undertake a workshop(s) to review the guidance for recording harms in BCI trials. |
| **Project design** | ***Four work packages:*** 1. Scoping literature review, 2. Qualitative interviews with experts, 3. Workshop(s), 4. Suggested principles and considerations for harms recording |
| **Participants (**qualitative interviews and workshop(s)) | UK-based clinical trialists who principally work on NIHR-funded trials. International candidates will be included where relevant and accessible.  |

# **2 Introduction**

# **2.1 Background**

Complex intervention trials often intend to change behaviour and/or provide peer or social support. These trials make up a significant proportion of the National Institute for Health Research (NIHR) clinical trials portfolio. A review of NIHR protocols from the Health Technology and Public Health Research programmes found wide variability and lack of transparency in recording harms in behavioural change intervention (BCI) trials [1]. Harms, typically termed Adverse Events (AEs), were often not defined or definitions varied, even between trials of similar interventions.

The review highlighted that there remains a misconception, as noted by others [2-4], that harms are not possible from these types of intervention [1].

Despite behavioural change interventions being well-intentioned, there are complex causal pathways and moderators of effect, hence the term *unintended harm.* Examples of such harms include:

* Obesity intervention/prevention resulting in risk compensation (change in one unhealthy behaviour is replaced with another), rebound effects (the intention to change behaviour results in the opposite behaviour e.g., intending to eat less results in eating more) and unsuccessful programmes leading to feelings of failure [2, 4, 5].
* Targeted social and emotional learning interventions in schools have been shown to cause negative labelling of individuals, stigmatisation, and unhelpful peer to peer knowledge exchange [6].
* Social/peer support in chronic health conditions has been perceived adversely, with unwanted attention or confrontation with a negative future cited as an undesirable effect [7].

Where AEs are recorded in BCI trials, there is a reliance on using ICH GCP definitions of AEs[[1]](#footnote-1) [1] which were designed originally for drug trials and are not wholly applicable or useful in the context of BCI trials [8].

Relevant AEs should be defined and recorded appropriately, whilst also paying attention to the efficiency of recording. The use of ICH GCP definitions, designed for drug trials, can make AE recording time-consuming, inefficient, and less relevant to the context. This is particularly pertinent in populations with high frequency AEs often unrelated to the trial intervention e.g., elderly [9, 10].

Alternative definitions, classifications and instruments have been proposed to capture specific harms related to psychotherapies [11, 12]. In public health, typologies or frameworks of harms have been suggested [2, 4]. However, these aren’t being used routinely in BCI trials [1]. These alternative definitions and approaches are not routinely discussed in NIHR trial protocols [1].

Extensions to the CONSORT statement (international recommendations on reporting standards for randomised controlled trials) also note the importance of reporting harms. The CONSORT harms extension [14] describes how to report harms in clinical trials. The CONSORT Social and Psychological Interventions (SPI) extension [15,16] recommends exploration of theory and mechanism of harmful effects [3]. However, neither extension provide details on AE recording. This includes defining AEs, how to operationalise AE recording and address the difficulties in relatedness assessment or determining what AEs might be expected from an intervention (or within a population).

# **2.2 Why is this important?**

***Potential to miss important harms***

Current approaches may miss important harms in BCI trials. ICH GCP definitions are ‘medical/clinical’ in nature. Using these definitions may miss unintended harms or consequences of changing behaviour important for evaluating the risk of harm from an intervention. The examples given in 1.1 demonstrate potential harms which don’t naturally fit into ICH GCP definitions. Attempts have been made to consider unintended harms outside of ICH GCP definitions. A public health trial of specialist home visiting for first time mothers, found *social events* (untoward events outside of the GCP AE definition) comprised 19% of all AEs [17].

Sometimes, investigators limit recording to serious AEs[[2]](#footnote-2) in BCI trials [1], which also risks failure to capture important harms. Unintended harms attributed to BCIs do not necessarily result in a serious event (defined as resulting in death, hospitalisation/prolonged hospitalisation, significant disability etc.) but are nonetheless important to record. It may be appropriate to extend the definition of events considered serious outside of GCP to improve risk-benefit analysis of interventions. There are good examples of this approach in some NIHR protocols [18, 19].

***Trial efficiency may be comprised***

There is a problem too in efficient trial implementation. AE recording requires considerable time including that of site staff, CTU staff and patients. In an older adult trial, SAE reporting was estimated to take up to 15 hours per week each for two research nurses-yet none of the SAEs were considered related to the trial intervention or unexpected [9]. It is important to direct resource to record relevant AEs to the intervention. During the planning/protocol writing stage of randomised controlled trials (RCTs), it is difficult to define potential harms. In drug trials, there are standard and routinely available documents which form the *reference safety information* which summarises all known potential harms potentially attributable and expected from an investigational medicinal product. There are no such equivalent documents for BCIs, and so the task of defining and deciding on what AEs should be recorded is a responsibly of the trial team.

***Comparison of trials is difficult***

There is currently wide variation and inconsistency in practice [1] and this makes comparison of trials difficult.

There is a need for expert consensus and guidelines on harms recording in BCI trials to improve transparency, consistency, and efficiency.

# **2.2.1 Aims and objectives**

***Research question:*** How should harms be recorded in trials involving BCIs?

***Aim:*** To collaborate across several Clinical Trials Units (CTUs) to determine appropriate practice for the collection and recording of harms in BCI trials to develop principles, considerations, and recommendations.

***Objectives:***

1. To scope and map the literature to identify definitions, typologies, instruments, and suggested principles for recording harms in BCI trials.

2. To elicit perspectives and experiences of CTU and NIHR investigators involved in designing and delivering BCI trials.

3. To undertake a workshop(s) to review the guidance for recording harms in BCI trials.

# **2.2.2 Scope of interventions covered**

We will focus on interventions intended to change behaviour or lifestyle. This includes (but is not an exhaustive list): psychological therapies, public health interventions such as weight management, physical activity, peer or social support, health communication or environmental policies and social and emotional learning.

# **3 Study management and membership**

A Project Management Group (PMG) and Project Steering Committee (PSC) will oversee the conduct of this research to ensure its completion and the delivery of research objectives. The PSC includes multi-disciplinary individuals from UK CRC Clinical Trials Units as well as methodological experts in qualitative research and workshops. The PSC members are: Diana Papaioannou, Cara Mooney, Sienna Hamer-Kiwacz, Kirsty Sprange, Alicia O’Cathain, Professor Cindy Cooper, Gwenllian Moody, Professor Mike Robling, and Dr Victoria Cornelius.

The PMG is a subset of PSC and will oversee the day-to-day study running of the project, consulting with the PSC as the need arises. Key decisions made by the PMG will be communicated to the PSC either via email correspondence or during scheduled meetings. Members of the SMG are Diana Papaioannou, Cara Mooney, Sienna Hamer-Kiwacz and Cindy Cooper, with input from Kirsty Sprange and Alicia O’Cathain as required for the qualitative study and consensus work respectively.

# **4 Methodology**

The project comprises three elements: a scoping review, qualitative interviews, and workshops.

# **4.1 Scoping review of methods**

***Rationale***

There are suggested approaches to recording harms in BCI trials. These include: typologies/frameworks of harms [2, 4, 5]; instruments to record side effects [11, 12] and general principles or methods [3, 17, 20, 21]. However, there is little evidence that these approaches are used routinely in BCI trials [1]. There is a need to collate and describe these approaches to allow signposting to clinical trialists and to inform a future consensus study on principles and recommendations for harms recording in BCI trials.

***Aim***

To identify suggested AE recording principles and approaches, including identifying frameworks or typologies of harms.

The aim of this scoping review is to provide an overview or map of the evidence [22] and descriptively summarise and disseminate findings [23, 24]. It is not expected that the results will be appraised or synthesised systematically. Where appropriate, frameworks or typologies may be synthesised with a view to assessing their convergence, divergence or any possible gaps based on harms discussed in other included studies.

***Objectives***

1. To identify and describe the literature on approaches or principles in harms recording in BCI trials.

2. To identify frameworks/typologies of harms or mechanisms of harms (and where appropriate to synthesise typologies and frameworks and/or highlight potential gaps).

3. To generate potential themes for the qualitative interviews in this research project

4. To inform the principles and recommendations for harms recording in BCI trials to be reviewed in the consensus study.

Although not an objective for this review, empirical research focused on population- or intervention-specific harms may be identified. These studies (quantitative and qualitative) will have key details summarised (e.g., population, key harms) and included within the review as examples/case studies of harms.

***Inclusion criteria***

**Sample:** Behaviour change interventions (BCIs) in which any intervention intends to modify behaviour for e.g., psychological therapies, public health interventions such as weight management, physical activity, peer or social support, health communication or environmental policies, social and emotional learning.

**Phenomenon of Interest:**

1) Frameworks or typologies of harms caused by BCIs, including any mechanisms of harm.

2) Any principles, methods, definitions of or approaches to harms recording.

3) Harms recorded in specific populations [For example see: 6, 7].

**Design:** All study designs will be considered including empirical research, literature reviews. Editorial/opinion pieces will be included.

**Evaluation/Reporting:** Researcher, research participant.

**Research Type:** All qualitative and quantitative empirical research or secondary research.

**Search terms**

This review intends to identify, summarise, and describe suggested methods and approaches.

The search strategy has been designed so it identifies articles whose *main focus* is on harms or unintended consequences arising from BCIs. With this in mind, terms are often limited to title fields. The search strategy may not be sensitive enough to identify harms mentioned as secondary outcomes in empirical research or as discussed in the full text of articles as (or more likely full text fields). However, this approach is fit for purpose for the aims of the review. It will likely pick up empirical research focused on population- or intervention-specific harms, but it is noted this may not be undertaken exhaustively. Search terms to capture disciplines (e.g., public health, psychology therapies) where BCIs commonly are used are incorporated into the search strategy.

The search strategy was presented to the Project Steering Committee on 19th October 2021 for critical appraisal to ensure it was fit for purpose for the review aims. The search strategy was agreed with some modifications and is available in Appendix A.

**Sources to search**

Searching of three electronic databases (Medline, PsycInfo and CINAHL) will be undertaken. Reference list checking of all included articles will be performed.

Citation searching will be performed on Google scholar for all included articles. Citation searching will be limited to the first 250 citations in the event of an article citation search exceeding this number.

**Sifting**

Retrieved articles will be reviewed by two reviewers at title, abstract and full-text level against the inclusion criteria above. All queries will be checked with another reviewer. A sample retrieved articles (10%) will be checked by another reviewer.

**Data extraction and synthesis**

It is difficult to define the complete set of data to be extracted given the heterogeneity of the literature to be included which has not yet been systematically read [25]. Therefore, data extraction will be iterative in nature due to the range of concepts in the literature as recommend by Gentles et al, 2016 [25]. An initial set of concepts will be defined, piloted, and amended as appropriate throughout the process of data extraction.

The findings will be written descriptively and will form a map of the literature in this area.

No formal synthesis or critical appraisal is planned which is appropriate for the aims of this scoping review [23].

Where multiple frameworks are identified, they will be assessed for convergence and divergence- and any gaps relating to harms categories (based on review against the other included articles) will be noted.

# **4.2. Qualitative interviews**

***Background***

The CONSORT SPI extension [15, 16] notes the potential for use of theorising harms in BCIs [3], However, there is no guidance on the details of how to determine what might be an expected event for a behavioural change intervention, whether relatedness can be usefully undertaken, and how restrictions to AE recording can be made.

Therefore, the detail of AE recording in BCI trials, is decided by researchers/clinical trialist themselves. In-depth interviews and focus groups with individuals involved in designing and delivering BCI trials will allow understanding of how these decisions are made, and whether the approach taken to AE recording has worked or was problematic.

***Aim***

To explore the experience of and perspective of individuals involved in designing and delivering BCI trials in relation to harms recording. The study will identify the operational considerations for monitoring harms during trials, including what has/hasn’t worked.

***Overall Design***

In depth interviews (up to 15) and two to three focus groups (5-6 people) will be undertaken with multi-disciplinary experts in designing and delivering behavioural change trials.

The focus groups (FG) will involve multi-disciplinary CTU staff to enable sharing of similar/contrasting experience. Individual qualitative interviews will focus on specialist views e.g., trial oversight committee members, PPI, Chief Investigators, Research nurses, Sponsors.

***Recruitment and Sampling***

Sampling will be purposive [26] to include a diverse range of stakeholders and BCI trials. Authors of key literature identified in the scoping review, individuals involved in designing or implementing NIHR trials (NIHR funding website, Papaioannou (2021 review), UK Clinical Research Collaboration (CRC) Clinical Trial Units webpages to identify trials unit staff, individuals known to co-investigators/project steering committee. We will identify PPI representatives through individual trials at UK CRC trials units. We will also discuss potential PPI participants with ScHARR staff (Dr Kate Fryer, Katie Biggs, Liz Such) involved in improving the diversity and inclusion of underserved groups in research.

We will aim for experienced individuals- i.e., ideally those who have been involved in design and delivery of more than one competed BCI trial where possible.

We will identify potential participants through a variety of routes: by alerting trial professionals via groups such as Trial Forge, UKCRC group networks e.g., TMN and the TMRP Outcomes working group, through the contacts of the PSC members, authors identified through the scoping literature review authors and review of funded research through the NIHR Funding and Awards Website.

Once identified, we will purposively select individuals to allow maximum diversity within our sample. This will be according to CTU and CTU staff role (Trial manager, statistician, QA, Director, Etc.), clinical field (for Chief Investigators), intervention type (public health, psychological therapy, peer/social support) and other stakeholder categories (PPI, steering committees/data collection roles, e.g., RNs, PIs and interventionists.

It is expected the majority of participants will be UK-based clinical trialists, with the inclusion of international candidates if relevant and accessible, and those who work on NIHR-funded trials.

***Data Collection***

***Individual interviews***

Potential participants will be approached by email with an information sheet providing details about the qualitative study, what participation involves, the harms literature, interview topic guide, and a copy of the consent form.

Interested participants will be contacted to arrange a suitable time and method of interview. It is anticipated that most interviews will be conducted remotely by telephone or the online media platform Google Meet. If it is not possible to use Google Meet or the organisation wishes to use an alternative platform, such as Microsoft Teams or ZOOM, then we will request exceptions to be able to use these platforms. We will obtain simple consent; therefore, it will be accepted as a return of email (to the invitation email) stating the participant has read and understood the information sheet and consent form and agrees to participate, with either a typed name or a drawn electronic signature. This correspondence will be filed as the record of informed consent. In addition, on the day of the interview, the researcher(s) will explain the study to the participants again, allow time for any questions they may have and confirm verbal 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.

The individual interviews will be audio-recorded on encrypted recording devices, following the audio recordings guidelines in the ScHARR IG Policy Section 3, then transcribed verbatim by the ScHARR transcriber’s group. Interviews will be checked before sharing transcripts with other team members. The audio recordings will then be deleted. The interview transcripts are classed as source data and will be retained as part of the project archive.

All interviews will be conducted by SHK and DP, overseen by KS who has over 10 years of experience in qualitative research.

Before each interview, the interviewer will familiarise themselves with the participant’s clinical trial role and the trials they have worked on.

A topic guide will be used to ensure key areas are covered, however with a view to keeping the interview process open and flexible to allow participants to raise issues that are personally relevant.

The guide was informed by the overall aim of the RHABIT project and early findings from the scoping review of approaches to harm recording in BCI trials.

Key areas covered by the guide will include:

* views on the purpose or need for monitoring harms in BCI trials
* perspectives on how AE recording should be undertaken exploring successful AE recording practice
* problems during implementation of AE data collection and interpretation.

***Focus Groups***

In addition to individual interviews, we may undertake 2-3 focus groups with multi-disciplinary CTU staff and PPI groups. In contrast, this approach enables those participating to identify and clarify views in relation to others who have a similar experience and support sharing of their ideas and similar or different opinions [30]. We anticipate 5-6 participants in each focus group to ensure the session is manageable but is representative of stakeholders.

The process for invitation and consent will be the same as that carried out for the interviews. The groups will also be audio recorded and transcribed with participant consent. We anticipate the groups to be delivered online, although face-to-face will be an option subject to current government guidelines on COVID-19.

The focus groups (FG) may be used to collect data amongst similar types of participants for e.g. CTU staff or PPI representatives to enable sharing of similar/contrasting experience. Individual qualitative interviews may focus on specialist views, for example, trial oversight committee members, Chief Investigators, Research nurses, Sponsors. The sampling and methods for the qualitative study will be iterative and determined by findings from interviews/focus groups guiding what further perspectives are required (and how to best collect data). For example, we may decide that focus groups are not required, or more input is required by one type of participant.

***Data Analysis***

 Thematic analysis of the qualitative data will be conducted in accordance with Braun and Clarke’s standard methods [28]. An inductive/deductive thematic approach [29] will be used to identify participants' perspectives regarding recording AEs in BCI trials.

Three researchers (SHK, KS and DP) will independently conduct initial open coding and categorisation of the transcripts with the aid of NVivo12, a qualitative data management software. 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 [#31? O’Connor & Joffe (2020)]. 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 [32]. 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 [33]. The triangulation will help the research team to develop a comprehensive understanding on different perspectives including decision making and the operational considerations for monitoring harms during BCI trials.

***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 Sheffield secure dedicated web server. Access will be restricted by user identifiers and passwords.

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.

Complete anonymity of participants amongst other members cannot be guaranteed in focus groups. To address this, participants will be asked to agree to 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.

Recordings of the interviews and focus groups will be transferred to the secured project shared drive as soon as possible by the research team. Transcripts will be anonymised and assigned a unique code. A password protected document showing the link between the code and the corresponding transcript will be kept separately and preserved until the end of the study.

# **4.3 Workshop(s)**

***Aims***

The analysed data from the scoping review and qualitative data will be used to develop a general guidance document for CTU and other investigators in how to record harms in BCI trials. The aim of this workshop is to review and discuss the guidance to assess its practicality and usefulness.

***Overall Design***

This guidance will present considerations, as well as signposts to useful resources and literature, to help trials teams identify and collect adverse events/harms in BCI trials drawing on data from the scoping review and qualitative interviews. This will be presented to the project steering committee prior to the workshops.

We will conduct the workshop(s) virtually using Google Meet. We will purposively recruit a multi-disciplinary panel of 12-15 experts in delivering trials, as well as PPI representatives, consisting of a mix of individuals who did take part in the qualitative interviews, and those who did not.

# **4.3.1 Participants selection**

Participants will include experienced CTU investigators and staff (e.g., Trial managers, quality assurance), Chief Investigators, TSC/DMEC member and PPI representatives across a range of trials.

Participants will be identified in a similar way to that described for the qualitative interviews. Trial professionals will be targeted through groups such as Trial Forge, UKCRC group networks, UKTMN and the TMRP Outcomes working group. The PSC members will be asked to recommend potential participants. Authors included in the scoping review (see 3.1) and investigators identified through the NIHR Funding and Awards website will also be a source of potential participants.

Individuals will be invited by email to take part in the study. This will include details on what their participation will involve. Emails will also be sent through distribution lists such as UKCRC subgroups informing them of the study and asking relevant individuals (experienced CTU investigators and staff (e.g., Trial managers, quality assurance), Chief Investigators, TSC/DMEC member and PPI representatives) to register their interest in participating.

# **4.3.2 Consent and withdrawal**

Participants will be provided with brief information prior to attending the workshop via email with initial agreement to attend the workshop. The guidance will be sent to all participants at least one week before the workshop. At the beginning of the workshop, this information will be recapped and details of data handling and use of data will also be provided. There will then be opportunity for participants to ask any questions. Participants will provide verbal consent during the workshop, those who decide not to provide verbal consent will be able to leave the meeting before the workshop activities begin. Participants will be informed that they can withdraw at any time, although we will keep their data up to the point of withdrawal.

All PPI participants will be invited to a briefing meeting prior to the workshops after the guidance has been sent to them to ensure that they understand the guidance and so that we can answer any questions they may have, and they will also be debriefed after the workshop.

# **4.3.3 Procedure**

The guidance document and resources will be sent to the participants around a week prior to the workshops. At the beginning of the workshop, all participants will be given an information of the workshop, such as its purpose and the timetable, followed by an introduction to the project, including the results of the previous work packages. They will be informed that the purpose of the workshop is to review the guidance document and any supporting documents and provide feedback on its usefulness and practicality, as well as any suggestions of what to include. Following this, the participants will be given the opportunity to ask any questions that they may have and verbal consent will then be taken for each participant. Facilitators will also attend the workshop to support discussions and answer any questions participants may have throughout the session.

# **5 Principles and recommendations for harms recording**

Following the workshops, an updated guidance document with draft recommendations and AE recording in BCI trials will be written and presented to the PSC. The recommendations will likely include principles for recording harms and operational considerations. If appropriate a broad typology of harms may be provided.

# **6 Outputs and Dissemination plan**

There are tangible outputs from each of the individual stages in this study: the scoping review, qualitative interviews/focus groups and the workshop(s). The scoping review will map and collate (and synthesise where applicable) suggested approaches or typologies of harms that may apply to BCI trials. The review will signpost investigators to relevant frameworks and types of harms, which could be applied when considering the potential harms for an individual BCI.

The qualitative study will describe operational experience on AE recording across UK CRC CTUs. Issues will be highlighted and practical experience of making AE recording more efficient shared. The qualitative interviews and focus groups will be summarised to share CTU experience of suggested approaches to efficient AE recording.

The workshops will result in refined and reviewed general guidance that makes recommendations for CTUs to ensure relevant AEs are recorded that better reflect the risk-benefit profile of BCIs and with improved efficiency.

Each individual part of the project (scoping review, qualitative study and workshop) will be published in peer-reviewed publications. In addition, a publication will detail the overall recommendations/principles for harms recording in BCI trials, along with an explanatory document. All publications will be within a relevant journal (e.g. Trials journal).

The recommendations/principles document developed at the end of the project will be shared with all UK CTU Directors and will be made freely available to download from the Sheffield CTU website.

The UKCRC, Trial Forge and the TMRP Outcomes working group will be approached to assist in disseminating the results of the study.

The results of the study will be presented at the Clinical Trials Methodology Conference (ICTMC) 2022.

As well as academic outputs, a short video to communicate the recommendations will be produced and disseminated through the aforementioned trial working groups.

# **7 Ethics approval**

The study received a favourable ethics approval (044669) from the Research Ethics Committee (REC) of the School of Health and Related Research (ScHARR) at the University of Sheffield. The conduct of the study will be guided by the granted ethics approval. A safeguarding plan has been written in line with both the ScHARR and NIHR ethics guidelines.

# **8 PPI Support**

There is no PPI group working alongside this project. However, PPI representatives will be invited to take part in the qualitative interviews and workshop(s). PPI representatives will be supported by SHK/DP. Support will include additional meetings, briefing before interviews to ensure understanding of the topic area and role of the interview, briefing before taking part in the workshop. A debrief meeting following the completion of the interview/workshop will also be offered to give the opportunity for PPI representatives to discuss anything further.

# **9 Funding and any additional support**

We gratefully acknowledge the funding of this project by the NIHR through CTU Support Funding.

# **10 Declaration of Conflict of Interest**

All members declare that they have no conflict of interest to disclose.

# **11 References**

1. Papaioannou, D., Cooper, C., Mooney, C., Glover, R., & Coates, E. (2021). Adverse event recording failed to reflect potential harms: a review of trial protocols of behavioral, lifestyle and psychological therapy interventions. *Journal of Clinical Epidemiology, 136*, 64-76. https://doi.org/10.1016/j.jclinepi.2021.03.002
2. Lorenc, T., & Oliver, K. (2014). Adverse effects of public health interventions: a conceptual framework. *Journal of Epidemiology and Community Health, 68*(3), 288-290. https://doi.org/10.1136/jech-2013-203118
3. Bonell, C., Jamal, F., Melendez-Torres, G. J., & Cummins, S. (2015). 'Dark logic': theorising the harmful consequences of public health interventions. *Journal of Epidemiology and Community Health, 69*(1), 95-98. https://doi.org/10.1136/jech-2014-204671
4. Allen-Scott, L. K., Hatfield, J. M., & McIntyre, L. (2014). A scoping review of unintended harm associated with public health interventions: towards a typology and an understanding of underlying factors. *International Journal of Public Health, 59*(1), 3-14. https://doi.org/10.1007/s00038-013-0526-6
5. Ogden, J. (2019). Do no harm: Balancing the costs and benefits of patient outcomes in health psychology research and practice. *Journal of Health Psychology, 24*(1), 25-37. https://doi.org/10.1177/1359105316648760
6. Evans, R., Scourfield, J., & Murphy, S. (2014). The unintended consequences of targeting: young people's lived experiences of social and emotional learning interventions. *British Educational Research Journal, 41*(3), 381-397. https://doi.org/https://doi.org/10.1002/berj.3155
7. Palant, A., & Himmel, W. (2019). Are there also negative effects of social support? A qualitative study of patients with inflammatory bowel disease. *BMJ Open, 9*(1), e022642. https://doi.org/10.1136/bmjopen-2018-022642
8. Ali, J., Andrews, J. E., Somkin, C. P., & Rabinovich, C. E. (2015). Harms, benefits, and the nature of interventions in pragmatic clinical trials. *Clinical Trials, 12*(5), 467-475. https://doi.org/10.1177/1740774515597686
9. Datta, R., Trentalange, M., Van Ness, P. H., McGloin, J. M., Guralnik, J. M., Miller, M. E., . . . Group, L. S. (2018). Serious adverse events of older adults in nursing home and community intervention trials. *Contemporary Clinical Trials Communications, 9*, 77-80. https://doi.org/10.1016/j.conctc.2017.12.004
10. Petry, N. M., Roll, J. M., Rounsaville, B. J., Ball, S. A., Stitzer, M., Peirce, J. M., . . . Carroll, K. M. (2008). Serious adverse events in randomized psychosocial treatment studies: safety or arbitrary edicts? *Journal of Consulting and Clinical Psychology, 76*(6), 1076-1082. https://doi.org/10.1037/a0013679
11. Linden, M. (2013). How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clinical Psychology and Psychotherapy, 20*(4), 286-296. https://doi.org/10.1002/cpp.1765
12. Herzog, P., Lauff, S., Rief, W., & Brakemeier, E. L. (2019). Assessing the unwanted: A systematic review of instruments used to assess negative effects of psychotherapy. *Brain Behaviour, 9*(12), e01447. https://doi.org/10.1002/brb3.1447
13. Duggan, C., Parry, G., McMurran, M., Davidson, K., & Dennis, J. (2014). The recording of adverse events from psychological treatments in clinical trials: evidence from a review of NIHR-funded trials. *Trials, 15*, 335. https://doi.org/10.1186/1745-6215-15-335
14. Ioannidis, J. P., Evans, S. J., Gøtzsche, P. C., O'Neill, R. T., Altman, D. G., Schulz, K., . . . Group, C. (2004). Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine, 141*(10), 781-788. https://doi.org/10.7326/0003-4819-141-10-200411160-00009
15. Montgomery, P., Grant, S., Mayo-Wilson, E., Macdonald, G., Michie, S., Hopewell, S., . . . Group, C.-S. (2018). Reporting randomised trials of social and psychological interventions: the CONSORT-SPI 2018 Extension. *Trials, 19*(1), 407. https://doi.org/10.1186/s13063-018-2733-1
16. Grant, S., Mayo-Wilson, E., Montgomery, P., Macdonald, G., Michie, S., Hopewell, S., . . . , o. b. o. t. C.-S. G. (2018). CONSORT-SPI 2018 Explanation and Elaboration: guidance for reporting social and psychological intervention trials. *Trials, 19*(1), 406. https://doi.org/10.1186/s13063-018-2735-z
17. Moody, G., Addison, K., Cannings-John, R., Sanders, J., Wallace, C., & Robling, M. (2019). Monitoring adverse social and medical events in public health trials: assessing predictors and interpretation against a proposed model of adverse event reporting. *Trials, 20*(1), 804. https://doi.org/10.1186/s13063-019-3961-8
18. Wyatt, K., Lloyd, J., Creanor, S., Green, C., Dean, S. G., Hillsdon, M., . . . Logan, S. (2018). Cluster randomised controlled trial and economic and process evaluation to determine the effectiveness and cost-effectiveness of a novel intervention [Healthy Lifestyles Programme (HeLP)] to prevent obesity in school children. *Public Health Research, 6*(1). https://doi.org/NBK476162
19. Daley, A., Jolly, K., Madigan, C., Griffin, R., Roalfe, A., Lewis, A., . . . Aveyard, P. (2019). A brief behavioural intervention to promote regular self-weighing to prevent weight regain after weight loss: a RCT. *Public Health Research, 7*(7), 1-66. https://doi.org/doi:10.3310/phr07070
20. Horigian, V. E., Robbins, M. S., Dominguez, R., Ucha, J., & Rosa, C. L. (2010). Principles for defining adverse events in behavioral intervention research: lessons from a family-focused adolescent drug abuse trial. *Clinical Trials, 7*(1), 58-68. https://doi.org/10.1177/1740774509356575
21. Czaja, S. J., Schulz, R., Belle, S. H., Burgio, L. D., Armstrong, N., Gitlin, L. N., . . . Stahl, S. M. (2006). Data and safety monitoring in social behavioral intervention trials: the REACH II experience. *Clinical Trials, 3*(2), 107-118. https://doi.org/10.1191/1740774506cn136oa
22. Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology, 18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x
23. Arksey, H., & O'Malley, L. (2005). Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology, 8*(1), 19-32.
24. Antman, E, Lau, J, Kupeinick, B, Mosteller, F and Chalmers, T. (1992). A comparison of results of meta‐analysis of RCTs and recommendations of clinical experts. *Journal of American Medical Association*, *268*, 240–248.
25. Gentles, S. J., Charles, C., Nicholas, D. B., Ploeg, J., & McKibbon, K. A. (2016). Reviewing the research methods literature: principles and strategies illustrated by a systematic overview of sampling in qualitative research. *Systematic Reviews, 5*(1), 172. https://doi.org/10.1186/s13643-016-0343-0
26. Palinkas, L. A., Horwitz, S. M., Green, C. A., Wisdom, J. P., Duan, N., & Hoagwood, K. (2015). Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. *Administration and Policy in Mental Health, 42*(5), 533-544. https://doi.org/10.1007/s10488-013-0528-y
27. Kitzinger, J. (1995). Qualitative research. Introducing focus groups. *BMJ, 311*(7000), 299-302. https://doi.org/10.1136/bmj.311.7000.299
28. Braun, V., & Clarke, V. (2008). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*(2), 77-101. https://doi.org/https://doi.org/10.1191/1478088706qp063oa
29. Fereday, J., & Muir-Cochrane, E. (2006). Demonstrating rigor using thematic analysis: a hybrid approach of inductive and deductive coding and theme development. International *Journal of Qualitative Methods, 5*(1), 80-92.
30. Cascio, M., Lee, E., N, V., & DA, F. (2019). A team-based approach to open coding: Considerations for creating intercoder consensus. *Field Methods, 31*(2), 116-130.

O’Connor, C., & Joffe, H. (2020). Intercoder reliability in qualitative research: Debates and practical guidelines. *International Journal of Qualitative Methods, 19*, 1-13. https://doi.org/10.1177/1609406919899220

1. O'Cathain, A., Murphy, E., & Nicholl, J. (2010). Three techniques for integrating data in mixed methods studies. *BMJ, 341*. https://doi.org/10.1136/bmj.c4587
2. Farmer, T., Robinson, K., Elliott, S. J., & Eyles, J. (2006). Developing and implementing a triangulation protocol for qualitative health research. *Qualitative Health Research, 16*(3), 377-394. https://doi.org/10.1177/1049732305285708
3. Dose Finding CONSORT Extension Project <http://www.icr.ac.uk/our-research/researchers-and-teams/professor-christina-yap/dose-finding-consort-extension-project>
4. https://doi.org/https://doi.org/10.1016/j.jclinepi.2013.12.002
5. Delbecq, A. L., Van de Ven, A. H., & Gustafson, D. H. (1975). Group techniques for program planning. Glenview, IL: Scott, Foresman, and Co

Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L., … & PAFS consensus group. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ (Clinical research edition), 355*. https://doi.org/10.1136/bmj.i5239

Kirkham, J.J., Gorst, S., Altman, D.G., Blazeby, J., Clarke, M., Devane, D., … & Williamson, P.R. (2015). Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLOS Medicine, 13*(10). https://doi/10.137/journal.pmed.1002148

**Appendices**

Appendix A – Final Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to October 25, 2021>

1 ((behavio?ral or social or psychological) adj2 (intervention$ or treatment$ or therap$ or program$ or strateg$)).tw.

2 (social adj2 (care or support)).ti.

3 (public adj2 health).ti.

4 psychotherapy/ or exp behavior therapy/

5 Public Health/

6 social support/

7 Social Learning/

8 (emotional adj2 learning).ti.

9 Health Promotion/

10 (peer adj2 support).ti.

11 Behavioral Medicine/

12 or/1-11

13 ((unanticipated or unintended or unwanted or unplanned) adj2 (event$ or effect$ or harm$ or consequence$ or impact$ or repercussion$)).ti.

14 (adverse adj2 (effect$ or event$ or consequence$)).ti.

15 (side adj2 effect$).ti.

16 harm$.ti.

17 \*Patient Harm/

18 (negative adj2 (effect$ or event$ or consequence$ or impact$ or repercussion$)).ti.

19 or/13-18

20 (behavio?r adj2 (change$ or modif$ or therap$)).tw.

21 Behavior Therapy/

22 Health Behavior/

23 (health adj2 psycholog$).tw.

24 ((behavio?ral or social or psychological) adj2 (intervention$ or treatment$ or therap$ or program$ or strateg$)).tw.

25 (social adj2 (care or support)).ti.

26 (public adj2 health).ti.

27 psychotherapy/ or exp behavior therapy/

28 Public Health/

29 social support/

30 Social Learning/

31 (emotional adj2 learning).ti.

32 Health Promotion/

33 (peer adj2 support).ti.

34 Behavioral Medicine/

35 (behavio?r adj2 (change$ or modif$ or therap$)).tw.

36 Behavior Therapy/

37 Health Behavior/

38 (health adj2 psycholog$).tw.

39 or/24-38

40 ((unanticipated or unintended or unwanted or unplanned) adj2 (event$ or effect$ or harm$ or consequence$ or impact$ or repercussion$)).ti.

41 (adverse adj2 (effect$ or event$ or consequence$)).ti.

42 (side adj2 effect$).ti.

43 harm$.ti.

44 \*Patient Harm/

45 (negative adj2 (effect$ or event$ or consequence$ or impact$ or repercussion$)).ti.

46 or/40-45

47 39 and 46

48 limit 47 to (english language and humans and yr="2011 -Current")

49 47 not 48

1. Adverse event- GCP definition- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. [↑](#footnote-ref-1)
2. Serious adverse event is an AE that at any dose results in death or is life-threatening (requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital abnormality/birth defect). [↑](#footnote-ref-2)