A collaborative study between CTUs and other researchers to identify the activities needed to improve representation of under-served groups in trials and understand their implementation - A Protocol

Project Name: ACCESS: A collaborative study between CTUs and other researchers to identify the activities needed to improve representation of under-served groups in trials and understand their implementation

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List of Abbreviations

CTIMPS Clinical Trials of Investigational Medicinal Products

CTU Clinical Trials Unit

INCLUDE Improving Inclusion of Under-Served Groups in Clinical Research

NIHR National Institute for Health Research

PPIE Patient and Public Involvement and Engagement

PSI Statisticians in the Pharmaceutical Industry

RCTs Randomised Controlled Trials

SWAT Study Within A Trial

TMRP Trial Management Research Partnership

UK United Kingdom

1. Introduction

1.1 Background

Research shows that participants in clinical trials rarely reflect the populations that could benefit from the treatments being investigated. For example, COVID-19 has been shown to disproportionately affect elderly people and those from ethnic minority groups, and even with this knowledge, these groups are underrepresented in the medical research in relation to vaccines and therapeutics[1] [2]. There are several negative consequences of participants in clinical trials not matching the populations in which treatment will be used. The benefits and harms that we see in trials may not translate to improved care, or it could lead to the research missing important findings that are specific to some groups of people. Clinicians, and regulators, may be reluctant to generalise trial findings to their population. For instance, initial lack of recruitment of older people in the AstraZeneca vaccine trial led to some international regulators being reluctant to endorse vaccinations for the over 60s with that product, and GPs have highlighted they need evidence for how to treat their diverse patients[3].

The NIHR INCLUDE project[4] was commissioned in 2017 to look at underrepresentation in clinical trials. It identified a range of under-served groups, which can vary across the types of studies, disease or condition being studied. There are some common barriers to trial participation in under-served groups, such as the research burden, language and communication differences and a lack of trust and engagement in healthcare or research more broadly. The INCLUDE project produced a roadmap[5] which identifies time points for potential intervention over the lifetime of a research project. This shows how researchers, funders, ethics committees, delivery teams, patients, and analysts can work together to successfully deliver research that is inclusive and sensitive to the needs of under-served groups.

The INCLUDE Ethnicity Framework[6] guides researchers through important questions when designing trials. The framework makes researchers think about which ethnic groups the trial results should apply to, whether ethnic groups may respond to the treatment in different ways, or if the treatment, comparator or trial design makes it more difficult for any particular group to take part. The framework aims to help researchers think about what can be done to reduce barriers for groups that are under-served due to their ethnicity (including culture, faith, and language). These changes might involve adjustments to their trial design or include specific activities to improve engagement between the trial team and specific ethnic minority groups. The Trial Management Research Partnership (TMRP) Inclusivity sub-group is currently developing similar frameworks for people with low socioeconomic status, adults that lack the capacity to consent and LGBTQIA+ groups.

Activities shown to improve representation of under-served groups in research (though not necessarily trials) include: transport or child care provision; gender matched staff; cultural and linguistic translation of documents; working alongside trusted interpreters; community engagement activities, increased patient and public involvement and engagement (PPIE); and innovations when it comes to recruitment methods; alternative consent processes; and alternative data collection methods[7] [8].

Historically, CTUs have not routinely included these focussed activities to improve representation in their trial populations. This is changing as health inequalities become more widely known, and much needed anti-racism work becomes more mainstream - the NIHR INCLUDE Project demonstrates this current focus. NIHR funding streams emphasise the need for consideration of inclusivity in NIHR trials, but CTUs likely lack the experience in this area and therefore may not know which activity should be included.

1.2 Aims and Objectives

- Review the literature to develop a list of activities/design features that have been effective in improving the representation of under-served groups in trials.

- Undertake roundtables to explore the findings and gather further examples of activities that aim to increase representation from the stakeholders.

- Redesign a number of case study trials to include the work needed to ensure these trials are including the necessary populations, including under-served groups.

- Undertake further collaborator meetings and interviews to explore facilitators and barriers to the implementation of activities or particular design features, and how barriers could be addressed

- Hold a meeting with collaborators and PPI members to determine best-practice guidance

- Develop a study within a trial (SWAT) proposal of an intervention that may improve the recruitment of a particular under-served population.

2. Methods

2.1. A review of the literature

A scoping literature review will be conducted to identify examples of 'good practice' or activities that have been included in trials to improve representation, aiming to produce a ‘starter' list of activities that could be included in a trial design. We will also assess if there is evidence for the effectiveness of these activities.

A draft Trial Forge Guidance document for recruiting and retaining ethnic minority groups will provide a solid starting point for ethnicity and be a model for other under-served groups. Through collaborators involved in the INCLUDE project, we will also build on the work done by NIHR Innovative Observatory for the INCLUDE project that identified innovations in design and delivery of trials that enhance inclusion.

Searches will be conducted using PubMed, ORRCA, and the NIHR Journals Library. A number of search terms will be used, for example under-served, underrepresented, minority, BAME, socioeconomic, in order to collate the relevant literature on a number of under-served groups. The search terms will be determined during initial scoping of the literature, and agreed by the collaborators.

The resulting articles will be screened, and any that do not report on an under-served population and/or were based outside of the UK or Ireland, will be excluded. This will be done by one reviewer and checked independently by a second reviewer. Full text articles will then be reviewed to extract data about the population, the treatments used, the recruitment strategies employed and their effectiveness.

The results of the review will be used to produce an overview of the activities currently being undertaken to improve representation of under-served populations in clinical research. The findings will feed into the roundtables to facilitate discussions about how best to increase recruitment and retention of underrepresented groups in trials.

2.2. Stakeholder roundtables

We will undertake a series of roundtables with the following stakeholders:

a) Clinicians and who have experience in improving representation of under-served groups in research, or may wish to do so in the future

b) Members of under-served groups who have participated, or might in future, in clinical trials

d) Others with an interest in improving representation of under-served populations in research

We will present the findings from the literature review to these groups and seek input from them to inform the guidance we will produce. The roundtables may take place either in person, online or a mixture of the two.

2.3. Participant Recruitment, Consent and Identifiable Data

Stakeholders will be approached via email. The team will reach out to their existing contacts and also find additional relevant stakeholders through:

a) Contacting those who have published work in this area
b) Research networks
c) PPI panels such as Deep End
d) Advertisement on People in Research

We will aim for one roundtable per population but we will conduct more if necessary to accommodate all participants, each attended by around 8-15 stakeholders. This should enable us to achieve a diverse range of opinions whilst remaining appropriate for the proposed design. We anticipate these to last between 90 minutes to two hours.

Roundtable participants will be provided with an information sheet prior to participation, which will explain the purpose and format of the discussion. We will confirm consent to participate at the beginning of each roundtable and this consent will be recorded.

The University of Sheffield will act as data controller for this study. Electronic files will be held in the project folder on the University of Sheffield's X drive, which has restricted access to members of the research team. Any identifiable data that is collected will be kept in a password-protected file and separate from any notes/screen recordings taken during the stakeholder roundtables. Screen recordings will be deleted immediately after thorough notes have been compiled. The identifiable information will only allow access to those members who need it and for contacting people about further research and will be destroyed one year after the publication of the study.

2.4. Draft guidance

Following the review of the literature and clinician and participant input to the roundtables, guidance will be drafted for the end of August 2022. The guidance will highlight what activities are appropriate for improving recruitment and retention of under-served groups in clinical research.

Further meetings with collaborators will be held to review the findings in the context of their experiences.

2.5. Redesign of trials for enhanced inclusivity

3-5 existing UK phase 3 trials for which protocols are available will be identified for redesign. Trials will be selected to include a range of types of intervention (for example, CTIMPs and non-CTIMPS, complex interventions), target populations and health conditions – (for example, diabetes, mental health and stroke rehabilitation). These three health conditions have been proposed as examples to try to focus on different under-served groups: ethnic minority communities, socio-economically disadvantaged/ unemployed/ low income and people who lack capacity to consent for themselves, but these categories of under-served groups would be confirmed at an early collaborator meeting. The number of trials will also be chosen to cover a range of underserved groups and activities that can be undertaken, whilst not overburdening collaborators.

A group with expertise in inclusivity and diversity in research, including study collaborators and PPI contributors, will review the protocols using the INCLUDE Ethnicity Framework or any companion frameworks relevant to the other population groups. Other similar frameworks are expected to be available from the TMRP covering other under-served groups by the time this project starts. The review process will aim to identify what could be done to improve the representativeness and diversity of the participants in the case study trials. The study team would then re-design the trials, detailing additional activities aiming to increase representation.

2.6. Exploring implementation of inclusive trial designs

Further collaborator meetings will be held to explore facilitators and barriers to implementing these activities in trials, and discuss potential solutions to the barriers and identify areas for further research.

Interviews will be held with potential trial participants and people working in clinical research – e.g. trial managers with experience of implementing more ‘inclusive’ designs and clinical trial support staff (up to 15 interviews). Participants will be identified during the course of the project and through networks of the collaborators, including through KB’s links to the Deep End PPI group in Sheffield, a PPI panel that is made up of people from the most socioeconomically deprived areas in Sheffield.

Semi-structured interviews will explore any experience the clinical research staff have had in implementing work aimed at improving representativeness, whether they were successful and the facilitators and barriers to their implementation.

Qualitative interviews will be transcribed and two researchers will independently code the interviews. Data analysis will use the National Centre for Social Research ‘Framework’ approach[9]: familiarisation; identifying a thematic framework; indexing; charting; and mapping and interpretation. Themes will be derived inductively from reading the transcripts.

We will combine the findings from the implementation meetings and interviews and incorporate recommendations for implementation of the activities identified in WP1-3.

2.7. Dissemination

These findings will be presented at a collaborator meeting, where we will finalise what will be included in the guidance for CTUs; the guidance will cover the inclusion of activities to improve representation of under-served groups in trials, and recommendations for their implementation. We will write up the guidelines and disseminate this across CTUs.

Although the aim of this research is not to develop an intervention that aims to improve representation, we may identify existing interventions aiming to improve trial representation in one or more under-served groups covered in the redesign of trials. We will scope opportunities to integrate findings into future SWAT (studies within a trial) designs to provide evidence based methods of achieving more representative and diverse study cohorts. Potential SWATs will be registered on the SWAT database hosted by Queen's University Northern Ireland.

3. Project Management & Expertise

This application will be a collaboration between Sheffield CTRU, Newcastle CTU, Cardiff CTU, Bristol CTU, York CTU, University of Aberdeen, University College London, University College Cork and The Centre for Black and Minority Ethnic (BME) Health at University of Leicester. The day to day project management will be undertaken by Sheffield CTRU.

4. Co-applicants:

Sheffield CTRU: Katie Biggs develops RCT research proposals with clinicians and oversees CTRU involvement. She has an interest in trial inclusivity and is working with the TMRP group developing the INCLUDE ethnicity framework to be applicable to other under-served groups in trials. KB will lead the project under the guidance of CC.

Newcastle CTU: Helen Hancock and Rebecca Maier are on the NIHR INCLUDE steering committee, experienced in managing trials and will contribute to the meetings and redesign of trials.

Cardiff CTU: Victoria Shepherd has an NIHR Advanced Fellowship conducting research relating to inclusion of adults who lack capacity to consent and has extensive knowledge of the inclusivity literature relating to this group of under-served groups.

Bristol CTU: Athene Lane is Co-director of Bristol Randomised Trials Collaboration with methodological expertise in recruitment and retention and was theme lead of the Feasibility studies and trial conduct theme in the MRC ConDuCT Hubs for Trials Methodology Research and will contribute to the meetings and redesign of trials.

York CTU: David Torgerson and Joy Adamson will contribute to the meetings and redesign of trials, and advise on SWAT design.

The following collaborators work outside of CTUs and are all members of the TMRP Inclusivity subgroup. They will provide valuable input to work packages 1, 2, 3 and collaborator meetings to ensure we utilise the knowledge and experience of people working to improve representation of under-served groups. This will ensure the guidance includes the experience of individuals who are active in trial inclusivity research, and is not based on a narrow focus or limited by a lack of previous CTU experience.

Dr Andrew Willis, The Centre for Ethnic Health Research, University of Leicester – will advise on work that can be done to improve inclusivity and provide examples and resources to aid the re-design of trials to improve inclusivity.

Prof Shaun Treweek and Dr Heidi Gardner, Health Services Research Unit, University of Aberdeen – They are both active in trial methodology, recruitment and inclusivity research, work with the Aberdeen CTU and will contribute in advisory roles via their roles in the TMRP inclusivity subgroup, which Prof Treweek co-leads. Dr Gardner will facilitate connections with groups outside of the academic space such as Egality Health (a non-profit working with medical research charities and community groups to ensure research is inclusive: https://www.egality.health/) and the Road to Equality taskforce which is being led by Egality, COUCH Health (https://www.couchhealth.co) and Innovative Trials (https://innovativetrials.com/).

Dr Talia Issacs, Institute of Education, University College London – Linguistics expert undertaking a project on language-related eligibility criteria in patient recruitment to trials. Dr Isaacs combines expertise in applied linguistics and language assessment with research in trial communication and the inclusion of underserved groups. She led two related studies: (a) a systematic review on the underrepresentation of ethnic minorities and role of language in patient recruitment to telehealth diabetes trials, and (b) the development of the first open access corpus (collection) of informed consent documents for cancer trials to generate evidence-based practice recommendations on improving information provision to patients. She will be able to highlight important literature related to this area, provide expertise on trial communication and contribute to the redesign of trials, particularly where language may be a factor.

Dr Frances Shiely, University College Cork (UCC) – Frances is Director of Education at the HRB Clinical Research Facility at University College Cork; Senior Lecturer Patient Focused Research/Epidemiology School of Public Health, UCC is active in trial methodology research and is PI for the Trial Methodology Research Network (HRB TMRN) in UCC and has links to clinical networks in Ireland. Based in a Clinical Research Facility (CRF) in Ireland, Frances will be able to bring a non-UK perspective to the project, and will have an understanding of the issues from a CRF point of view.

5. Funding

This project is funded by the National Institute for Health Research (NIHR) through the NIHR CTU Support Funding scheme (Efficient Studies call).

6. Ethics

The research will be ethically reviewed by the University of Sheffield's School of Health and Related Research's independent Ethics Committee. The research will follow the Research Governance guidelines of the University of Sheffield.

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