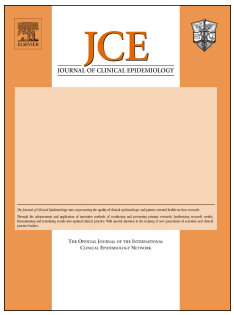

Most UK cardiovascular disease trial protocols feature criteria that exclude ethnic minority participants: systematic review

Jhulia dos Santos, Shoba Dawson, Carmel Conefrey, Talia Isaacs, Mahwar Khanum, Saba Faisal, Sangeetha Paramasivan

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Most UK cardiovascular disease trial protocols feature criteria that exclude ethnic minority participants: systematic review

Jhulia dos Santos[1], Shoba Dawson[1], Carmel Conefrey[1], Talia Isaacs[2], Mahwar Khanum[1], Saba Faisal[1], Sangeetha Paramasivan[1*]

1. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom
2. UCL Centre for Applied Linguistics, IOE, UCL's Faculty of Education and Society, University College London, London, United Kingdom

Correspondence: Sangeetha Paramasivan, 39 Canynge Hall, Whatley Road, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2PS, United Kingdom, sangeetha.paramasivan@bristol.ac.uk; Phone: +44 117 455 5675

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Authors' contributions

Conception and design of the study: SP and SD

Acquisition of data: JdS, SP, SD, CC, MK, SF, TI

Analysis and interpretation of data: JdS, SP, SD, CC, MK, SF, TI

Drafting the article: JdS, SP, SD

Revisiting article critically for important intellectual content: SP, SD, JdS, CC, TI, MK, SF

Final approval of version to be submitted: SP, SD, JdS, CC, TI, MK, SF

Abstract

Objectives

We systematically reviewed UK cardiovascular disease (CVD) randomised controlled trial (RCT) protocols to identify the proportion featuring eligibility criteria that may disproportionately exclude ethnic minority (EM) participants.

Methods

We searched MEDLINE, Embase and Cochrane Library databases, January 2014-June 2022, to identify UK CVD RCT protocols. We extracted non-clinical eligibility criteria from trial protocols and inductively categorised the trials by their language, consent and broad (ambiguous) criteria. Findings are narratively reported.

Results

Of the seventy included RCT protocols, most (87.1%; 61/70) mentioned consent within the eligibility criteria, with more than two thirds (68.9%; 42/61) indicating a requirement for 'written' consent. Alternative consent pathways that can aid EM participation were absent. English language requirement was present in 22.9% (16/70) of the studies and 37.1% (26/70) featured broad criteria that are open to interpretation and subject to recruiter bias. Only 4.3% (3/70) protocols mentioned the provision of translation services.

Conclusion

Most UK CVD trial protocols feature eligibility criteria that potentially exclude EM groups. Trial eligibility criteria must be situated within a larger inclusive recruitment framework, where ethnicity is considered alongside other intersecting and disadvantaging identities.

Keywords

Recruitment, Randomized controlled trials, Cardiovascular diseases, Systematic review, Ethnic minority groups, Equitable research

Running title

Most UK cardiovascular disease trial protocols feature criteria that exclude ethnic minority participants

Word count: 183

What is new?

Key findings

- More than two thirds of UK cardiovascular disease (CVD) trial protocols require 'written' consent; none reported alternative consent pathways.
- One in five require participants to speak, understand or read English; more than a third feature broad (ambiguous) criteria that might lead to recruitment bias.
- Less than one in 20 included measures to aid ethnic minority (EM) participation (e.g., translation services).

What this adds to what is known?

- Despite higher burden of CVD for EM groups in the UK, most CVD trial protocols routinely feature eligibility criteria that exclude EM participants.

What is the implication and what should change now?

- For meaningful strides towards better inclusion, ethnicity has to be considered alongside other intersecting identities that create social disadvantage; equitable trial eligibility criteria have to be placed within a larger inclusive framework of recruitment.

1. Introduction

Ethnic minority (EM) populations are disproportionately affected by conditions such as diabetes, cardiovascular diseases (CVD) and COVID-19 (1). For instance, South Asians have the highest mortality from heart disease and Black groups have a higher-than-average incidence of mortality from hypertension and stroke (1). Yet EM groups are under-represented in randomised controlled trials (RCTs) focusing on these conditions (2–5). South Asians account for 11.2% of the UK population and are disproportionately affected by type 2 diabetes, yet the mean South Asian involvement in UK diabetes trials is only 5.5% (5). This means that the trial treatments' benefits and harms may not translate into the real world, with findings not generalisable to population groups that were not part of the study. Systematic reviews have identified a range of barriers to inclusive recruitment (e.g., language and communication issues, lack of trust in health services, inadequate or unclear eligibility criteria) (6) and a limited number of strategies to recruit people from EM groups (e.g., recruitment from ethnically diverse areas and from community/religious organisations) (7). However, there is little robust evidence on the effectiveness of such strategies and interventions. Since the pandemic, there have been frameworks, practical guidance and recommendations to help researchers recruit participants from diverse ethnic groups in the UK (8–10).

The onus of ensuring inclusive recruitment across multiple under-served groups, including those from EM groups, rightly rests with the research community and is acknowledged as imperative to conducting methodologically and ethically sound research (8). This is especially relevant in countries like the UK, which have a sizeable EM population. Census data in England and Wales show an increase in the proportion of people identifying as belonging to EM groups including white minorities (11). This includes Asian, Asian British or Asian Welsh (7.5% in 2011 to 9.3% in 2021), other White (4.4% in 2011 to 6.2%), and Black, Black British, Black Welsh, Caribbean or African (1.8% in 2011 to 2.5% in 2021) (12).

RCT protocols guide trial conduct and outcomes and hold the potential to generate high-quality evidence to improve population health (13). As a crucial component of RCT protocols, eligibility criteria are expected to present a clear description of potential trial participants, determine who can participate in trials and ensure that trial participants are broadly representative of future potential

recipients of the intervention (14,15). However, eligibility criteria can feature narrow consent and language requirements that disproportionately exclude already under-served groups in research (9,16). For instance, reviews of diabetes (17) and breast cancer RCTs (18) demonstrate that many employ eligibility criteria that contribute towards the exclusion of under-served groups, including EM patients. This lack of diversity in trial populations impairs the generalisability of trial findings, leading to calls for action to redress the issues (19).

We systematically reviewed the eligibility criteria outlined in UK RCT protocols of CVD as this has not been comprehensively reviewed previously. We aimed to identify criteria that limit or aid the equitable participation of EM groups, with particular attention to language and consent requirements.

2. Methods

We registered this systematic review protocol with PROSPERO (CRD42022345043) (20) and have completed the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 guidelines and the PRISMA-Equity extension (21) (supplementary files 1a and 1b).

2.1 Search strategy and selection criteria

A comprehensive search strategy was developed (SD, SP), reviewed by an information specialist and applied across three databases, MEDLINE (Ovid), Embase (Ovid) and Cochrane Library (Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL)) to locate UK CVD protocols published between 1st January 2014 and 1st June 2022 (note: PsycINFO was intended for inclusion at protocol registration stage, but this was later not considered relevant for this review's topic area). Our timeframe corresponds to the publication of the Template for Intervention Description and Replication (TIDieR) (22), which aimed to improve the quality of intervention description in publications, including details of the trial population and participant selection. We used a combination of Medical Subject Headings (MeSH) and free-text terms for "cardiovascular diseases" AND "randomised/randomized controlled trial" AND "United Kingdom" (see supplementary file 2 for example search strategy). We limited our search to articles published in English and employed inclusion/exclusion criteria to select articles (Table 1).

Table 1: Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Adults aged 18 or over	Anyone aged under 18 years
Types of studies	Published RCT protocols (including feasibility, pilot and main RCTs)	Non-RCT study designs
Context	RCTs where the primary outcome was directly* or indirectly** related to CVD	RCTs with no particular CVD link, i.e., where the primary outcome is not directly* or indirectly** related to CVD
Setting	UK based, i.e., where data collection took place in the UK, or where the trial was managed by a trials unit based in the UK	Non-UK based, i.e. where data collection did not take place in the UK, or where the trials unit was not based in the UK

***** *Directly related – e.g. studies addressing coronary heart disease, high blood pressure and heart failure*

** *Indirectly related – e.g. studies addressing diabetes and chronic kidney disease or where the trial population comprised participants with a CVD diagnosis or comprising interventions intended to decrease CVD risk through the increase of physical activity*

2.2 Study selection and screening

We used Rayyan (23) to combine, export and screen records from database searches. After deduplication, titles and abstracts were independently screened by at least two reviewers (JDS, SP, CC, MK) in pairs and discrepancies were resolved through discussion. Similarly full texts were independently screened (JDS, SP) in pairs, with discordances resolved through group discussions with team members CC, SD.

2.3 Data extraction and management

We developed a data extraction form informed by an existing systematic review protocol on language-related eligibility criteria (24). We tested it on a random sample of studies (n=10), refined and applied it to the entire dataset. Data was extracted on study characteristics such as trial location and recruitment settings, as well as eligibility criteria, particularly on language ability, consent mechanisms, and broad criteria that are ambiguous and open to interpretation (see supplementary file 3 for data items). Some information related to non-clinical criteria, such as the type of consent required, was often reported outside of the eligibility criteria list, so we sought and extracted this information separately. Data extraction was conducted independently by one reviewer (JDS) using Microsoft Forms, generating a Microsoft Excel spreadsheet with data from the included protocols. This was checked by at least one other reviewer (SP, SD, TI, CC, SF) and reconciled through

consensus. Quality appraisal of the included studies was not conducted as the focus was on eligibility criteria, irrespective of the quality of the RCTs.

2.4 Data synthesis

We synthesised the data following Popay et al.'s guidance for narrative synthesis (25). Firstly, a preliminary synthesis was developed by grouping studies according to the features in their non-clinical eligibility criteria (e.g., whether or not they included a language requirement), followed by tabulation to represent the data visually. This helped identify patterns and relationships within and across studies. A coding frame was inductively developed (JDS) and refined following independent coding (SP, SD) of the eligibility criteria. The framework was then applied to all included protocols to guide the analysis of non-clinical eligibility criteria and classify trials into those that featured narrow language and informed consent criteria, broad criteria that could lead to bias at recruitment stage, language-related accommodations and alternative consent pathways, if present. These categories were not mutually exclusive.

3. Results

Our search yielded a total of 5,353 records and after deduplication we screened 4,672 titles and abstracts for eligibility. Following the full-text screening of 228 studies, we included 70 protocols in our review (26–95).

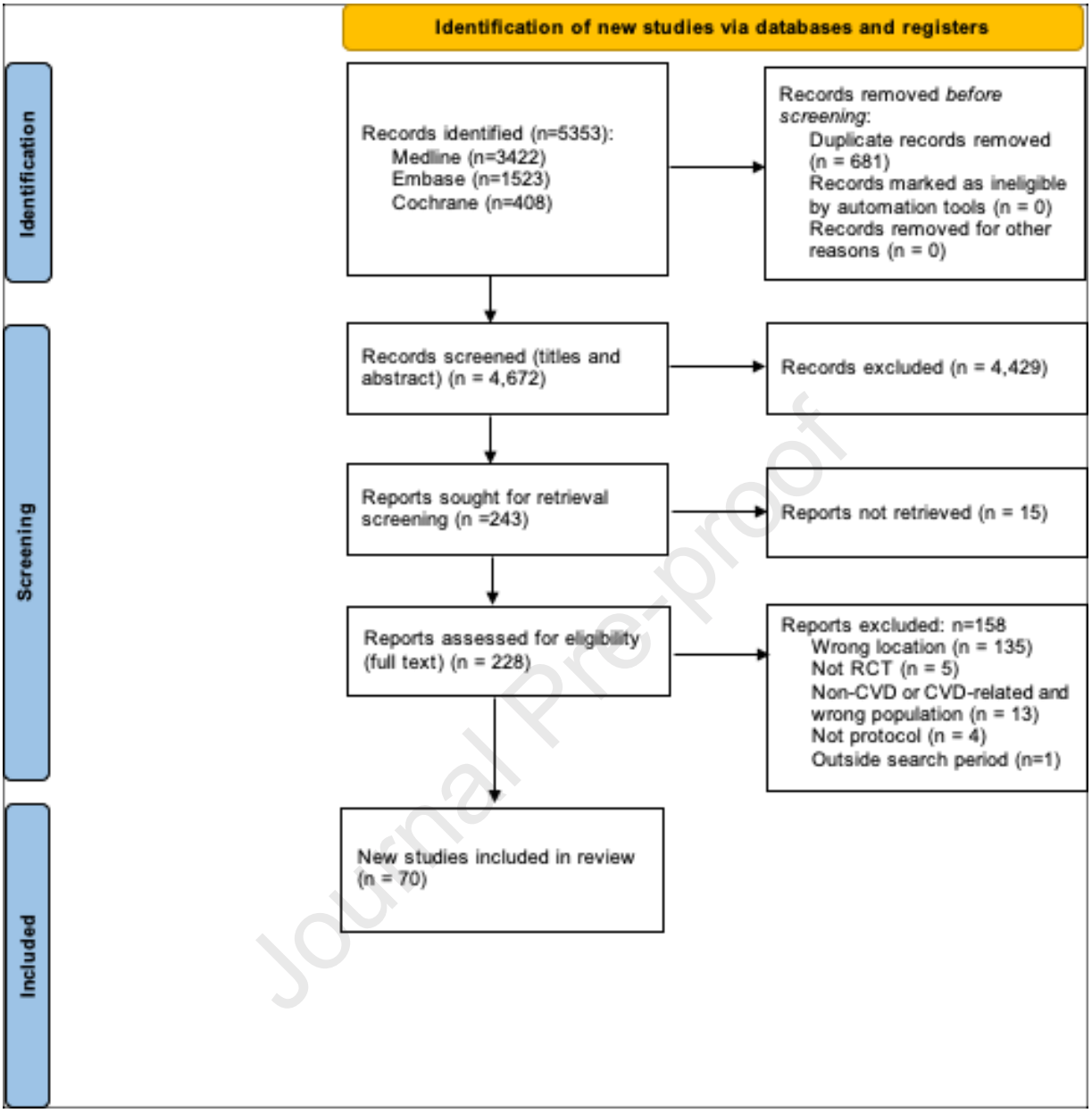

Figure 1: PRISMA 2020 Flow diagram of screening the literature

3.1 Characteristics of the included trial protocols

All 70 studies were UK-based and most (95.7%; 67/70) did not include secondary data collection sites outside the UK (see Table 2). Most of the included trials (65.7%; 46/70) were designed to take place in England, over half (58.6%; 41/70) were described as multi-centre.

Trials recruited more from hospital clinics (34.3%) and General Practice surgeries (21.4%) than community (2.9%) or mixed settings (20%). The intention to collect participants' demographic

data, such as socioeconomic status and ethnicity, was not mentioned in more than half (55.7%; 39/70) the protocols.

Table 2: Characteristics of trials included (n = 70, 100%)

Characteristic	Category	*N*	%
Trial location	UK only	67	95.7
	UK and other countries (1 in France and Germany; 1 in Australia, Canada, Denmark, Netherlands; 1 in 35 unspecified countries from North and South America Europe, Africa, Asia and Australasia)	3	4.3
Country or countries within the UK	England	38	54.3
	Scotland	11	15.7
	Northern Ireland	0	0
	Mixed (including Wales, England and Scotland)	8	11.4
	Not specified	13	18.6
Single or multi-centre	Single centre	22	31.4
	Multi-centre	41	58.6
	Unclear	1	1.4
	Not reported	6	8.6
Outcome*	Directly related to CVD**	37	52.9
	Indirectly related to CVD	33	47.1
Recruitment settings	Hospital clinics	24	34.3
	GP surgeries	15	21.4
	Community	2	2.9
	Other (including databases, unspecified investigator centres and recruitment posters in visible areas)	9	12.8
	Mixed (multiple settings including hospitals, GP practices, community and other)	14	20
	Not reported	6	8.6
Mention of collection of socio-demographic data from participants	Reported with details (including one or more of the following: gender and/or sex, age, ethnicity/race self-reported or not, occupational/employment status, literacy, marital status, preferred language, numeracy, education and living arrangements)	20	28.6

	Other socioeconomic variables but not specified	11	15.7
	Not reported	39	55.7

* RCTs where the primary outcome was directly related to CVD (e.g., coronary heart disease, high blood pressure and heart failure) or indirectly related to CVD (e.g., RCTs addressing diabetes and chronic kidney disease or where the trial population comprised patients with a CVD diagnosis or comprising interventions intended to decrease CVD risk through the increase of physical activity)

Abbreviations: UK – United Kingdom; CVD – Cardiovascular disease; GP – General Practice

3.2 Non-clinical eligibility criteria

Non-clinical eligibility criteria (see supplementary file 4) included information such as the age range of potential participants and further requirements related to informed consent, language and broad criteria (see below). The proportions of different criteria featured, alongside examples of how they were phrased, are described in Table 3.

3.2.1 Method of acquiring informed consent

Although the majority of studies (87.1%; 61/70) mentioned consent within the eligibility criteria or elsewhere in the protocol, a small number did not (12.9%;9/70); of those that mentioned consent, more than two-thirds (68.9%; 42/61) featured a requirement to provide written consent, which might disproportionately exclude EM groups' participation. About a third (31.1%; 19/61) did not describe how participants would be consented. A few studies (9.8%; 6/61) reported an alternative consent pathway, but on a closer look these were not aspects that could aid EM participation. For instance, in two studies where verbal consent was mentioned in relation to the RCT, it was intended as a temporary measure in emergency situations to help initiate treatment/care, still relying on a subsequent written consent for trial participation (34, 61). One of these studies (61) provided a rationale for this centred on previous studies in acute conditions suggesting that oral information is much better received, processed and recalled by patients than the written form. Other instances where verbal consent was mentioned was in relation to qualitative interviews (68) and medical procedures such as blood tests (67) rather than for trial participation. Online consent was mentioned in two studies (67, 69). Only one study mentioned a truly alternative consent pathway by allowing participants who cannot sign and date the document to mark the document along with a witness statement and signature from a carer or equivalent. However, this was intended to cater to an elderly population (participants had to be $\geq$ 75 years of age to participate) and there was no mention of this measure being used for other underserved groups, such as EM participants.

3.2.2 Language requirement

About one in five (22.9%; 16/70) of the protocols featured language criteria such as a requirement to read, speak, be fluent or have a good understanding of English that could be a barrier to the participation of EM groups. None of the trials, including those featuring a language-related exclusion criteria, mentioned how language would be assessed. Additionally, it was very rare for studies (4.3%; 3/70) to mention the employment of translation or interpretation services to account for potential language-related barriers and promote inclusive participation. These studies did not specify the languages available for translation or interpretation provision.

3.2.3 Broad criteria that may lead to bias

The review also found that more than a third of the protocols (37.1%; 26/70) featured 'broad criteria' that may potentially lead to the exclusion of EM groups as they are open to interpretation and recruiter bias (Table 3). Within these 26 protocols, the broad criteria were centred around three main aspects (not mutually exclusive) – a) ability to comply with or complete study processes (n=16); b) ability to give informed consent and/or understand the study information (n=11); and c) the healthcare professional or research team's judgement or opinion on patient's appropriateness for the study based on any other reason (n=9). Sixteen of the 26 protocols had only one of these broad criteria, 9 had two of these broad criteria and 1 had all three broad criteria.

Table 3: Non-clinical eligibility criteria of included studies that can limit or aid participation of Ethnic Minority (EM) groups

Criteria	Reported in the protocol?	*N* (%)
Consent mentioned	Yes	61 (87.1%)
	• Consent mentioned in the eligibility criteria	29
	• Consent mentioned elsewhere in the protocol	32
	No	9 (12.9%)
Of those that mentioned consent (n=61), indication of type of consent	Written consent only (limits EM participation)	42 (68.9%)
	Written plus alternative consent pathway (i.e., verbal or informed assent) or online consent	6 (9.8%)
	Not mentioned	13 (21.3%)
Language ability mentioned (n=70)	Yes	16 (22.9%)
	No	54 (77.1%)
Translation or interpretation services mentioned (n = 70)	Yes	3 (4.3%)
	No	67 (95.7%)

Mention of broad criteria (n=70)	Yes	26 (37.1%)
	No	44 (62.9%)

4. Discussion

The key systematic review findings indicate that there is a high proportion of eligibility criteria that could indirectly exclude EM participants from UK CVD RCTs. In the protocols that mentioned consent, more than two-thirds relied heavily on written consent processes. This is likely to exclude EM participants whose first language is not English, as well as members of the general population with limited English literacy skills (96). This type of exclusion could be more common than we found, given that over a tenth of the protocols did not report on consent processes and a third of those that mentioned consent did not outline the type of consent, i.e., written, verbal or other. Other barriers to inclusive recruitment were eligibility criteria related to participants' English language ability in a fifth of the protocols and broad criteria that are open to interpretation and recruiter bias (e.g., where participants' GP judges them unsuitable for the study (63)) in a third of the protocols. Measures to facilitate the participation of EM groups, such as providing translation services and alternative consent pathways, were minimal or absent.

Informed written consent has been a cornerstone of ethical research for decades, with the emphasis on it likely drawing from multiple quarters, i.e., international guidelines (97), the complex history of informed consent in research over the past century (98) and ethical and legal requirements (99–101), all of which necessitates documentary evidence of consent. However, there are no known requirements for written consent to be the only mode of consent and relying on a single consent type is unlikely to cater to the needs of different groups. Alternative ways of acquiring consent in addition to written consent, such as orally recorded consent, can be particularly suited to increasing participant diversity in research, as recognised in recent good practice NHS guidance (102). This is especially important for the recruitment of EM groups, given that ethnicity coupled with level

of education can be an important predictor of low proficiency in literacy, numeracy and problem solving (103,104). Additionally, factors such as comprehension of informed consent should be considered, given that providing written consent does not guarantee participants' understanding of the risks and benefits of the study.

A recent review on breast cancer trial protocols (18) reported that twice the proportion of studies than in our review (75% versus 37%) featured *broad inclusion criteria statements on investigator opinion on ability to comply with or follow trial protocol*, which could indirectly exclude under-served groups, including those from EM backgrounds. Language-related requirements in eligibility criteria can be similarly exclusionary, with a systematic review of type 2 diabetes telehealth trials (17) reporting that twice the proportion of studies than in our review employed such criteria (50% versus 23%). The number of studies that could potentially exclude participants due to a language requirement in our review is likely higher if we consider that studies where language was not mentioned, there may have been an assumption that most participants would be able to speak English. It has been previously suggested that criteria such as *having sufficient verbal fluency* could be subject to bias (17). Our review identified similar phrases (e.g., *have good understanding of the English language* (67)), where depending on the recruiter's perception, participants could be unnecessarily excluded. A systematic review of physiotherapy RCTs for low back pain (105) reported that an equivalent of 12.5% of randomised participants were excluded because of language proficiency requirements. A similar reality may be the case in cardiovascular trials given the high proportion of written consent criteria found in our review.

Given the above three key eligibility criteria related barriers to the recruitment of EM groups in this review (i.e., the reliance on written consent, language proficiency related requirements and broad eligibility criteria), the absence of remedial measures to recruit EM groups is particularly stark. Such barriers can be minimised if translation services were to be offered, but that was only the case in three (4.3%) (33,66,68) of the seventy studies. Also missing from most protocols (55.7%) was a statement that described whether participant demographic data, including ethnicity and language, will be collected. It is unclear if this is a reporting issue or whether trial teams do not collect these background data. In either case, the diversity of the study population taking part in trials cannot be assessed nor will we know to what extent the findings are generalisable. Lack

of reporting on language has been previously documented in the systematic review on telehealth type 2 diabetes RCTs mentioned above (17), with the authors emphasising the need to disentangle ethnicity and language.

Unlike the US (106), there is no legislation in the UK that mandates the inclusion of EM groups in clinical research (101). However, the NHS Act (107) states that NHS England *must have regard to the need to reduce inequalities between patients* in relation to access to health services and health outcomes. It could be argued that this emphasis on promoting equitable access to services for all members of the UK public requires the provision of language support through professional interpreters and translated materials within the NHS (108), including for research purposes. In one of the included protocols in our review (68), the authors noted that *consistent with routine practice in delivering psychological therapy, NHS translation resources will be employed to assist participants where required.* This may be feasible when the trial intervention is part of routine care, but is likely to include extra costs for those that are outside of routine care. We know little about the feasibility, acceptability, effectiveness, and cost-effectiveness of using routine NHS translation services for trial recruitment purposes, a potential area for future research. There is still a need to develop the evidence base for interventions and research methodologies that have the potential to facilitate inclusivity. Such endeavours should take the researcher, participant and organisational barriers to the recruitment of EM groups into consideration. Meanwhile, it is important for trial teams to adequately budget for translated materials and interpreters and for funders to provide greater support for such costs (see Dawson et al's (9) practical guidance document on recruiting and retaining individuals from EM groups for sample translation/interpretation costings).

Co-producing research with patient and public involvement (PPI) from EM groups can be helpful in designing equitable eligibility criteria. It is important to acknowledge that in the pursuit of equity in relation to one characteristic, such as ethnicity in this review, we run the risk of working in silos and overlooking other intersecting identities (e.g., gender, class, ability, sexuality) (109) that create social disadvantage. In a critical examination of an intervention development study prior to a large-scale RCT, Rai et al. (110) reflect on trial recruitment and note that *usual, normative and taken-for-granted* research practices, such as the ones prevalent in the trials we have reviewed, are *unwittingly exclusionary* and *fail to address material and social disadvantage and discrimination*.

Similarly, eligibility criteria are one aspect of RCTs that can lead to exclusionary practices, with a multitude of other aspects that need to be simultaneously addressed for truly inclusive trial recruitment. This includes, amongst other things, PPI that is not seen as an 'add-on' or 'nice to have' but an essential component of trial delivery and design (111) and sufficient upfront and ring-fenced funding for inclusive measures in RCTs.

This review provides some initial insights on eligibility criteria in CVD RCTs that potentially limits the participation of EM groups, specific to the UK context. The review was conducted as part of an MSc student dissertation, which meant there were time and resource restrictions that imposed certain limitations on the review. Using the PRISMA-Equity (21) checklist from the outset would have helped the review, but using it retrospectively was still useful as it improved the reporting. Similarly, the search strategy would have benefitted from being peer-reviewed using the PRESS checklist (112) to ensure we did not miss any UK CVD RCTs within the time period of our search. It is possible we missed articles by not searching trial registries, by looking broadly at CVD instead of specific CVD conditions, and by using the restrict to focus function when searching. Potential publication bias cannot be ruled out as the search strategy did not include studies published in non-English languages, but such a bias is likely to be minimal considering the review was focused on UK CVD trials.

The inclusion of a PPI component would have helped us gain the insights of those affected by the issue of exclusion of underserved groups (97), but this could not be accommodated within a post-graduate dissertation project. Our review did not set out to investigate the published results of the included trials (where available), including data on ethnicity, which could have strengthened our findings. Also, while we focussed solely on eligibility criteria within trial protocols, future research could examine the entire protocol to investigate the use of existing guidance to promote inclusive research (6,8).

5. Conclusion

Most UK CVD RCTs included in this review featured criteria that can exclude people from EM groups and routinely did not provide accommodations that could lead to a more diverse sample.

Inclusive, equitable and fair eligibility criteria are fundamental to the recruitment of individuals from EM groups to trials. In order to facilitate this, funders should mandate the use of available frameworks and practical guidance (8–10) from the planning and grant application stage of trials, particularly in trials of conditions known to disproportionately affect specific under-served groups. This should also be made a requirement by trial registries and journals when registering trial protocols and reporting study findings. There is an urgent need to develop interventions and research methodologies, with input from members of the public, to optimise inclusivity in RCTs. For truly inclusive trial recruitment, ethnicity has to be considered alongside other intersecting and disadvantaging identities, while equitable eligibility criteria should be situated within an overarching inclusive framework of recruitment to ensure that research benefits all that could possibly benefit from it. These measures have resource implications, such as adequate budgets for interpreters and translated materials at the application stage that need to be met by funders. Beyond pleasing participant groups or funding bodies, the use of inclusive practices has the potential to contribute to more moral, ethical, rigorous and generalisable research.

Word count: 3477

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Most UK cardiovascular disease trial protocols feature criteria that exclude ethnic minority participants: systematic review

What is new?

Key findings

- More than two thirds of UK cardiovascular disease (CVD) trial protocols require 'written' consent; none reported alternative consent pathways.
- One in five require participants to speak, understand or read English; more than a third feature broad (ambiguous) criteria that might lead to recruitment bias.
- Less than one in 20 included measures to aid ethnic minority (EM) participation (e.g., translation services).

What this adds to what is known?

- Despite higher burden of CVD for EM groups in the UK, most CVD trial protocols routinely feature eligibility criteria that exclude EM participants.

What is the implication and what should change now?

- For meaningful strides towards better inclusion, ethnicity has to be considered alongside other intersecting identities that create social disadvantage; equitable trial eligibility criteria have to be placed within a larger inclusive framework of recruitment.