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

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Abstract

Objectives: We systematically reviewed UK cardiovascular disease (CVD) randomized 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 nonclinical eligibility criteria from trial protocols and inductively categorized 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

1. Introduction

Ethnic minority (EM) populations are disproportionately affected by conditions such as diabetes, cardiovascular diseases (CVDs), 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 underrepresented in randomized 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 generalizable to population groups that were not part of the study. Systematic reviews have identified a range of barriers to inclusive recruitment (eg, 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 (eg, recruitment from ethnically diverse areas and from community/religious organizations) [7]. However, there is little robust evidence on the effectiveness of such strategies and interventions. Since the pandemic, there have been

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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 (eg, translation services).

What this adds to what is known?

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

What is the implication and what should change now?

- For meaningful strides toward 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.

frameworks, practical guidance, and recommendations to help researchers recruit participants from diverse ethnic groups in the United Kingdom [8−10].

The onus of ensuring inclusive recruitment across multiple underserved 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 United Kingdom, which have a sizable 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 underserved groups in research [9,16]. For instance, reviews of diabetes [17] and breast cancer RCTs [18] demonstrate that many employ eligibility criteria that contribute toward the exclusion of underserved groups, including EM patients. This lack of diversity in trial populations impairs the generalizability 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 (international prospective register of systematic reviews; 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 (S.D., S.P.), 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 January 1, 2014, and June 1, 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 time frame 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, eg, search strategy). We limited our search to articles published in English and employed inclusion/exclusion criteria to select articles (Table 1).

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 (J.D.S., S.P., C.C., M.K.) in pairs, and

Table 1. Study inclusion and exclusion criteria

Study characteristics	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[a] or indirectly[b] related to CVD	RCTs with no particular CVD link, ie, where the primary outcome is not directly[a] or indirectly[b] related to CVD
Setting	UK based, ie, 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, ie, where data collection did not take place in the UK or where the trials unit was not based in the UK

Abbreviations: UK, United Kingdom; CVD, cardiovascular disease; RCT, randomized controlled trial.
[a] Directly related—eg, studies addressing coronary heart disease, high blood pressure, and heart failure.
[b] Indirectly related—eg, 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.

discrepancies were resolved through discussion. Similarly, full texts were independently screened in pairs (J.D.S., S.P.), with discordances resolved through group discussions with team members (C.C., S.D).

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 were 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 nonclinical 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 (J.D.S.) using Microsoft Forms, generating a Microsoft Excel spreadsheet with data from the included protocols. This was checked by at least one other reviewer (S.P., S.D., T.I., C.C., S.F.) 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 synthesized the data following Popay et al.'s [25] guidance for narrative synthesis. Firstly, a preliminary synthesis was developed by grouping studies according to the features in their nonclinical eligibility criteria (eg, 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 (J.D.S.) and refined following independent coding (S.P., S.D.) of the eligibility criteria. The framework was then applied to all included protocols to guide the analysis of nonclinical eligibility criteria and classify trials into those that featured narrow language and informed consent criteria, broad criteria that could lead to bias at the 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] (Fig 1).

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, and over half (58.6%; 41/70) were described as multicenter.

Trials recruited more from hospital clinics (34.3%) and general practice (GP) 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) of the protocols.

3.2. Nonclinical eligibility criteria

Nonclinical 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

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, and the 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 multicenter	Single center	22	31.4
	Multicenter	41	58.6
	Unclear	1	1.4
	Not reported	6	8.6
Outcome[a]	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 centers, 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 sociodemographic 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

Abbreviations: UK, United Kingdom; CVD, cardiovascular disease; GP, general practice.

[a] RCTs where the primary outcome was directly related to CVD (eg, coronary heart disease, high blood pressure, and heart failure) or indirectly related to CVD (eg, 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).

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 centered 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

Table 3. Nonclinical 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 (ie, 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%)

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 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 centered 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 judgment 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, nine had two of these broad criteria, and 1 had all three broad criteria.

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 10th of the protocols did not report on consent processes and a third of those that mentioned consent did not outline the type of consent, that is, 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 (eg, where participants' GP judges them unsuitable for the study [63]) in a third of the protocols. Measures to facilitate the participation of EM groups,

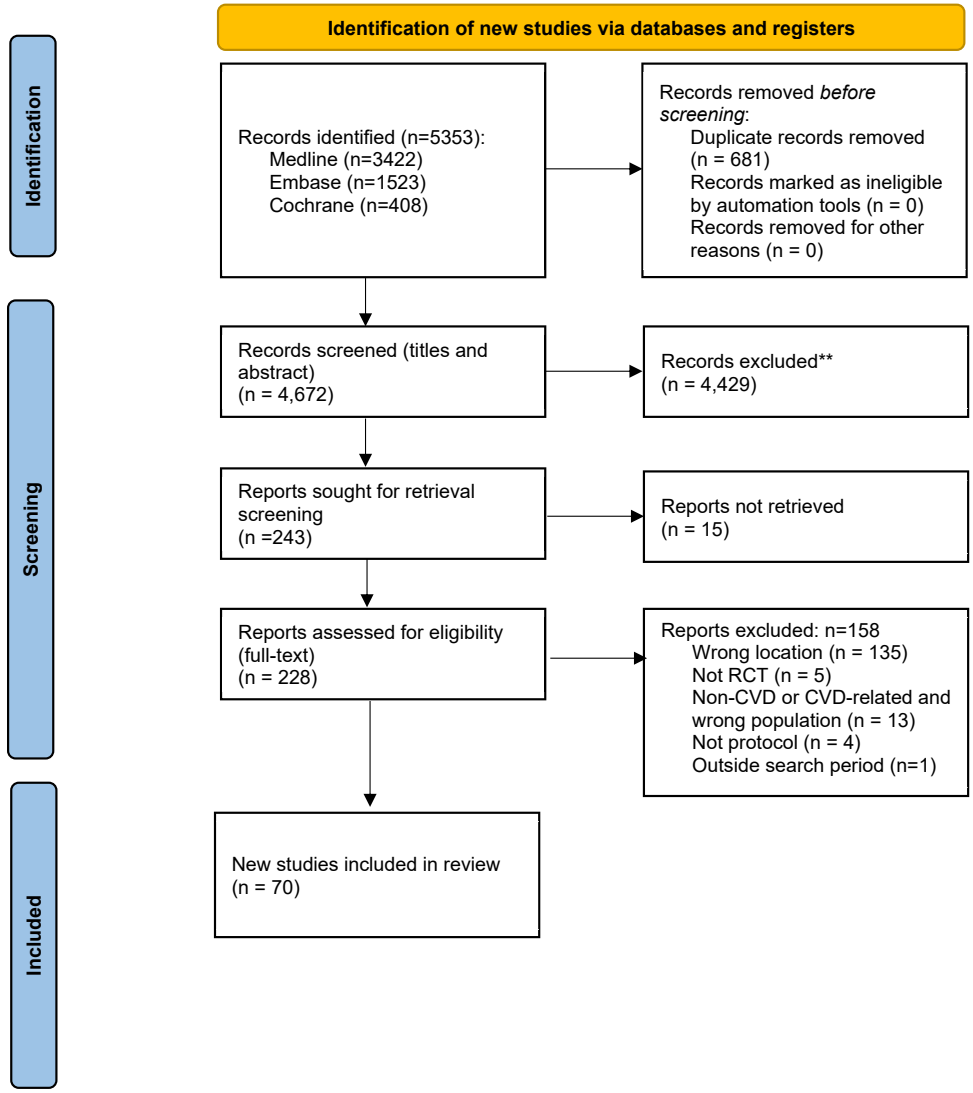

Fig. 1. PRISMA 2020 flow diagram of screening the literature. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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, that is, 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 recognized in recent good practice National Health Service (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% vs. 37%) featured *broad inclusion criteria statements on investigator opinion on ability to comply with or follow trial protocol*, which could indirectly exclude underserved 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% vs. 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 (eg, have a 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 randomized 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 to barriers to the recruitment of EM groups in this review (ie, 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 minimized 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 generalizable. 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 emphasizing the need to disentangle ethnicity and language.

Unlike the United States [106], there is no legislation in the United Kingdom 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 endeavors should take the researcher, participant, and organizational 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).

Coproducing 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 (eg, 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, among 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 limit 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 postgraduate 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 focused 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. 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 underserved 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 optimize 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 generalizable research.

CRediT authorship contribution statement

Jhulia dos Santos: Data curation, Formal analysis, Funding acquisition, Writing − original draft, Writing − review & editing, Investigation. **Shoba Dawson:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing − original draft, Writing − review & editing. **Carmel Conefrey:** Data curation, Formal analysis, Supervision, Writing − review & editing. **Talia Isaacs:** Data curation, Formal analysis, Writing − review & editing. **Mahwar Khanum:** Data curation, Formal analysis, Writing − review & editing. **Saba Faisal:** Data curation, Formal analysis, Writing − review & editing. **Sangeetha Paramasivan:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing − original draft, Writing − review & editing, Investigation.

Data availability

All included articles are publicly available.

Declaration of competing interest

None.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2024.111259.

References

[1] Raleigh V. The health of people from ethnic minority groups in England. London: The King's Fund; 2023. Available at: https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england. Accessed January 31, 2024.
[2] Walker RJ, Williams JS, Egede LE. Influence of race, ethnicity and social determinants of health on diabetes outcomes. Am J Med Sci 2016;351(4):366−73.
[3] Lip GY, Barnett AH, Bradbury A, Cappuccio FP, Gill PS, Hughes E, et al. Ethnicity and cardiovascular disease prevention in the United Kingdom: a practical approach to management. J Hum Hypertens 2007;21(3):183−211.
[4] Chaturvedi N. Ethnic differences in cardiovascular disease. Heart 2003;89:681−6.
[5] Treweek S, Forouhi NG, Narayan KMV, Khunti K. COVID-19 and ethnicity: who will research results apply to? Lancet 2020;395:1955−7.
[6] Bodicoat DH, Routen AC, Willis A, Ekezie W, Gillies C, Lawson C, et al. Promoting inclusion in clinical trials-a rapid review of the literature and recommendations for action. Trials 2021;22(1):880.
[7] Masood Y, Bower P, Waheed MW, Brown G, Waheed W. Synthesis of researcher reported strategies to recruit adults of ethnic minorities to clinical trials in the United Kingdom: a systematic review. Contemp Clin Trials 2019;78:1−10.
[8] Treweek S, Banister K, Bower P, Cotton S, Devane D, Gardner HR, et al. Developing the INCLUDE Ethnicity Framework-a tool to help trialists design trials that better reflect the communities they serve. Trials 2021;22(1):337.
[9] Dawson S, Banister K, Biggs K, Cotton S, Devane D, Gardner H, et al. Trial Forge Guidance 3: randomised trials and how to recruit and retain individuals from ethnic minority groups-practical guidance to support better practice. Trials 2022;23(1):672.
[10] Trial Forge. STRIDE: SupporTing Recruitment and retention Improvements for Diverse Ethnicities. How to decide which ethnic groups your trial needs. Trial Forge; 2023. Available at: https://www.trialforge.org/trial-forge-centre/how-to-decide-which-ethnic-groups-your-trial-needs/. Accessed January 31, 2024.
[11] Catney G, Lloyd CD, Ellis M, Wright R, Finney N, Jivraj S, et al. Ethnic diversification and neighbourhood mixing: a rapid response analysis of the 2021 Census of England and Wales. Geogr J 2023;189:63−77.

[12] ONS. Ethnic Group. England and Wales: Census 2021 [Internet]. 2022. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021. [Accessed 2 March 2023].
[13] Witham MD, Anderson E, Carroll C, Dark PM, Down K, Hall AS, et al. Developing a roadmap to improve trial delivery for underserved groups: results from a UK multi-stakeholder process. Trials 2020;21(1):694.
[14] Cragg WJ, McMahon K, Oughton JB, Sigsworth R, Taylor C, Napp V. Clinical trial recruiters' experiences working with trial eligibility criteria: results of an exploratory, cross-sectional, online survey in the UK. Trials 2021;22(1):736.
[15] Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200−7.
[16] Bonevski B, Randell M, Paul C, Chapman K, Twyman L, Bryant J, et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC Med Res Methodol 2014;14:42.
[17] Isaacs T, Hunt D, Ward D, Rooshenas L, Edwards L. The inclusion of ethnic minority patients and the role of language in telehealth trials for type 2 diabetes: a systematic review. J Med Internet Res 2016;18(9):e256.
[18] Moloney C, Shiely F. Underserved groups remain underserved as eligibility criteria routinely exclude them from breast cancer trials. J Clin Epidemiol 2022;147:132−41.
[19] Striving for diversity in research studies. In: Rubin E, editor. N Engl J Med 2021;385:1429−30.
[20] dos Santos J., Paramasivan S., Dawson S., Conefrey C. Eligibility criteria that preclude ethnic minority groups from participation in UK cardiovascular disease randomised controlled trials: a systematic review. PROSPERO 2022 CRD42022345043. [Internet] Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345043. [Accessed 2 March 2023].
[21] Welch V, Petticrew M, Petkovic J, Moher D, Waters E, White H, et al. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. J Clin Epidemiol 2015;70:68−89.
[22] Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.
[23] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
[24] Isaacs T., Vaughan A., Shiely F., Finucane E., Gillies K., Nurr N., et al. Systematic review of the prevalence and assessment of language-related eligibility criteria in patient recruitment to type 2 diabetes and depression trials. PROSPERO CRD 42021267905 [Internet] Available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=267905; 2021. [Accessed 2 March 2023].
[25] Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme 2006: b92. Available at: Version 1. https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSynthesisguidanceVersion1-April2006.pdf. Accessed January 31, 2024.
[26] Baos S, Underwood W, Culliford L, Reeves BC, Rogers CA, Bowles R, et al. Platelet inhibition during ticagrelor monotherapy versus ticagrelor plus aspirin in patients with coronary artery disease (TEMPLATE study): study protocol for a randomised controlled trial. Trials 2017;18(1):529.
[27] Bayley A, de Zoysa N, Cook DG, Whincup PH, Stahl D, Twist K, et al. Comparing the effectiveness of an enhanced MOtiVational intErviewing InTervention (MOVE IT) with usual care for reducing cardiovascular risk in high risk subjects: study protocol for a randomised controlled trial. Trials 2015;16:112.
[28] Billany RE, Vadaszy N, Bishop NC, Wilkinson TJ, Adenwalla SF, Robinson KA, et al. A pilot randomised controlled trial of a structured, home-based exercise programme on cardiovascular structure and function in kidney transplant recipients: the ECSERT study design and methods. BMJ Open 2021;11(10):e046945.
[29] Cacciottolo PJ, Kostapanos MS, Sancho EH, Pavey H, Kaloyirou F, Vamvaka E, et al. Investigating the lowest threshold of vascular benefits from LDL cholesterol lowering with a PCSK9 mAb inhibitor (Alirocumab) in patients with stable cardiovascular disease (INTENSITY-HIGH): protocol and study rationale for a randomised, open label, parallel group, mechanistic study. BMJ Open 2021;11(4):e037457.
[30] Brown AJM, Lang C, McCrimmon R, Struthers A. Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo-controlled study. BMC Cardiovasc Disord 2017;17(1):229.
[31] Davies AK, McGale N, Humphries SE, Hirani SP, Beaney KE, Bappa DAS, et al. Effectiveness of a self-management intervention with personalised genetic and lifestyle-related risk information on coronary heart disease and diabetes-related risk in type 2 diabetes (CoRDia): study protocol for a randomised controlled trial. Trials 2015;16:547.
[32] Eyre V, Lang CC, Smith K, Jolly K, Davis R, Hayward C, et al. Rehabilitation Enablement in Chronic Heart Failure-a facilitated self-care rehabilitation intervention in patients with heart failure with preserved ejection fraction (REACH-HFpEF) and their caregivers: rationale and protocol for a single-centre pilot randomised controlled trial. BMJ Open 2016;6(10):e012853.
[33] Elguindy M, Stables R, Nicholas Z, Kemp I, Curzen N. Design and rationale of the RIPCORD 2 trial (does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?): a randomized controlled trial to compare routine pressure wire assessment with conventional angiography in the management of patients with coronary artery disease. Circ Cardiovasc Qual Outcomes 2018;11(2):e004191.
[34] Everett CC, Fox KAA, Reynolds C, Fernandez C, Sharples L, Stocken DD, et al. Evaluation of the impact of the GRACE risk score on the management and outcome of patients hospitalised with non-ST elevation acute coronary syndrome in the UK: protocol of the UKGRIS cluster-randomised registry-based trial. BMJ Open 2019 5;9(9):e032165.
[35] Farrow MT, Maher J, Thompson D, Bilzon JLJ. Effect of high-intensity interval training on cardiometabolic component risks in persons with paraplegia: protocol for a randomized controlled trial. Exp Physiol 2021;106(5):1159−65.
[36] Hill NR, Lasserson D, Thompson B, Perera-Salazar R, Wolstenholme J, Bower P, et al. Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) trial-a multi-centre, prospective, randomised, open, blinded end-point, 36-month study of 2,616 patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg once daily in addition to routine care on mortality and cardiovascular outcomes versus routine care alone: study protocol for a randomized controlled trial. Trials 2014;15:160.
[37] Herrett E, Williamson E, Beaumont D, Prowse D, Youssouf N, Brack K, et al. Study protocol for statin web-based investigation of side effects (StatinWISE): a series of randomised controlled N-of-1 trials comparing atorvastatin and placebo in UK primary care. BMJ Open 2017;7(12):e016604.
[38] Herring LY, Dallosso H, Chatterjee S, Bodicoat D, Schreder S, Khunti K, et al. Physical Activity after Cardiac EventS (PACES) - a group education programme with subsequent text-message support designed to increase physical activity in individuals with diagnosed coronary heart disease: study protocol for a randomised controlled trial. Trials 2018;19(1):537.
[39] Gallagher H, Dumbleton J, Maishman T, Whitehead A, Moore MV, Fuat A, et al. Aspirin to target arterial events in chronic kidney

disease (ATTACK): study protocol for a multicentre, prospective, randomised, open-label, blinded endpoint, parallel group trial of low-dose aspirin vs. standard care for the primary prevention of cardiovascular disease in people with chronic kidney disease. Trials 2022;23(1):331.

[40] Htike ZZ, Yates T, Brady EM, Webb D, Gray LJ, Swarbrick D, et al. Rationale and design of the randomised controlled trial to assess the impact of liraglutide on cardiac function and structure in young adults with type 2 diabetes (the LYDIA study). Cardiovasc Diabetol 2016;15(1):102.

[41] Gulsin GS, Brady EM, Swarbrick DJ, Athithan L, Henson J, Baldry E, et al. Rationale, design and study protocol of the randomised controlled trial: diabetes interventional Assessment of Slimming or training tO Lessen Inconspicuous cardiovascular Dysfunction (the DIASTOLIC study). BMJ Open 2019;9(3): e023207.

[42] Hundertmark MJ, Agbaje OF, Coleman R, George JT, Grempler R, Holman RR, et al. Design and rationale of the EMPA-VISION trial: investigating the metabolic effects of empagliflozin in patients with heart failure. ESC Heart Fail 2021;8(4):2580−90.

[43] Gue YX, Kanji R, Wellsted DM, Srinivasan M, Wyatt S, Gorog DA. Rationale and design of "Can Very Low Dose Rivaroxaban (VLDR) in addition to dual antiplatelet therapy improve thrombotic status in acute coronary syndrome (VaLiDate-R)" study : a randomised trial modulating endogenous fibrinolysis in patients with acute coronary syndrome. J Thromb Thrombolysis 2020;49(2):192−8.

[44] Gray AJ, Roobottom C, Smith JE, Goodacre S, Oatey K, O'brien R, et al. The RAPID-CTCA trial (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA) - a multicentre parallel-group randomised trial to compare early computerised tomography coronary angiography versus standard care in patients presenting with suspected or confirmed acute coronary syndrome: study protocol for a randomised controlled trial. Trials 2016;17(1):579.

[45] Joseph JP, Reyes E, Guzman J, O'Doherty J, McConkey H, Arri S, et al. CXCR2 Inhibition - a novel approach to treating CoronAry heart DiseAse (CICADA): study protocol for a randomised controlled trial. Trials 2017;18(1):473.

[46] Khawaja MZ, Wang D, Pocock S, Redwood SR, Thomas MR. The percutaneous coronary intervention prior to transcatheter aortic valve implantation (ACTIVATION) trial: study protocol for a randomized controlled trial. Trials 2014;15:300.

[47] Keene D, Arnold A, Shun-Shin MJ, Howard JP, Sohaib SMA, Moore P, et al. Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for heart failure (HOPE-HF) trial. ESC Heart Fail 2018;5(5):965−76.

[48] Mackenzie IS, Ford I, Walker A, Hawkey C, Begg A, Avery A, et al. Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study. BMJ Open 2016;6(9):e013774.

[49] Lewis GA, Schelbert EB, Naish JH, Bedson E, Dodd S, Eccleson H, et al. Pirfenidone in heart failure with preserved ejection fraction-rationale and design of the PIROUETTE trial. Cardiovasc Drugs Ther 2019;33(4):461−70.

[50] Khan TZ, Pottle A, Pennell DJ, Barbir MS. The impact of lipoprotein apheresis in patients with refractory angina and raised lipoprotein(a): objectives and methods of a randomised controlled trial. Atheroscler Suppl 2015;18:103−8.

[51] Klonizakis M, Crank H, Gumber A, Brose LS. Smokers making a quit attempt using e-cigarettes with or without nicotine or prescription nicotine replacement therapy: impact on cardiovascular function (ISME-NRT) - a study protocol. BMC Publ Health 2017;17: 293.

[52] Mahmoudi M, Nicholas Z, Nuttall J, Bresser M, Maishman T, Berry C, et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: rationale and design of the FORECAST trial. Cardiovasc Revasc Med 2020;21(7):890−6.

[53] Lees JS, Mangion K, Rutherford E, Witham MD, Woodward R, Roditi G, et al. Vitamin K for kidney transplant organ recipients: investigating vessel stiffness (ViKTORIES): study rationale and protocol of a randomised controlled trial. Open Heart 2020;7(2):e001070.

[54] Munro J, Adams R, Campbell A, Campbell S, Donaldson C, Godwin J, et al. CRIB–the use of cardiac rehabilitation services to aid the recovery of patients with bowel cancer: a pilot randomised controlled trial (RCT) with embedded feasibility study. BMJ Open 2014;4(2):e004684.

[55] Kunadian V, Chan D, Ali H, Wilkinson N, Howe N, McColl E, et al. Antiplatelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease: protocol of a randomised controlled proof-of-concept trial (APPLE COPD-ICON 2). BMJ Open 2018;8(5):e020713.

[56] Perera D, Clayton T, Petrie MC, Greenwood JP, O'Kane PD, Evans R, et al. Percutaneous Revascularization for Ischemic ventricular Dysfunction: rationale and design of the REVIVED-BCIS2 trial: percutaneous coronary intervention for Ischemic Cardiomyopathy. JACC Heart Fail 2018;6(6):517−26.

[57] Ng KP, Jain P, Heer G, Redman V, Chagoury OL, Dowswell G, et al. Spironolactone to prevent cardiovascular events in early-stage chronic kidney disease (STOP-CKD): study protocol for a randomized controlled pilot trial. Trials 2014;15:158.

[58] Murphy D, Ster IC, Kaski JC, Anderson L, Banerjee D. The LIFT trial: study protocol for a double-blind, randomised, placebo-controlled trial of K^+-binder Lokelma for maximisation of RAAS inhibition in CKD patients with heart failure. BMC Nephrol 2021;22(1):254.

[59] Petrie JR, Chaturvedi N, Ford I, Hramiak I, Hughes AD, Jenkins AJ, et al. Metformin in adults with type 1 diabetes: design and methods of REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL): an international multicentre trial. Diabetes Obes Metab 2017;19:509−16.

[60] Osborn D, Burton A, Walters K, Nazareth I, Heinkel S, Atkins L, et al. Evaluating the clinical and cost effectiveness of a behaviour change intervention for lowering cardiovascular disease risk for people with severe mental illnesses in primary care (PRIMROSE study): study protocol for a cluster randomised controlled trial. Trials 2016;17:80.

[61] Nazir SA, Khan JN, Mahmoud IZ, Greenwood JP, Blackman DJ, Kunadian V, et al. The REFLO-STEMI trial comparing intracoronary adenosine, sodium nitroprusside and standard therapy for the attenuation of infarct size and microvascular obstruction during primary percutaneous coronary intervention: study protocol for a randomised controlled trial. Trials 2014;15:371.

[62] Paton MF, Gierula J, Jamil HA, Lowry JE, Byrom R, Gillott RG, et al. Optimising pacemaker therapy and medical therapy in pacemaker patients for heart failure: protocol for the OPT-PACE randomised controlled trial. BMJ Open 2019;9(7):e028613.

[63] Piernas C, Tsiountsioura M, Astbury NM, Madigan C, Aveyard P, Jebb SA. Primary Care SHOPping intervention for cardiovascular disease prevention (PC-SHOP): protocol for a randomised controlled trial to reduce saturated fat intake. BMJ Open 2019; 9(4):e027035.

[64] Okorie M, Ali K, Bremner S, Beckett N, Jackson S, Quirk R, et al. Treatment of white coat HYpertension in the very elderly trial (HYVET 2)-Feasibility of a randomized controlled trial (study protocol). Artery Res 2019;25(1−2):19−25.

[65] Rathod KS, Jones DA, Van-Eijl TJA, Tsang H, Warren H, Hamshere SM, et al. Randomised, double-blind, placebo-controlled study investigating the effects of inorganic nitrate on vascular function, platelet reactivity and restenosis in stable angina: protocol of the NITRATE-OCT study. BMJ Open 2016;6(12):e012728.

[66] Shantsila E, Haynes R, Calvert M, Fisher J, Kirchhof P, Gill PS, et al. IMproved exercise tolerance in patients with PReserved

Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation rationale and design of the IMPRESS-AF randomised controlled trial. BMJ Open 2016;6(10):e012241.

[67] Silarova B, Lucas J, Butterworth AS, Di Angelantonio E, Girling C, Lawrence K, et al. Information and Risk Modification Trial (INFORM): design of a randomised controlled trial of communicating different types of information about coronary heart disease risk, alongside lifestyle advice, to achieve change in health-related behaviour. BMC Public Health 2015;15:868.

[68] Richards SH, Dickens C, Anderson R, Richards DA, Taylor RS, Ukoumunne OC, et al. Assessing the effectiveness of enhanced psychological care for patients with depressive symptoms attending cardiac rehabilitation compared with treatment as usual (CADENCE): study protocol for a pilot cluster randomised controlled trial. Trials 2016;17:59.

[69] Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, et al. Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment in Morning versus Evening (TIME) study. BMJ Open 2016;6(2):e010313.

[70] Rogers A, Flynn A, Mackenzie IS, McConnachie L, Barr R, Flynn RWV, et al. Evaluating Diuretics in Normal Care (EVIDENCE): protocol of a cluster randomised controlled equivalence trial of prescribing policy to compare the effectiveness of thiazide-type diuretics in hypertension. Trials 2021;22(1):814.

[71] Singh JSS, Fathi A, Vickneson K, Mordi I, Mohan M, Houston JG, et al. Research into the effect of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design. Cardiovasc Diabetol 2016;15:97.

[72] Stradling C, Thomas GN, Hemming K, Frost G, Garcia-Perez I, Redwood S, et al. Randomised controlled pilot study to assess the feasibility of a Mediterranean Portfolio dietary intervention for cardiovascular risk reduction in HIV dyslipidaemia: a study protocol. BMJ Open 2016;6(2):e010821.

[73] Singh S, Beadle R, Cameron D, Rudd A, Bruce M, Jagpal B, et al. Randomized double-blind placebo-controlled trial of perhexiline in heart failure with preserved ejection fraction syndrome. Future Cardiol 2014;10(6):693−8.

[74] Taylor RS, Hayward C, Eyre V, Austin J, Davies R, Doherty P, et al. Clinical effectiveness and cost-effectiveness of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) facilitated self-care rehabilitation intervention in heart failure patients and caregivers: rationale and protocol for a multicentre randomised controlled trial. BMJ Open 2015;5(12):e009994.

[75] Thirunavukarasu S, Brown LAE, Chowdhary A, Jex N, Swoboda P, Greenwood JP, et al. Rationale and design of the randomised controlled cross-over trial: cardiovascular effects of empaglifozin in diabetes mellitus. Diab Vasc Dis Res 2021;18(3):14791641211021585.

[76] Thomas CL, Man MS, O'Cathain A, Hollinghurst S, Large S, Edwards L, et al. Effectiveness and cost-effectiveness of a telehealth intervention to support the management of long-term conditions: study protocol for two linked randomized controlled trials. Trials 2014;15:36.

[77] Ford TJ, Corcoran D, Oldroyd KG, McEntegart M, Rocchiccioli P, Watkins S, et al. Rationale and design of the British heart Foundation (BHF) coronary microvascular angina (CorMicA) stratified medicine clinical trial. Am Heart J 2018;201:86−94.

[78] Woodward A, Broom D, Dalton C, Metwally M, Klonizakis M. Supervised exercise training and increased physical activity to reduce cardiovascular disease risk in women with polycystic ovary syndrome: study protocol for a randomized controlled feasibility trial. Trials 2020;21(1):101.

[79] Tudor K, Brooks J, Howick J, Fox R, Aveyard P. Tackling statin intolerance with n-of-1 trials (TaSINI) in primary care: protocol for a feasibility randomised trial to increase statin adherence. BMJ Open 2020;10(2):e033070.

[80] Whinnett ZI, Sohaib SM, Jones S, Kyriacou A, March K, Coady E, et al. British randomised controlled trial of AV and VV optimization ("BRAVO") study: rationale, design, and endpoints. BMC Cardiovasc Disord 2014;14:42.

[81] Zhao TX, Kostapanos M, Griffiths C, Arbon EL, Hubsch A, Kaloyirou F, et al. Low-dose interleukin-2 in patients with stable ischaemic heart disease and acute coronary syndromes (LILACS): protocol and study rationale for a randomised, double-blind, placebo-controlled, phase I/II clinical trial. BMJ Open 2018;8(9):e022452.

[82] Withers TM, Croft L, Goosey-Tolfrey VL, Dunstan DW, Leicht CA, Bailey DP. Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol. BMJ Open 2018;8(6):e021936.

[83] Chung R, Maulik A, Hamarneh A, Hochhauser D, Hausenloy DJ, Walker JM, et al. Effect of remote ischaemic conditioning in Oncology patients Undergoing Chemotherapy: rationale and design of the ERIC-ONC study–A single-center, blinded, randomized controlled trial. Clin Cardiol 2016;39(2):72−82.

[84] Wells A, McNicol K, Reeves D, Salmon P, Davies L, Heagerty A, et al. Improving the effectiveness of psychological interventions for depression and anxiety in the cardiac rehabilitation pathway using group-based metacognitive therapy (PATHWAY Group MCT): study protocol for a randomised controlled trial. Trials 2018;19(1):215.

[85] Morgan JM, Dimitrov BD, Gill J, Kitt S, Ng GA, McComb JM, et al. Rationale and study design of the REM-HF study: remote management of heart failure using implanted devices and formalized follow-up procedures. Eur J Heart Fail 2014;16(9):1039−45.

[86] Mordi NA, Mordi IR, Singh JS, Baig F, Choy AM, McCrimmon RJ, et al. Renal and Cardiovascular Effects of sodium-glucose cotransporter 2 (SGLT2) inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure (RECEDE-CHF): protocol for a randomised controlled double-blind cross-over trial. BMJ Open 2017;7(10):e018097.

[87] Mohan M, McSwiggan S, Baig F, Rutherford L, Lang CC. Metformin and its effects on myocardial dimension and left ventricular hypertrophy in normotensive patients with coronary heart disease (the MET-REMODEL study): rationale and design of the MET-REMODEL study. Cardiovasc Ther 2015;33(1):1−8.

[88] Rahimi K, Nazarzadeh M, Pinho-Gomes AC, Woodward M, Salimi-Khorshidi G, Ohkuma T, et al. Home monitoring with technology-supported management in chronic heart failure: a randomised trial. Heart 2020;106:1573−8.

[89] Holman RR, Bethel MA, George J, Sourij H, Doran Z, Keenan J, et al. Rationale and design of the EXenatide study of cardiovascular event lowering (EXSCEL) trial. Am Heart J 2016;174:103−10.

[90] McGregor G, Nichols S, Hamborg T, Bryning L, Tudor-Edwards R, Markland D, et al. High-intensity interval training versus moderate-intensity steady-state training in UK cardiac rehabilitation programmes (HIIT or MISS UK): study protocol for a multicentre randomised controlled trial and economic evaluation. BMJ Open 2016;6(11):e012843.

[91] Sidik NP, McEntegart M, Roditi G, Ford TJ, McDermott M, Morrow A, et al. Rationale and design of the British heart Foundation (BHF) coronary microvascular function and CT coronary Angiogram (CorCTCA) study. Am Heart J 2020;221:48−59.

[92] Wells A, McNicol K, Reeves D, Salmon P, Davies L, Heagerty A, et al. Metacognitive therapy home-based self-help for cardiac rehabilitation patients experiencing anxiety and depressive symptoms: study protocol for a feasibility randomised controlled trial (PATHWAY Home-MCT). Trials 2018;19(1):444.

[93] Peacock OJ, Western MJ, Batterham AM, Stathi A, Standage M, Tapp A, et al. Multidimensional individualised Physical ACTivity (Mi-PACT)–a technology-enabled intervention to promote physical

activity in primary care: study protocol for a randomised controlled trial. Trials 2015;16:381.

[94] Moreau LA, Holloway I, Fylan B, Hartley S, Cundill B, Fergusson A, et al. Using routine healthcare data to evaluate the impact of the Medicines at Transitions Intervention (MaTI) on clinical outcomes of patients hospitalised with heart failure: protocol for the Improving the Safety and Continuity of Medicines management at Transitions of care (ISCOMAT) cluster randomised controlled trial with embedded process evaluation, health economics evaluation and internal pilot. BMJ Open 2022;12(4):e054274.

[95] Sinclair J, Shadwell G, Dillon S, Allan R, Butters B, Bottoms L. Effects of montmorency tart cherry and blueberry juice on cardiometabolic outcomes in healthy individuals: protocol for a 3-arm placebo randomized controlled trial. Int J Environ Res Public Health 2021;18(18):9759.

[96] Willis A, Isaacs T, Khunti K. Improving diversity in research and trial participation: the challenges of language. Lancet Public Health 2021;6(7):e445−6.

[97] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191−4.

[98] Bazzano LA, Durant J, Brantley PR. A modern history of informed consent and the role of key information. Ochsner J Spring 2021; 21(1):81−5.

[99] Beskow LM, Friedman JY, Hardy NC, Lin L, Weinfurt KP. Simplifying informed consent for biorepositories: stakeholder perspectives. Genet Med 2010;12:567−72.

[100] Burman W, Breese P, Weis S, Bock N, Bernardo J, Vernon A, et al. The effects of local review on informed consent documents from a multicenter clinical trials consortium. Control Clin Trials 2003;24:245−55.

[101] Isaacs T, Murdoch J, Demjén Z, Stevenson F. Examining the language demands of informed consent documents in patient recruitment to cancer trials using tools from corpus and computational linguistics. Health (London) 2022;26(4):431−56.

[102] NHS England. Increasing diversity in research participation: A good practice guide for engaging with underrepresented groups [Internet]; 2023. Available at https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2023/02/B1905-increasing-diversity-in-research-participation.pdf. Accessed March 7, 2023.

[103] Wheater R, Burge B, Sewell J, Sizmur J, Worth J, Williams J. The International Survey of Adult Skills 2012: Adult literacy, numeracy and problem solving skills in Northern Ireland. Belfast: Department for Employment and Learning; 2013.

[104] Wheater R, Burge B, Sewell J, Sizmur J, Worth J, Williams J. The international survey of adult skills 2012: adult literacy, numeracy and problem solving skills in England. London: Department for Business, Innovation and Skills; 2013.

[105] Chen Q, Sánchez Medina CM, Maher CG, Ferreira GE, Olivares Hernández AE, Valderrama Godínez V, et al. Almost one in five physiotherapy trials excluded people due to lack of language proficiency: a meta-epidemiological study. J Clin Epidemiol 2022;152: 13−22.

[106] National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research 2001.

[107] National Health Service Act. c41 2006. https://www.legislation.gov.uk/ukpga/2006/41/contents. Accessed January 31, 2024.

[108] NHS England. Guidance Note: Commissioning Interpreting and Translation Services in Primary Care [Internet]. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/09/guidance-for-commissioners-interpreting-and-translation-services-in-primary-care.pdf. Accessed March 7, 2023.

[109] Mbuagbaw L, Aves T, Shea B, Jull J, Welch V, Taljaard M, et al. Considerations and guidance in designing equity-relevant clinical trials. Int J Equity Health 2017;16(1):93.

[110] Rai T, Hinton L, McManus RJ, Pope C. What would it take to meaningfully attend to ethnicity and race in health research? Learning from a trial intervention development study. Sociol Health Illn 2022;44:57−72.

[111] National Institute of Health and Care Research (NIHR). "There's always time to work with patients" - patient and public involvement during the rapid development of a Long Covid treatment trial. Available at: https://www.nihr.ac.uk/documents/case-studies/theres-always-time-to-work-with-patients-patient-and-public-involvement-during-the-rapid-development-of-a-long-covid-treatment-trial/31819. Accessed March 7, 2023.

[112] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40−6.