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Strategies to enhance the racial and ethnic diversity of breast cancer clinical drug trials

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Abstract

(i) Breast cancer (BC) is the most diagnosed cancer worldwide, with around 2.3 million estimated new cases in 2022. BC disproportionately affects ethnic minorities, with young Black women in particular experiencing poorer health outcomes, most notably from the aggressive and poor prognosis sub-type known as triple-negative breast cancer (TNBC). (ii) Despite these poorer health outcomes, BC clinical trials often show poor ethnic diversity. (iii) We used a rapid review approach to screen outputs from the Medline, Embase, and Scopus databases, based on key search terms and clear inclusion/exclusion criteria, to identify strategies to enhance the racial and ethnic diversity of breast cancer trial populations. (iv) Our review indicates that multiple strategies must be used simultaneously to respond to the challenge of racial and ethnic minority (REM) recruitment. The most impactful strategies include engaging with minority communities and making accommodations, for example, using staff trained in cultural competency and trusted community members to aid in the design and delivery of clinical trial recruitment models in the community. Eight key strategic themes arose and were used to create a new Racial and Minority Growth (RMG) model. The model brings together recommended strategies from the literature, highlighting actions to be first tested and then integrated alongside current initiatives to enhance clinical trial diversity. (v) Future studies should trial RMG-inspired strategies and collect quantitative data to assess effectiveness and sustainability. Drug regulators should continue to push for trial diversity and transparency, guided by the 2024 United States (US) Food and Drug Administration (FDA) draft mandate to increase underrepresented racial and ethnic populations in clinical trials. In turn, healthcare professionals have a duty to recognise and value diversity, and ensure fair treatment of all patients, in line with the United Nations Sustainable Development Goals on 'Good Health and Wellbeing' and 'Reduced Inequalities'.

Keywords: *breast cancer, clinical trials, racial and ethnic minority (REM), underrepresentation, poor health outcomes*

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1. Introduction

In 2022, there were around 2.3 million women diagnosed with breast cancer (BC) and 670,000 deaths worldwide, making breast cancer the most diagnosed cancer type [1]. However, these statistics mask huge disease complexity and breast cancer sub-types, each with different underlying biology, management and treatment options, and disease outcomes [2]. It is also well understood that breast cancer disproportionately affects racial and ethnic minority (REM) groups, particularly younger Black women who often experience poorer overall health outcomes [3–10].

In the Western world, the 'gold standard' route by which new efficacious therapies are tested and subsequently approved in (cancer) patients is through randomised double-blinded clinical trials [11, 12]. Clinical trials (CTs) of this kind are carried out on enrolled patients, ranging from early-phase studies on small patient numbers (<100) to late-phase international trials on several thousands of patients [12]. Drug registration trial data should be generalisable to the wider global patient population; but very often, this is not the case, especially for common diseases affecting millions of patients such as breast cancer. Despite disproportionate adverse health outcomes for REM patients [3–10], BC clinical trials historically show poor ethnic diversity amongst participants [4, 13–23]. The ensuing impacts of poor trial diversity include poor generalisability of BC trial results, pharmacogenomic (PGx) consequences (relating to drug metabolism), and socio-economic impacts [4, 14, 16, 23]. These adverse impacts have recently led to regulatory authorities such as the US FDA mandating an increase in 'underrepresented racial and ethnic populations' in clinical trials [24].

The magnitude of the underrepresentation of REM patients in clinical trials within developed countries such as the UK is unknown, as historically, there has been a lack of obligation to record and publish minority participation data [25, 26]. However, a University College London case study found that minority groups were 30% less likely to participate in trials than their White counterparts [20].

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In the US, where over 13% of the population are Black Americans, only 2–9% are estimated to participate in clinical trials overall, where BC trials led to the approval of four new treatments in 2020 [13]. A review also identified several major US BC trials, where only 2.1% of participants were Black, 3.7% Hispanic, and 15.5% Asian, much lower than the wider minority populations [15].

This lack of diversity amongst trial participants is problematic, as REM patients are disproportionately affected by BC, for example, presenting with less favourable tumour characteristics [3, 4, 6, 9, 10]. In the US, for example, non-Hispanic Black women are more likely to die from BC [5, 13] and often are more likely to be diagnosed with more aggressive sub-types, such as triple-negative breast cancer (TNBC) [4, 6, 7]. TNBC is an aggressive and poor prognosis disease sub-type, accounting for around 15% of overall breast cancer incidence, but it is more prevalent in younger Black women and lacks efficacious targeted therapies [6–10, 27].

In contrast to popular perception, REM groups are not 'hard to reach' and are often excluded by trial design [28–30]. For example, trials may also use inclusion/exclusion criteria with the intention of ensuring a 'healthy' patient cohort. However, this may unintentionally exclude minority groups, who are often more likely to have comorbidities such as HIV and kidney disease [20, 25, 26, 29]. Further factors commonly cited in the literature as 'barriers to access' include institutional factors and 'medical mistrust', both of which are inherently intertwined [31–35]. 'Medical mistrust' is a complex concept with a long history, and it is recognised as a potential factor contributing to minority groups being less willing to engage in medical research or interventions due to historical medical deception and mistreatment [32]. We note the significance of key historical events such as the Tuskegee Syphilis Study (1932–1972), where the US Public Health Service bypassed key ethical standards by experimenting on African American males, leading to 128 patient deaths [36–38] (see Supplementary Information for more detail).

Poor trial diversity and its impacts are connected to the barriers shown in **Figure 1**. We note here existing frameworks for promoting racial and ethnic diversity within trials such as the NIHR INCLUDE Ethnicity Framework (www.trialforge.org/trial-diversity/include/) which offers a more general approach to trial design and inclusion compared to our study specifically focused on breast cancer clinical trials. The economic impact of poor trial diversity needs to be considered, with a review finding BC treatment costs to be 95% and 109% higher in stages 3 and 4, compared to stage 1 [39]. Economic impacts need to be considered in relation to data showing that REM women are likely to be diagnosed at a later stage than White women [8]. In turn, improved trial diversity may reduce the cost of wider health inequities that are reported to cost 1.4% of the European Union's gross domestic product [40]. In the US, poor trial diversity is reported to skew American medicine, costing the economy billions of dollars due to poor health and early deaths [23]. Improvements in trial diversity at all trial stages may help to alleviate these economic impacts and allow REM patients to experience the benefits of improved care and monitoring whilst participating in trials of the most advanced targeted medicines. This could also produce more REM trial data, further improving patient outcomes and hopefully reducing current disparities in oncology and wider fields [11, 29].

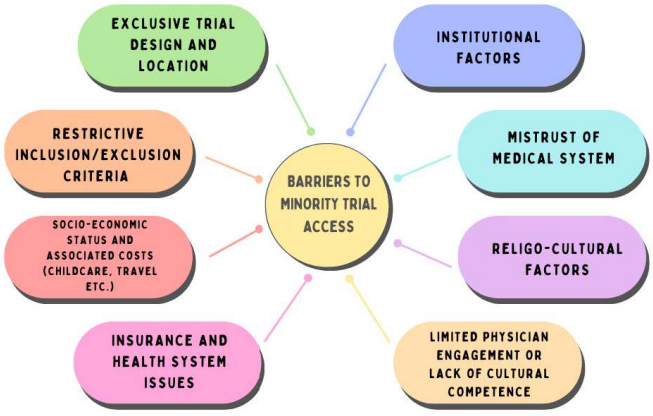

Figure 1 • Diagram showing the interconnected barriers to minority trial access, often cited in the literature [31–35]. Inspired by the Socio-Ecological model and the Hamel et al. multilevel model [31, 41].

Pharmacogenomics considers how individual patient genetics can influence drug response [42]. REM patients are reported to frequently have mutations in key drug metabolism genes, compared to their non-Hispanic White population counterparts that are often well represented in trial populations [4, 42]. This is especially important for immunological drugs which depend on a host–tumour interaction mediated by genetics and are often influenced by race. REM groups may metabolise drugs differently, which could manifest in additional toxicities (due to higher-than-average blood drug levels) or sub-optimal therapy (due to lower-than-average blood drug levels) [14]. African genomes, for example, are known to have the most frequent genetic variations in the DYPD gene, leading to polymorphisms in the drug-metabolising DPYD enzyme associated with adverse toxicities following fluoropyrimidine-based chemotherapy [42]. These PGx polymorphism effects could reduce a patient's quality of life, especially if they are already experiencing effects or complications from the cancer itself. If trial populations are not diverse, clinicians and healthcare professionals could be unaware of the complex pharmacogenetics at play during drug therapy [14].

Breast cancer is a major cause of cancer death globally [1]. Whilst the literature recognises the multifaceted challenges in diversifying cancer trial populations, reports often reaffirm barriers to trial access [31–33], and published strategy models tend to address cancer only in general terms [43–47]. Underrepresentation of REM patients in clinical trials has been identified by many regulatory organisations, including the FDA and the Medicines and Healthcare products Regulatory Agency (MHRA), and has fuelled a recent project by the National Health Service (NHS) Race and Health Observatory [24, 48, 49]. Mandates date back to 1993 (National Institute of Health Revitalisation Act), and initiatives are still being launched to the present day [50]. To date, it is unclear whether these initiatives have been successful in creating substantial improvements in trial population diversity, with <2% of National Cancer Institute (NCI) trials focusing on minority patients as a primary emphasis [51]. In response, this rapid review aims to produce a set of evidence-based strategies (aided by a newly designed model) to improve the racial and ethnic diversity of breast cancer clinical trials. We hope that this review could underpin future trial

principles to push for safer drugs across diverse populations to build patient and provider confidence. Our motivation is to take a global perspective on these important issues to help diminish the barriers to diverse trial access as outlined in **Figure 1**. We hope that our conclusions can be extrapolated to help trial diversification across wider cancer sites and other therapeutic areas, as well as inspire studies involving other underrepresented groups.

2. Materials and methods

The research used a rapid review approach, based on searching the Medline (OVID), Embase (OVID) and Scopus (Elsevier) databases, using key search terms {'clinical trial' AND 'racial and ethnic minority' AND 'breast cancer' AND 'patient enrolment'}, plus close derivatives of these terms. A wide range of keywords surrounding racial and ethnic groups were used (mapped to subject headings where appropriate) to capture the wide literature terminology around these groups. The NHS Learning and Knowledge Service search blocks were used as a starting point, with keywords such as 'Japanese' or 'Korean' added to address groups that were missed [52]. To further enhance the search, index words from relevant papers were added. In the context of the review, REM refers to all groups apart from non-Hispanic White populations that are most often well represented in clinical trials [17]. Application of clear inclusion criteria (English language; peer-reviewed) and exclusion criteria (conference papers/abstracts; indirect relevance such as gender diversity; only identifying barriers, not diversification strategies) were applied to further structure the search. Indirectly relevant papers were discarded or used as background and/or grey literature. There was no date (up to November 2023) or geographical restrictions on the papers considered. The aim was to produce a high-quality, iterative search to reduce publication bias; therefore, the search was kept relatively wide so results could be manually sifted to increase precision. Inspired by the Population, Intervention, Comparison, and Outcome (PICO) framework, keywords were organised by concept, using 'OR' to separate synonyms of each keyword [53].

Following the optimised search as described above, titles and abstracts were screened for relevance according to inclusion/exclusion criteria, with the process depicted by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram in **Figure 2** [54]. Critical appraisal of paper quality was undertaken through a combination of reviewer expertise and CASP tool checklists [55].

3. Results

Seventeen papers were selected for detailed analysis following sifting [56–72]. Eight selected papers implemented specific strategies to enhance trial diversity and observed their effects on minority recruitment [60, 63, 64, 66–69, 72], three papers collected feedback from minority groups [62, 65, 71], and two papers carried out both [57, 61]. Four papers discussed strategies in response to known barriers [56, 58, 59, 70]. All papers that successfully recruited REM populations used four or more strategies, creating significant increases in REM trial participation ranging from 62 to 373% [58, 60, 64, 66–69]. **Table 1** summarises the final papers and their findings.

Eight key themes arose across the selected papers (outlined below) and were used to compile a new Racial Minority Growth (RMG) model, shown in **Figure 3**. The model constructed here aims to portray the process of addressing the challenge of REM recruitment with multiple strategies, using puzzle pieces fitting together to create a bigger strategic picture.

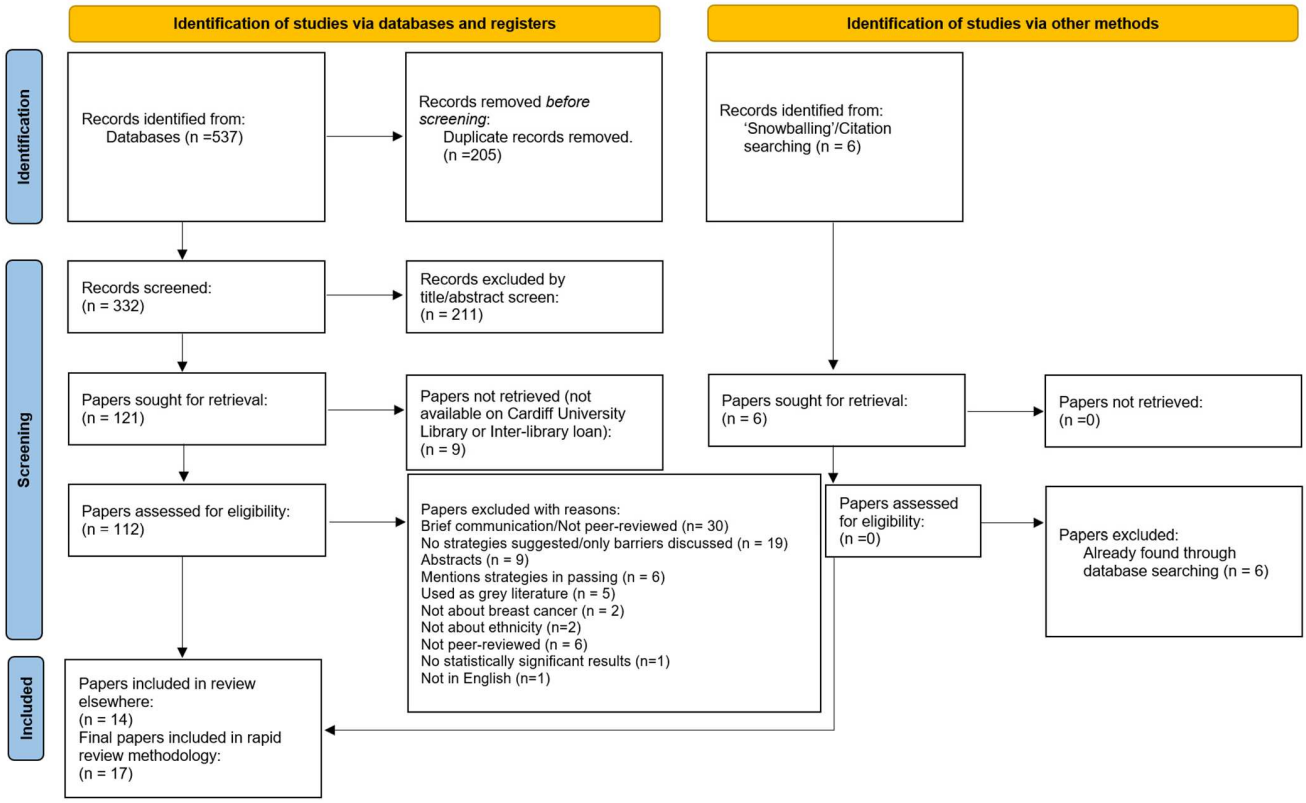

Figure 2 • Summary of the PRISMA rapid review screening giving rise to the final selected papers.

Table 1 • Summary of final papers identified.

Paper	Summary	Quantitative findings
Tharakan et al. 2021 [56]	US systematic review exploring the effect of globalisation on Black participant cancer CT enrolment.	N/A
Slade et al. 2021 [57]	United Kingdom (UK) systematic review and qualitative interviews with stakeholders. Assessing the cultural validity of patient-reported outcome measures used in cancer CTs registered on the EPiC database.	N/A
Arring et al. 2022 [58]	US scoping review which identifies interventions that increased Black adult participation in BC trials.	All studies [8] with an acceptance rate of 50% or over implemented five or more strategies, with an average of seven strategies used.
Borrayo et al. 2005 [62]	US qualitative semi-structured interviews with Latina women to identify facilitating factors for BC prevention CTs.	N/A
Cyrus-David M.S 2006 [59]	Systematic review assessing the landscape of minority underrepresentation in BC chemoprevention trials.	N/A
Wallington et al. 2016 [60]	US cohort study (Washington DC) that assesses the effect of location and cultural competency on African American (AA) trial accrual.	From 2012 to 2014, a total of 559 participants were enrolled across six non-therapeutic CTs, representing a 62% increase in the enrolment of Black people in clinical research.
Herman and Larkey 2006 [61]	US non-randomised controlled study with questionnaire, comparing an art-based curriculum to a non-art-based curriculum to assess which best improves Latina willingness to participate in a hypothetical CT.	Overall knowledge was increased with the use of promotoras and a community-developed programme.
Du et al. 2009 [63]	US randomised controlled trial (RCT) including newly diagnosed BC patients (45% AA). Assessing the effect of an educational video on therapeutic clinical trial enrolment.	Likelihood to enrol score for AA [1–5] Baseline: 3.2 ± 1.1 (SD) Follow-up: 3.1 ± 1.3 (SD) Educational videos had little or no effect on therapeutic clinical trial enrolment.
Holmes et al. 2012 [64]	US non-randomised study using Black BC patients eligible for University of Southern California CTs. Evaluating the impact of oncology nurse navigation as an innovative approach to increasing Black adult CT participation.	In total, 86% (50/59) of eligible Black patients were enrolled in one or more CTs. During the same 2-year period, the accrual of Black patients to USC Norris cancer CTs went from 3 to 7%.
Sadler et al. 2010 [65]	US qualitative focus group study with AA and Hispanic American (HA) women, to gain views on what they would like to see in CT education programmes.	N/A
Mandelblatt et al. 2005 [72]	US RCT with Latina women eligible for the Study of Tamoxifen and Raloxifene (STAR) BC prevention trials. Trial compares brief counselling and print materials to print materials alone to assess how effective the interventions are in increasing intent to participate in preventative BC trials.	Recruitment efforts will require careful framing of the risk–benefit ratio of chemotherapy; intention to enrol decreased with the discussion of mild side effects (SEs). General intent to participate, i.e., might, probably, or definitely would, was seen in the intervention of 118 people (50.9%) where SEs were discussed. General intent to participate, i.e., might, probably, or definitely would, was seen in 118 people (54.1%) in the control.

Table 1 • *Cont.*

Paper	Summary	Quantitative findings
Germino et al. 2011 [66]	US RCT with a focus on AA women under 50 and at least 1-4 years post-BC treatment completion. Using culturally informed, population-specific recruitment strategies and observing how this affects accrual.	Accrual of younger AA breast cancer survivors increased by 373% in 11 months (from 22 to 104 individuals). The final sample contained 31% AA breast cancer survivors, exceeding the approx. 21% proportion of AAs in the state.
Sturgeon et al. 2018 [67]	US RCT exploring how effective active recruitment methods are in increasing Black BC survivor enrolment in the Women In Steady Exercise Research (WISER) clinical trial.	The most successful strategies for recruiting non-White participants are as follows: 79% via state registry letters only 26% via hospital registry letters only 127 Black women (BC survivor with lymphedema) were recruited in the trial. Over 35% of participants were Black women – higher than average for trials of this kind (usually a range of 1.2% to 10.2%)
Smith et al. 2018 [68]	US case–control study evaluating how effective community-based participatory approaches are in recruiting AA women in a genetic research study.	A total of 364 AA women participated in the STAR study. Most people were recruited at the following events: Workshops—205/364; Breast Cancer Walk—132/364 recruited; Live! Annual event (30 min seminar with Q&A)—112 recruited; Support group—93 recruited; Clinic—27/364 recruited.
Trant et al. 2020 [69]	US cohort study which reports the results of the Oncology Welcomes New Haven into Trials (OWN IT) initiative and its interventions at the Yale Cancer Centre. The strategy used is a multi-tiered approach to increasing breast cancer minority accrual. A survey was also taken to gauge awareness of and access to CTs.	There was a significant increase in the number of minority patients (AA and Hispanic) who participated in clinical trials at Smilow Cancer Centre from 2016 (95/750) to 2018 (155/944) (p = 0.0325), 12.7% vs. 16.4%, respectively. This is higher than the national average of minority enrolment in BC CTs in 2016 which was 8.6%.
Bayard et al. 2022 [70]	A systematic review that collates suggestions about how electronic health records can be used to improve minority enrolment in BC CTs.	N/A
Riggan et al. 2023 [71]	US qualitative interviews with Black/AA women diagnosed with BC from a safety net clinic. The study collates recommendations from these patients on how to improve minority enrolment in CTs.	N/A

Theme 1: Multilevel, multi-pronged, mixed-method strategies.

The overarching theme indicated by the final papers is that strategies must be used in a mixed-method approach to successfully recruit REM groups. Where single interventions were used, there was no improvement in REM recruitment to clinical trials [63]. This is supported by Du et al.'s RCT [63] which showed no statistical difference between likelihood to enrol scoring between groups shown an educational video and the control. However, where multiple interventions were implemented, REM recruitment in trials was much more effective [58, 60, 64, 66–69, 71].

Theme 2: More expansive reporting of race data and/or use of diversity targets.

A systematic review by Tharakan et al. 2021 [56] primarily concluded that the globalisation of cancer clinical trial recruitment is associated with decreased accrual of Black patients. Alongside this, the review recognised the implications of poor ethnicity data collection, and recommended that 'race data should be considered for mandatory reporting along with the other mandatory reporting requirements in existing clinical trial registries'. The review also encouraged more detailed race/ancestry data to be integrated into trial designs. While this was not their primary focus, it was noted that current limited race categories do not reflect the heterogeneity of its individuals and the barriers they face [56]. A semi-structured interview by Slade et al. 2021 [57] also found that a potential facilitator to enhance REM trial diversity could be to ensure more clarity

Figure 3 • The Racial Minority Growth (RMG) model—a strategic framework to improve REM accrual into BC trials, bringing together key themes from the selected papers.

around race data reporting and to inform the design of culturally sensitive patient-reported outcomes (PROs). Another suggested facilitator was to tie diversity targets to funding to incentivise engagement [56, 57].

Theme 3: Making cultural accommodations, e.g., longer enrolment deadlines, culturally sensitive resources, etc.

Eleven papers supported the notion that in order to recruit REM groups for clinical trials, cultural accommodations need to be made [57–60, 64–69, 72]. This could involve adopting more flexible recruitment strategies such as, for example, extending enrolment deadlines [59, 66] and using holding lists to ensure that potential participants are re-contacted, instead of removing them after a few failed contact attempts [58, 66]. This can also extend to staff, with three papers showing staff cultural competency training to be one of many strategies used to aid recruitment efforts [58, 60, 67]. For these three papers, cultural competency can be defined as staff knowing how to integrate culture and language effectively into the delivery of health care, to address key cultural nuances. All cultural competency training models delivered one-off didactic sessions and/or online resources, however the aim was to emphasise the need for continued learning, with the real lessons being learnt from the experiences of REM groups [58, 60, 67]. This cultural competency training could aid recommendations by Mandelblatt et al. in recruiting staff to carefully frame the risk–benefit ratio of trial participation, after discussion of side effects reduced intention to participate in trials [72]. Finally, cultural accommodations can be made to the resources used to support CTs. This includes addressing pertinent issues for REM groups in the promotional literature such as, for example, insurance coverage, common fears, and safety concerns. Resources should also use lay, inviting language such as, for example, first-person plural phrasing to build comradery. Patient-reported outcome measures (PROMs) can be surveys, questionnaires, and scales that capture a patient's experience during a CT. They can identify additional patient impairments, treatment benefits, or harms/ADRs (adverse drug reactions) that are otherwise missed. Suggestions from Slade et al. encourage ensuring these are culturally sensitive and accessible, e.g., in terms of language [57]. REM community members could input during the PROM design process to further enhance cultural sensitivity linking to theme 4: community engagement [57, 58, 66].

Theme 4: Community involvement and engagement.

Several papers suggested active and early engagement with trusted REM community members in the recruitment process/design [57–61, 69, 71]. This could include religious leaders, breast cancer survivors, and academics, who can act as cultural brokers and combat medical mistrust [57, 58, 60, 66, 68, 71]. Germino et al. found sensitive engagement with religious leaders and extended REM friends and family networks to be a successful strategy paired with others outlined in the model [66]. Another key strategy was establishing community advisory boards (CABs) to allow REM groups to 'sense-check' proposed recruitment strategies before they were implemented [58, 60]. Community involvement also extends to making use of community facilities such as, for example, using academic sites already embedded in minority communities [60]. Several papers made use of, or encouraged the use of town halls as recruitment hubs or for focus groups to improve accessibility [58, 60, 61, 68, 69]. Another successful strategy involved setting up stands at community events including, for example, sports games and charity events to raise awareness of the need for REM participation in clinical trials [66, 68].

Theme 5: Innovative job roles and diverse staff/faculty.

Papers by both Arring et al. and Holmes et al. explored the impact of oncology nurse navigators (ONNs) on minority trial participation [58, 64]. This came about by merging the role of a traditional oncology research nurse and a professional patient navigator. These nurse navigators served as a knowledgeable patient resource, providing emotional, logistical, and clinical support, all whilst working alongside physicians to support minority enrolment in cancer clinical trials. Their role included facilitating community-based recruitment by conducting patient screening, follow-ups, examinations, and procedures such as blood tests and vital signs in the community setting. The ONNs also provided education about the patient's disease state and identified suitable clinical trials aided by culturally sensitive brochures in lay language [58]. Unfortunately, no survey instruments were used by Holmes et al. to objectively quantify and systematically review the impact of oncology nurse navigation. However, they found that 86% (50/59) of eligible Black patients for the University of Southern California (USC) breast cancer trials were enrolled in one or more trials, and during the same 2-year period, accrual of Black patients to USC Norris Cancer Centre CT's went from 3 to 7% [64].

Several papers ensured there was a diverse staff and faculty to support minority enrolment [60, 66, 67, 71]. Germino et al. used African American recruiters to recruit potential African American participants, allowing recruiters to use culturally relevant dialogue to ensure transparent communication. Recruiters also made follow-up calls from home so participants could see a name, rather than an unknown university phone number [66]. Black women diagnosed with breast cancer from a safety net clinic in the US fed back that increased representation of Black physicians and researchers would reassure Black participants that their concerns and interests would be advocated for. These women expressed that clinical trials being 'endorsed by' medical professionals who look like them might 'cause [them] to feel more inclined (to participate)' [71].

Theme 6: Appropriate resources to inform inclusion/exclusion criteria and identify eligible patients.

Recommendations by Cyrus-David et al. include ensuring models used to determine trial eligibility are inclusive of minority women with breast cancer [59]. The Gail model, for example,

was developed from a population of Caucasian women who were breast cancer screening participants. Cyrus-David et al. suggest that this model could lead to the underestimation of the breast cancer risk for minority women. Instead, the paper encourages the use of peer-reviewed alternatives such as the IBIS-1 selection criteria. Long-term recommendations include optimising current models with cohort studies including minority groups, to gather high-quality information about breast cancer risk factors, recurrence, and mortality [59]. Stakeholder interviews also suggest that research ethics committees should ensure that eligibility criteria are not arbitrarily restrictive [57].

Further suggested strategies include considering non-biased recruitment strategies, such as identifying eligible patients through state registries [67, 70]. A randomised controlled trial by Sturgeon et al. found that the most successful strategy to recruit non-White patients for a breast cancer trial (WISER survivor trial) was via state registry letters, with 79% of participants being enrolled by this method. This involved mailing letters to breast cancer survivors identified by state registries [67]. A 2022 systematic review by Bayard et al. suggests the use of electronic health records (EHRs) as another non-biased strategy to identify eligible participants. This could involve notifying patients and providers about available trials, which could be supplemented with 'opt-out' policies to allow universal access and eliminate requirements for active enrolment [70].

Theme 7: Language resources supplemented with bilingual healthcare providers/system navigators.

Reviews by Slade et al. and Arring et al. suggested the use of diverse language resources to aid minority participation [57, 58]. This suggestion is bolstered by semi-structured interviews undertaken. Borrayo et al. found that Spanish-speaking Latinas would be more encouraged to participate in a clinical trial if information was available in their language. Latinas also felt that their willingness to participate would further improve if bilingual health care providers or system navigators were available, as they could build relationships and trust with participants [62]. Overall knowledge of clinical trials increased with the use of promotoras (Latina lay health workers) [61].

Theme 8: Geographical considerations inc. de-centralisation.

Interventions considering trial-site geography in relation to where minority groups live, work, study, play, and worship, were shown to be a successful strategy [60]. Views of Black women diagnosed with breast cancer supported this notion, with one subject suggesting building clinics 'in the centre of the Black community' as opposed to 'way over there on the other side of town, nowhere near anybody' [71]. De-centralisation was another key theme, which involves moving trial activity away from traditional large academic centres and embedding more sites in the community that can act as clinics and recruitment hubs [56]. This could further facilitate innovative community job roles, e.g., ONNs as mentioned in theme 4, that can maximise patient convenience by reducing the need for consultations at academic/cancer centres, which are often challenging for REM patients to access [58, 64, 71].

Table 2 shows a summary of the successful strategic themes used, identified, or suggested by the selected papers. The Supplementary Information includes more details of the strategies used by each paper to aid minority enrolment in breast cancer clinical trials.

Table 2 • Strategic themes extracted from papers and linked to the RMG model (**Figure 3**).

Theme	Part of model	Suggested strategies
Reporting of race data and/or diversity targets [56–58]		• Adhere to mandatory participant race data reporting guidance [57] • More expansive ethnicity reporting to specifically understand REM participation [56] • Trial organisers to set diversity targets in action plans as mandated; plans must be sent to regulators and regularly reviewed; consider linking to funding/grants to incentivise engagement [57, 58]
Appropriate cultural accommodations, e.g., longer enrolment deadlines, PROMs, education, resources [57–60, 64–69, 72]		Culturally sensitive accommodations could include the following: • Flexible recruitment strategies, e.g., using holding lists and contacting participants at a better time instead of removing them after one failed attempt [66] • Longer enrolment deadlines [59, 66] • Lay, inviting language used in enrolment and education resources, e.g., 1st person plural phrasing to build comradery [64–66, 69] • Using images/videos of REM patients in the promotional literature [58, 65, 66, 68] • Didactic workshops [69] • Staff cultural competency training [58, 60, 67] • Addressing pertinent issues for REM patients in educational resources, such as insurance coverage, fear, safety, etc. [65] • Recruiters carefully framing the risk–benefit ratio of participation [72] • Follow-up calls could be made from home so patients can see a contact name rather than an unknown university/study number [66] • Ensure PROMs are culturally sensitive [57]; PROMs can be surveys, questionnaires, and scales that capture a patient's experience on a CT; REM community members' input could further enhance cultural sensitivity [57, 58, 66]

Table 2 • *Cont.*

Theme	Part of model	Suggested strategies
Community involvement and engagement [57–61, 66, 68, 69, 71]		• Include (trusted) REM community members in the process, e.g., religious leaders, BC survivors, non-profit organisations, academics, etc., who can combat medical mistrust and act as cultural brokers to aid the design, research, and delivery of CTs [57, 58, 60, 66, 68, 71] • Active and early engagement with these community members [71] • Sensitive engagement with religious leaders, e.g., sending letters to places of worship to encourage recruitment by linking beliefs to active research participation [66] • Making use of the REM extended family and friendship networks to promote CTs [66] • Establishing community advisory boards to 'sense-check' recruitment strategies [58, 60] • Making use of community facilities, e.g., using town halls as recruitment hubs, for focus groups and community needs assessment meetings [58, 60, 61, 68, 69] • Setting up stands at community events, e.g., sports games, charity events, support group meetings to raise awareness of the need to participate in trials [66, 68]
Innovative job roles and diverse staff/faculty [57, 58, 60–62, 64, 66, 67, 71]		Ensure staff are diverse and strive to have increased representation of REM doctors, researchers, and recruiters [60, 66, 67, 71]. • Tie this in with bilingual system navigator strategies [61]. • Consider having translation officers to support translated/culturally adapted PROMs and other translated resources [57, 62]. Introducing innovative job roles such as oncology nurse navigators who can [58, 64] • Facilitate community-based recruitment • Reduce workload at academic centres • Educate eligible REM patients (supplemented with culturally sensitive resources) • Provide emotional support and advocate for patients • System navigation, e.g., coordinating appointments, transportation assistance, medical record handling, etc. • Undertake trial-related services, e.g., physical examinations, blood tests
Appropriate resources to inform inclusion/exclusion criteria and identify eligible patients [57, 59, 67, 70]		• Evaluate current mathematical models used to determine eligibility criteria, e.g., the Gail model [59] • Consider peer-reviewed alternatives such as the IBIS-1 selection criteria where appropriate [59] • Research ethics committees to ensure eligibility criteria are not arbitrarily restrictive [57] • Where possible, use non-biased sources such as state registries and EHRs to identify and notify eligible patients about trials [67, 70] • Allow universal access to EHRs via 'opt-out' policies [70]
Language resources aided by bilingual healthcare providers/ system navigators [57, 58, 61, 62]		• Use diverse language resources, e.g., translated PROMs [57, 58, 61, 62] • Resources to be supplemented with bilingual system navigators/staff [57, 58, 61, 62] • Use bilingual team members to build relationships and trust with participants [61, 62] • For Spanish-speaking Latinas specifically, consider using 'promotoras' (Latina lay health workers) to improve CT knowledge and increase willingness to participate [61]

Table 2 • *Cont.*

Theme	Part of model	Suggested strategies
Multilevel, multi-pronged, mixed-method strategies [58, 60, 63, 65–69, 71]		• The results encourage the use of all aspects of the model in a mixed-method approach • This is supported by several studies identified by the review [58, 60, 63, 65–69, 71] • REM patients suggested that research participation is nuanced and multifactorial, so diversification efforts should reflect this [71] • Single interventions were unsuccessful [63, 65], whereas multi-pronged strategies increased REM trial participation; studies with the highest REM acceptance rate used 5 or more strategies [58]
Geographical considerations inc. de-centralisation [56, 58, 60, 64, 71]		• Consider clinic and recruitment centre location relative to where the majority of REM patients are [60, 71] Trial-site geography should consider where REM patients work, study, play, and worship [60] • Implement de-centralisation, moving trial activity away from traditional large academic centres and embedding more sites in the community that can act as clinics and recruitment hubs [60, 64, 71] • This could further facilitate innovative community job roles, e.g., nurse navigators, that can maximise patient convenience by reducing the need for consultations at academic/cancer centres, which are often challenging for REM patients to access [58, 64]

CTs—clinical trials; PROMs—patient-reported outcome measures; EHRs—electronic health records.

4. Discussion

This review demonstrates that the multifaceted challenge of increasing REM recruitment in BC clinical trials needs to be tackled with multi-pronged strategies, a theme consistent across the selected studies. The results are responsive to the barriers outlined in **Figure 1**, including, for example, cultural competence and community engagement strategies that could respond to 'medical mistrust'. Similar to a 2021 review by Bodicoat et al. [73], our results show that interventions are not successful in recruiting REM groups when used in isolation. It is not surprising that efforts which fail to address several of the barriers outlined in **Figure 1** do not improve REM access to clinical trials. Whilst our model promotes the use of all strategies across the eight thematic areas discussed in the Results section above, we note the strategies that were supported by the largest number of papers were making cultural accommodations (theme 3), community engagement (theme 4), and diverse trial staff (theme 5) with innovative job roles such as ONNs.

4.1. Link to wider literature/context

The results of the review align with other related models, e.g., INCLUDE and DRIVE, which acknowledge that the factors leading to inequity are 'highly complex and interwoven' [44, 74]. The RMG model builds on established frameworks, such as INCLUDE, which take a more general approach, by taking a more specific and multi-pronged stance as summarised in **Table 2**. The main takeaway from the RMG model is the importance of implementing multiple strategies in order to successfully recruit minority groups, and we hope this becomes integrated (alongside other findings) into FDA, MHRA, and NHS policy. One project of note is a pilot by the NHS Race and Health Observatory, which intends to innovate the way minority patients access breast cancer CTs, aided by two specialist nurses [49]. It is promising to see the nurse navigation model being implemented locally, with the opportunity to collect quantitative data to support its use. This will create a case study which, alongside our model, we hope will shape future clinical trial recruitment approaches. Our RMG model principles agree with the common theme in the literature that strategies must be used simultaneously [33, 44, 74–77]. The model uses segments 'A', 'I', and 'L' to respond to calls to go beyond enhanced trial invitation and instead tackle institutional barriers [4, 78]. Importantly, the review outcomes also link to the 2024 FDA draft guidance [24], with the 'R' (reporting of race data and/or diversity targets) relating to the diversity action plan that the FDA will require trial sponsors to submit [24]. It is promising that the RMG model links to real-world guidance, as it aims to bring together published recommendations and inspire future policies for use by clinicians and researchers. The 'R' segment also links to calls made for more consistent race reporting and granular data [19, 25, 33]. By knowing specifically which minority groups participate, we can know the full extent of the inequity, appropriately engage with people from these groups, and make targeted, culturally appropriate adjustments as the model suggests. Alongside this, much like efforts made by NCI-sponsored breast cancer trials, this review suggests the use of community-based sites as part of a successful strategy known as site de-centralisation [79]. Our model, however, does not capture all possible strategies. For example, the Heiney–Adams recruitment framework uses social media marketing to aid African American BC patient recruitment [80]. In a world where social media is becoming more prevalent as a recruitment tool, its role in healthcare more generally needs to be further investigated. Additionally, the review only partly addresses eligibility criteria by discussing the faults of the Gail model referenced by Cyrus-David [59, 81]. Comorbidities are often more common in REM patients and can limit access if eligibility criteria are arbitrarily restrictive [20, 25, 26, 29, 82]. One of the seventeen selected studies found that the greatest recruitment barrier was the lack of suitable clinical trials for 46% of patients studied [64]. Considering this, in 2020, the American Society of Clinical Oncology (ASCO); the US non-profit think tank and advocacy group, Friends of Cancer Research; and the FDA published joint recommendations to promote broader eligibility criteria for trials [83–86]. A true FDA mandate-driven model should help to address some of the most urgent recruitment challenges amongst REM populations.

4.2. Limitations, caveats, and cautions

This review aimed to produce a set of evidence-based strategies with wide-ranging applications; however, we did not capture non-English language publications, nor non-peer-reviewed publications. This could limit how generalisable the recommended strategies are, particularly as REM inclusion challenges may vary by cultural context and language, noting that the English language is by far the language of choice in the biomedical peer-reviewed journal literature. However, the review intends to be exploratory in nature and first needs testing before implementation. This feature alongside the lack of randomisation amongst two published studies [61, 64] could introduce bias into the review outputs. The generalisability of the results to the wider REM BC populations could be questioned on several levels. Three of the selected studies explored cancer trial recruitment in a general sense [56, 57, 65], creating the issue of whether the strategies discussed are compatible with BC trials specifically. Studies focusing on BC may not be generalisable for a variety of reasons. Hypothetical trial enrolment may not translate into actual enrolment. Patients may have been aware of interventions due to a lack of blinding or a study environment not reflecting a 'real-life' scenario. This could introduce performance bias, with patients agreeing to enrol in trials they usually would not, creating an overestimation of recruitment data and strategic success. Furthermore, the results analysed may not be transferable to all geographies as the insurance-driven US healthcare system, for example, greatly differs from the NHS in the UK. Some qualitative studies from the database search included niche populations, such as Latina women from Phoenix, Arizona [61], and Black women from a safety net clinic in the US [71]. The perspectives of these patients are relatable to their experience but could be challenging to apply to other communities and geographies. Not all REM patients are underprivileged with a deep-rooted sense of 'medical mistrust', and it is equally important to reach out to these patients. Caution will have to be taken when considering how to implement the model in different parts of the world, especially third-world countries that the model currently captures well.

It is also challenging to apply these diversification enhancement strategies to all minority groups. Each group will have different social, religious, and economic factors that will influence their lifestyle, and hence willingness to enrol in clinical trials. With the encouragement of more granular race reporting, perhaps we will see how specific minority groups respond to diversification efforts. There are also challenges surrounding undocumented individuals who would not be reached by state registries or electronic health records.

The model is partly based on REM opinions, appropriately so, as there is a clear community influence on REM perception of CTs—with the model itself encouraging us to do so [57–61, 66, 68, 69, 71]. While these opinions are not evidence-based, they are valuable perspectives from real experts in minority participation, which should be tested before implementation.

The proposed RMG model is only a starting point, so its use is cautioned as a stand-alone strategy. Its principles should be used alongside other related models, such as DRIVE and the Minority-Based Community Clinical Oncology Program [44, 87], to inspire future recruitment efforts. We must also note that increased funding lies at the crux of most successful strategy implementation efforts. Whilst not identified as a specific strategy, it is evident that funding is instrumental to success in driving trial diversification efforts. It is also understood that implementing multiple strategies will be resource-intensive, time-consuming, and not without logistical challenges. There are deep-rooted traumas following historical events such as the Tuskegee Study, and strategy implementation will clearly not be a quick fix.

5. Conclusions

Based on the findings of our review and ensuing recommendations, RMG-inspired strategies must be implemented in hypothesis-driven randomised clinical trials to promote enrolment diversification, bolstered by quantitative data collection. Empirical research is needed to support theoretical frameworks [65, 66], aligning with Wenzel et al. [77]. Recommendations to test models across disparate populations and diverse medical conditions, such as multiple sclerosis [88], will be important to help gain wider acceptance. It is imperative to make clear, practical, and evidence-based strategies that are accessible to clinical trial sponsors. Diversification needs to go deeper than clinical trials, to the core of who and what (models, criteria, policies) dictate the operation of our healthcare systems. Future strategies need to also shift to long-term patient retention in trials to evaluate strategic sustainability. Drug regulators such as the UK MHRA should follow FDA diversity action plans, holding trial organisers accountable, and using funding to incentivise engagement. These collective changes have the potential to diversify trials of established breast cancer therapeutics, but also for innovative targeted treatments such as immunotherapies and individualised cellular therapies. Our RMG model could further evolve to include a wider range of healthcare professionals, such as pharmacists aligning with reported nurse navigation models [70, 78], given that pharmacists are often community-based with established patient relationships [89, 90].

In summary, we hope that the RMG model proposed here will assist in efforts to increase racial and ethnic minority group clinical trial diversification, both in breast and related cancers, alongside other major diseases of unmet medical need.

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Conflict of interest

The authors declare no conflicts of interest.

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Supplementary materials

The Supplementary Materials, covering further methodological detail and search terms, plus more detailed summaries of the final selected papers, are available at [https://doi.org/10.20935/AcadOnco7480].

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