Improving Inclusivity, Equity, and Diversity in Oncology Clinical Trials: A European Perspective

Editor's Pick

My Editor's Pick for this edition of *EMJ Oncology* is a fascinating review article, in which the authors analyse the lack of representation of diverse populations in oncology clinical trials. Michie et al. look at how this discrepancy may affect medication efficacy and toxicity. The authors describe how making clinical trials more inclusive may help us to improve our knowledge of disease in various groups.

Ahmad Awada
Head of the Oncology Medicine Department, Jules Bordet Cancer Institute, Brussels, Belgium

Authors: Benjamin Langley,[1] Sophie Talas,[1] Karim Hussien El-Shakankery,[1] *Caroline Michie[1]

1. Department of Medical Oncology, Edinburgh Cancer Centre, UK
*Correspondence to Caroline.Michie@nhslothian.scot.nhs.uk

Disclosure: The authors declare no conflicts of interest. Langley and Talas contributed equally to this work.

Received: 29.06.23

Accepted: 06.11.23

Keywords: Cancer, clinical trials, diversity, equality, health literacy, INCLUDE, socioeconomic status.

Citation: EMJ Oncol. 2023;11[1]:68-80. DOI/10.33590/emjoncol/10303428. https://doi.org/10.33590/emjoncol/10303428.

Corrigendum: This article was first published on 5th December 2023. Since then, a corrigendum was made. The corrigendum can be seen here.

Abstract

Historically, clinical trials in cancer medicine are, unfortunately, often poorly representative of the diverse populations who ultimately receive the intervention in real-world settings. This discrepancy could relate to age, extent of comorbidity, ethnicity, socioeconomic status (SES), and/or disability. This is particularly important, as medication efficacy and/or toxicity are known to be influenced by such variables. Many cancers also disproportionately affect individuals in underserved communities. If a highly selected cohort of individuals are recruited to a trial, theoretically, the findings should only be translated to equivalent cohorts in the community. Therefore, the more representative a trial cohort is of the target population, the more generalisable and applicable findings will be. If we aim to lessen disparities and improve equity, clinical trials must strive to become more inclusive, improving our knowledge of disease in these underserved groups, and therefore improving the care we provide to them in wider clinical practice.

This review summarises the current European perspective on this topical issue, suggesting potential strategies to proactively improve inclusivity and diversity in cancer trials, by encouraging enthusiastic collaboration between the pharmaceutical industry, healthcare authorities, study sponsors, research networks, and clinicians.

Key Points

1. Clinical trials in cancer medicine have been criticised as, historically, trial populations have often not truly reflected real-world patient populations, with a significant number of underrepresented groups with respect to, for example, age, ethnicity, disability, socioeconomic status, or patients with sociolinguistic barriers. This limits the generalisability of the data, and creates an inequality for patients who could benefit from inclusion in clinical research.

2. This review summarises the current European perspective on this important and topical issue, suggesting potential strategies to improve inclusivity and diversity in cancer trials, drawing on evidence to date from other countries.

3. To improve diversity in clinical trials, a proactive approach, with collaboration between the pharmaceutical industry, healthcare authorities, study sponsors, research networks, and clinicians, will be required. Only when these inequalities have been properly addressed, can we say that clinical trials are truly representative of the populations they serve.

BACKGROUND

Although clinical trials form the backbone of evidence-based medicine, cohorts participating in clinical trials are often poorly representative of the diverse populations who ultimately receive the intervention in real-world settings. This discrepancy may relate to age, extent of comorbidity, ethnicity, socioeconomic status (SES), and/or disability.[1] This is particularly important, considering the medical literature tells us that medication efficacy and/or toxicity can be influenced by age, sex, ethnicity, and other variables.[2] We also know that many cancers disproportionately affect individuals in underserved communities.[3,4] If a highly selected cohort of individuals are recruited to a trial, theoretically, the findings should only be translated to equivalent cohorts in the community. Therefore, the more representative a trial cohort is of the target population, the more generalisable and applicable findings will be.[5]

If we aim to lessen disparities and improve equity, clinical trials must strive to become more inclusive, improving our knowledge of disease in these underserved groups, and therefore improving the care we provide to them.[5] Prior to discussing this further, the authors define diversity, inclusivity, and equity below in Table 1.[1,6]

In 2022, the U.S. Food and Drug Administration (FDA) issued guidance on improving trial racial inclusivity, including a requirement for all trial sponsors in the USA to formally submit a 'Race and Ethnicity Diversity Plan'. The plan should highlight any existing evidence as to whether efficacy of the trial intervention/agent is influenced by race and/or ethnicity, alongside listing 'goals and plans for enrolment of underrepresented racial and ethnic participants'.[7] Supporting this, the United States Congress' end-of-year budget allocated funding to develop interventions that improve trial diversity.[8] Presently, no such requirements exist for other underrepresented groups.

This review explores the challenges that underserved groups face regarding clinical trial involvement. With the USA taking proactive steps to counteract such issues, the authors consider what Europe and its leading organisations are doing to improve trial inclusivity, alongside discussing various innovative solutions aimed to improve recruitment and the representation of underrepresented parties. In writing this review, for each key inequality challenge, a separate search was undertaken using the individual challenge as a search term, together with "clinical trials," in order to select appropriate literature. The authors focus here on bringing together a European perspective.

CHALLENGES

Ethnicity

An ethnic group is defined as a large collection of 'people classed according to common racial, national, tribal, religious, linguistic, or cultural

Table 1: Key terminology and definitions.

Terminology and definitions	
Diversity	Refers to the variety of characteristics, personalities, and behaviours of individuals.
Inclusivity	Encompasses actions that ensure all people are respected, appreciated, and valued, permitting diversity to prosper.
Equity	Ensures all individuals have fair opportunities to access resources and achieve their best health, regardless of their characteristics or background. Equity involves distributing resources based on need, rather than equally between all individuals/groups.

origin or background', while an ethnic minority group describes those 'living in a country where most people are from a different ethnic group'. In contrast, race is defined as a group in which people belong, classified by physical characteristics one perceives them to share; although the definition shares similarities with ethnicity/ethnic groups, the terms should not be used interchangeably.[9-11]

In 2022, the National Institute for Health and Care Research (NIHR) reported that only 60% of 148 UK randomised controlled trials (RCT) provided data on participant ethnicity.[12] Furthermore, in trials that do report ethnicity, underrepresentation is often apparent. For example, Smith et al.[13] analysed data from 943 RCTs crucial to medication authorisation by the European Commission (EC), showing that Black and Asian populations were underrepresented in almost 50% of trials. The review highlights the abundance of literature discussing trial ethnic diversity stemming from the USA, relative to European counterparts; this is perhaps driven by a combination of historical and attitudinal differences.[13] Despite knowing that ethnic minorities in Europe also face disparities in cancer care, one must consider whether European research is comparably as committed to prioritising equity for these groups.[14,15]

Aimed at enhancing trial ethnic diversity, Schwartz et al.[16] state three key goals: building trust, promoting equity, and increasing biomedical knowledge. Described in American literature, distrust of the medical profession draws on historical abuses and modern-day inequalities.[17,18] However, European literature on this subject is lacking, so whether the reasons underpinning American distrust translate to this population is difficult to say. Secondly, equity recognises that potential benefits of trial participation should be made accessible to all, regardless of background and characteristics. This benefit comes not only from the trial intervention, but also from participation in general; inequity limits access to groups that may need it most.[19-22] Such benefits include dedicated support by a trials team, enhancing continuity of care, and increased (and often quicker) access to investigations, blood tests, and appointments with a healthcare professional.[19,20,23] Finally, biomedical knowledge is gained through diversity, because cohorts highly representative of the diverse target population increase the generalisability of results. Pharmaco-ethnicity considers ethnicity-dependent variations in treatment response and toxicity,[24] and though individual trials are usually underpowered to robustly identify these differences, it emphasises why inclusivity makes for more applicable data.[16]

Indeed, achieving equity may not mean proportional representation with regard to the general population, but representation weighted to reflect that some cancers affect certain ethnicities to a greater degree. For example, mortality incidence in African American patients with triple negative breast cancer (TNBC) is almost twice that of White counterparts.[25,26] Nevertheless, social factors may play a significant role in TNBC survival in this group, which may also form barriers to trial participation, widening inequity.[26] However, the pressing need to improve care for this subgroup is not reflected in clinical trial recruitment. For example, in one of the most recent practice-changing studies in TNBC, ethnicity data were not reported until recently, where <5% were Black or African American.[27,28]

We must also recognise that ethnicity intersects with socioeconomic, educational, language, and geographical factors, all of which may contribute. The term 'ethnic minority' refers not to a homogenous population, but describes diverse peoples with different cultures, history, and genetics. Moreover, Europe is a diverse continent, with variation between countries not only in ethnic and linguistic makeup, but in healthcare access, resources, governing bodies, historical tensions, politics, migration, and attitudes towards equality. Therefore, inclusion strategies must be both multifaceted, and regionally tailored.

Language and Health Literacy

Language is a well-recognised barrier to trial inclusion.[29-35] For an individual to provide capacitous consent, they must be able to understand, retain, weigh up, and communicate their decision.[36] The Centers for Disease Control and Prevention (CDC) defines health literacy as the ability of individuals to "find, understand, and use information and services to inform health-related decisions and actions for themselves and others."[37]

Alongside verbal explanations, trials also involve significant volumes of written information and paperwork, including written consent. It may not always be immediately evident that a language barrier exists. For example, someone with good conversational English may have difficulties with written language, and/or be unfamiliar with medical jargon. National Health Service (NHS) England's Increasing Diversity In Research Participation guide recognises further language-related barriers, like poor health literacy, culturally inappropriate explanations, use of acronyms, and poor access to quality translation.[29] A 2020 study objectively assessing the readability of patient information documents from 154 different UK clinical trials found that not one met the recommended mean reading age of <12 years, recommended by the American Medical Association (AMA).[38] Consideration should also be applied to communication needs in populations prone to language barriers, including visually/hearing impaired, cognitively impaired, learning disability groups, and groups for whom the trial participant's first language differs from the primary language used in the country that the trial is based.[30,39-41]

Sociolinguistic Disabilities

Communication of trial information can be equally difficult for sociolinguistic minorities, such as those with impaired hearing or vision. Without adequate accessibility and support for these patients, lower involvement in clinical trials is inevitable. Deaf patients are particularly prone to lower levels of health literacy, and may also have unique reservations with regard to research participation, such as fears of confidentiality breaches via translators likely to be within the same social circles as themselves.[41]

Rural Communities

Several studies, primarily conducted in the USA, have demonstrated that people from rural communities may have a shorter life expectancy,[42] present with more advanced cancers,[43,44] and are less likely to participate in clinical trials.[42,45,46] Possible reasons for this are numerous, including lower education and SES in rurality,[37] patient perception that healthcare is less accessible,[39] fear of associated costs,[41] and poor trial recruitment effort rurally.[47] To some degree, many of these likely translate to corresponding European populations.

Individuals living in remote areas are considered an underserved group by the NIHR Innovations in Clinical Trial Design and Delivery for the Under-served (INCLUDE) project.[34] Regarding healthcare distributions, Europe has a distinct rural-urban divide, concentrating workforces in urban populations.[35] A 2020 UK-based YouGov poll of clinical trials participants found that those in urban regions travelled 10–20 miles on average for cancer care, while rural participants travelled an average of 20–50 miles.[48] Additionally, despite modern solutions to increase digital presence, and minimise face-to-face contact for participants, rural communities may still find themselves digitally isolated.[30]

Socioeconomic Status

Cancer incidence is known to vary according to SES, with cancers such as cervical and lung more common in those of low SES living in income-deprived areas.[49] Despite those from deprived areas representing a significant proportion of the general cancer population, most individuals enrolling in clinical trials tend to be affluent, limiting generalisability of the data to real-world

settings.[8,50,51] Created by the UK government, the Index of Multiple Deprivation (IMD) score is a measure of socioeconomic deprivation, summarising how deprived individuals living within a geographical area are; it is often considered deeply related to socio-economic status.[52,53] Supporting the above, Noor et al.[54] observed that patients with an IMD score of 5 (most deprived quintile) were significantly less likely to be referred for early Phase (Phase I) trials in an England-based cancer centre (odds ratio: 0.53; 95% confidence interval: 0.38–0.74).

Potential barriers have been postulated that may prevent deprived individuals from accessing trials, including lower health-seeking behaviours, distrust, lack of awareness/understanding, and language/cultural barriers.[55-58] Furthermore, in those showing interest, associated costs may also limit engagement. These include expenses for more frequent travel, commonly to trial centres further away than their local hospital, secondary to additional appointments, and more frequent imaging.[59,60] Time away from their employment and/or other caring responsibilities may also deter individuals from lower SES more than those who are affluent. Furthermore, poor retention in clinical trials has commonly been attributed to financial, time, or other practical reasons.[61]

With research highlighting a clear relationship between SES and physical health, those of lower SES may also be disproportionately excluded from trials via eligibility criteria that include various comorbidities and lower performance statuses. Several factors may result in worse physical health in those of lower SES, including housing conditions, nutritional status, income, and the likelihood to undertake manual labour work.[62,63]

Elderly Populations

Considering older individuals are more likely to be frail and/or comorbid, alongside being more susceptible to treatment toxicities, it is perhaps easier to understand the reduced representation of elderly patients in clinical trials involving potentially harmful interventions. Additionally, they may have different perspectives on quality versus quantity of life. However, despite these factors undoubtedly influencing patient eligibility, evidence suggests older patients are no less willing to participate in research. As 42% of the cancer population are >70 years, their participation is valuable. Despite this, only 10% of this cohort are involved in National Cancer Institute (NCI)-sponsored clinical trials.[64,65] Therefore, one must consider if unnecessary barriers are preventing involvement.

In particular, we understand that there are notable biological differences in the handling of medications by the elderly. These include changes in gastric acid production and gut transit time (influencing absorption and peak drug concentration), declining serum albumin, impaired hepatic and renal drug clearance, and differences in body composition.[66] These may serve to alter the therapeutic benefits or possible side effects of medications, and the overall effect of a particular drug in this population will only be truly established when opportunities are provided to test them. Indeed, any appropriate dose adjustments could be best defined prior to a treatment going to market.

Alongside drug metabolism concerns, a 2021 systematic review identified several other barriers at both care provider and patient levels.[64] These included strict eligibility criteria, choice of language in consenting, reluctance from healthcare professionals secondary to fears of toxicity or comorbidities, poor awareness of available trials, and even general concerns solely around the patient's age. Finally, patients themselves may lack comprehensive understanding of what trials entail, and/or may worry about logistical implications, such as reliance on family members for travel, and time commitments.

There has, however, been some progress, with the European Organisation for the Research and Treatment of Cancer (EORTC) Elderly Task Force initiating an Older Adult Council thinktank to 'actively promote clinical and translational research in older adults over 70'. Several of their tumour subgroups have collaborated with this taskforce to initiate a number of trials dedicated to elderly populations.[67] Furthermore, geriatric oncology is also now a specialist field in its own right, promoted and supported by the International Society of Geriatric Oncology (Société Internationale d'Oncologie Gériatrique [SIOG] in French). This was set up in 2000 in Europe as a multidisciplinary network, and

presently boasts members from >80 countries worldwide. Research and education are two of its main strategic priorities.[68]

POSSIBLE SOLUTIONS

Reasons for underrepresentation of the above groups are both numerous and broad. Though some innovative ideas may benefit more than one population, no one-size-fits-all solution exists; each group should be considered in turn to optimise outcomes.

The INCLUDE Framework

Several European groups have been working to improve inclusivity of underserved groups, including the NIHR and their INCLUDE framework, which considers several under-served populations, including those listed in Table 2. The guidance encourages research teams to carefully consider their target/study population, specifically highlighting relevant underserved groups, and any potential barriers to participation. Through helpful definitions, examples, and questions, the framework prompts researchers to reflect on the inclusivity of their work.[34] In considering inclusion and exclusion criteria, research teams are strongly encouraged to justify why such criteria are merited if they are likely to prevent underserved groups from being eligible to participate.[34]

Possible Solutions: Ethnicity

To generate solutions, one must first consider the many postulated barriers to participation faced by ethnic minorities. These include distrust in medical communities;[17,29-33,69] lacking knowledge around trials;[30] financial worries;[29,30,32,34] associated logistical issues, such as transport, or care responsibilities;[30,31] cultural barriers, including stigmas about disease;[29-34] language barriers;[29-35] and excessive exclusion criteria.[30-34] Multiple studies suggest that ethnic minorities are no less willing to participate than their counterparts, and so the discrepancy cannot be dismissed as purely attitudinal.[70,71]

Of the numerous proposed and tested strategies, the most notable include: cultural competency training, where trial staff are educated in respecting, understanding, and communicating appropriately with patients from different cultures;[29,30,72,73] video education interventions that provide simple, culturally-sensitive explanations of trials;[34,73] community-based approaches, e.g., partnership with community organisations and leaders, alongside involving them in study design/implementation;[30-32] and use of trusted or respected medical professionals.[32] Non-discriminatory and carefully selected exclusion criteria also consider that certain comorbidities, for example, are more prevalent amongst particular minority groups, and may not truly need to be excluded.[30,33,34] However, strategies must avoid becoming coercive, or paint an unbalanced view of trial involvement.

Table 2: Underserved groups highlighted within the National Institute for Health and Care Research (NIHR) INCLUDE project.

Demographic Factors	Social and Economic Factors	Health Status Factors	Disease-Specific Factors
Age, ethnicity, sexual orientation, educational disadvantage.	Residing in deprived areas, full-time employment, living remotely, carers for family and/or friends, language barriers, stigmatised groups.	Mental health conditions, those lacking capacity, learning disabilities, cognitive impairment, physical disability, pregnant females, comorbidities, visually/hearing impaired, smokers, obesity.	Rare cancer subtypes, patients with brain metastases.

Looking forward, the INCLUDE project has produced a catalogue of available multimedia resources and an ethnicity framework,[74] amongst other resources, which challenge teams to evaluate their trial design. Similarly, the UK Engineering and Physical Science Research Council (EPSRC) has produced an Equality, Diversity, and Inclusivity (EDI) strategy, encompassing a variety of themes, from good recruitment practices to accessible environments, as well as diversity of study recruitment.[75] This effectively demonstrates that EDI should permeate all aspects of research, and that inclusive trials should be the fruit of inclusive organisations. Furthermore, 'Increasing Diversity in Research Participation', a good practice guide from NHS England, proposes and categorises practical recommendations into pre-research planning, involvement, and respect during research, and post-research feedback and improvement.[29] As one of its key targets within the 2021-22 Clinical Research Delivery Implementation plan, the UK government has also published several recommendations, with the intention of working with the NIHR to make research 'more diverse and more relevant to the whole UK'.[76]

Outside of government-led organisations, Egality are a startup agency with the goal of improving clinical trial diversity by facilitating the engagement of researchers with diverse communities.[77] Through these relationships and practical experience, they have generated recommendations targeted at the national, organisational, and individual level, to encourage the first steps towards improvement.[77] Meanwhile, the European Medicines Agency (EMA) stress the importance of diversity in several of their International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, emphasising representative participant selection.[78,79] The Medicines and Healthcare products Regulatory Agency (MHRA) are also set to release a new framework that contains guidance on improving diversity in trials.[80]

However, despite the above concerted efforts, there remains no requirement for trial publications to report ethnicity data (unlike examples in the USA),[81] and no standardised way of recording this.[12] In the meantime, it remains to be seen whether European nations value inclusive trials, and are making meaningful steps forward.

Possible Solutions: Language and Sociolinguistic Minorities

Considering language and its associated barriers, multiple solutions exist. Using bilingual staff has been shown to be effective, as has access to professional interpreters.[30] Written material available in the participant's preferred language can be helpful,[30,31] but straightforward translation of documents may not give much benefit, and a more tailored approach is needed;[32,82] these include pitching writing at an appropriate literacy and cultural level, creating simpler and more concise documents, and making use of multimedia materials.[29-31,72,82] Non-written patient education materials, such as videos, pictographs, and audiotapes, have been shown to increase patient understanding,[83] and trial information videos with sign language would further facilitate participation of deaf patients.[34,84] It is also important to recognise not only the huge volumes of languages widely spoken in diverse European countries, but also the nuances of different languages. One example of this is Gujarati, which is predominantly a spoken language, making written translations largely redundant.[32] Additionally, the language does not have a word for cancer, so much care has to be taken to communicate concepts effectively.[32] This highlights the importance of cultural competency alongside language tools, seeking to ensure communication is not only effective, but considerate and informed.[72]

Possible Solutions: Rural

Proposed strategies for reducing inequalities for rural patients in clinical trials include employing technology for virtual appointments;[85] reimbursing expenses;[4,46,85] providing transport;[86,87] and using satellite sites for clinics, appointments, scans, and/or treatments.[88] Improving physician education around the challenges for rural populations will also be imperative.[45,46,87] One organisation actively addressing the urban-rural divide is the International Institute for Rural Health (LIIRH), based in Lincoln, UK.[89] In particular, they hope to use the European Code of Cancer Practice, which summarises the pillars of a quality cancer service, to evaluate rural cancer care.[90] The

current paucity of research into rural population involvement in European clinical trials means these communities are likely to remain underserved.

Possible Solutions: Socioeconomic Status

Despite disparity in oncology trial participation having always been present, only now is there a slowly growing body of research attempting to address it. The NIHR-INCLUDE guidance contains a 'Socioeconomic Disadvantage Framework',[34,91] which specifically seeks to increase participation of poorer patient groups. The framework also encourages research teams to ensure trial outcomes are relevant to the broader population, and not just the typically over-represented affluent trial participants. Four key questions are proposed to encourage trial organisers to optimise inclusion of those of lower SES:

1. Are people from different socioeconomic backgrounds likely to respond to the intervention in different ways?

2. Will my trial intervention and/or comparator make it harder for people from different socioeconomic backgrounds to take part in the trial?

3. Will the way I have planned and designed my trial make it harder for people from different socioeconomic backgrounds to take part in the trial?

4. What factors might affect the reporting and dissemination of trial results?

Patients of lower SES are more vulnerable to the financial stressors of trial participation, including travel and childcare costs. To improve recruitment and retention, trial sponsors must consider compensating for such expenses, and addressing concerns of potential trial participants.

Possible Solutions: Elderly Patients

Reassuringly, more seems to have been actioned at a legislative level with regard to elderly involvement in trials.

The guideline ICH E7, initially published in 1994, laid out the fundamental principle that "drugs should be studied in all age groups, including the elderly, for which they will have significant utility."[92] Their guidance made specific requirements for adequate representation of elderly patients, with at least 100 older patients included in trials where the disease is not unique to the elderly. They clearly state that upper age limits should be avoided, as should excluding patients with comorbidities, where possible. The guideline also highlighted the importance of pharmacokinetic and pharmacodynamic studies in this population, alongside research into novel drug-drug interactions. A decade later, the World Health Organization (WHO) encouraged the development of laws and guidelines that would obligate the inclusion of the elderly in clinical trials, stating that these patients were 'unjustifiably excluded'.[93] They advocated for tailored formulations of drugs for the elderly, to maximise adherence, and recommended thorough monitoring for adverse reactions.

In 2006, the EMA reviewed 10 dossiers of recently approved medications to assess their compliance with ICH E7, which, on the whole, showed good compliance.[94] They also made recommendations for how they believed ICH E7 could be improved upon, such as necessitating the involvement of both the elderly and very elderly participants as discreet subgroups in the clinical testing of medications.

While guidelines have laid groundwork for better inclusion of the elderly, barriers preventing optimal patient involvement still remain. One proposed solution is 'geriatrising' trial design;[64] this includes trying to use standardised measures of frailty, and choosing appropriate endpoints, such as active life expectancy, as well as specifically designing studies that investigate dosing, tolerability, benefits, and toxicities in the elderly.[95] Indeed, these measures will require widespread support alongside commitment of dedicated funds and resources for success. Easing logistical barriers through telehealth appointments, or assisting with travel and/or lodging, may also encourage enrolment.[64,96] Furthermore, improving communication and providing information tailored to elderly patients is another important step in aiding accessibility and understanding. Finally, psychosocial barriers, such as physician bias, must be tackled; in part,

this may be addressed through availability of high-quality data and literature, aiding clinicians to make evidence-based decisions.[96]

PHARMA PERSPECTIVE

Data from the EMA suggest that of approximately 2,800 clinical trials authorised each year for human medicines, 60% of these are commercially funded. Hence, the pharmaceutical industry must show active engagement in processes to improve diversity, and enact meaningful change.[97] Since the COVID-19 pandemic, improving diversity has become a hot topic of discussion. Literature stemming from several companies highlights trial diversity as an area of unmet need.[98-102]

Companies are already starting to implement many of the solutions discussed above; notable examples include community engagement and advocacy groups,[98,99,102] diversity-specific staff training, increased recruitment of female and minority ethnic trial investigators,[99] increased ethnic minority representation within pharmaceutical organisations alongside gender parity,[98] and dedicated/ringfenced funding to ensure equity and diversity commitments are upheld within organisations and trials.[98] Other companies are also setting their own in-house targets, aiming for >75% of trials to have an outlined participant demographic plan, specifically and appropriately aligned with the epidemiology of the disease being studied; this was achieved in 100% of their Phase III studies in 2022.[102]

Aiming to build trust, work is also underway to improve access to patient-facing materials, such as videos to explain trials in multiple languages, and patient testimonies of trial involvement, especially from participants of underserved groups (unpublished correspondence). It should be highlighted, however, that these resources should be treated the same as any patient information correspondence, and therefore will be subject to the same regulatory and ethical restrictions, incurring cost and time. It is imperative that any digital communications are used as explanatory aids, and not as an 'advert'. Furthermore, confidentiality, and the ability to easily share digital resources further than their intended population, is also a risk that must be balanced (unpublished correspondence).

FUTURE DIRECTIONS AND STRATEGIES

Though many solutions show great potential, ensuring these are implemented in practice remains challenging. Although progress is being made, more is required. Previous research, primarily from the USA and the FDA, has demonstrated that legislation and recommendations from official public bodies, with associated accountability for actions, does translate to effective outcomes.[8] At present, no such legal requirements have been proposed by European organisations.

In a similar vein, the Fair Inclusion Score (FIS) for clinical trial diversity has been developed, generating an index/score based on trial participant sex, age, and ethnicity.[8,103] The score, intended to be publicly visible alongside published research, considers transparency of demographic data in published trials, alongside demographic representations in those that do present this data, compared to official demographics of the relevant target population. The score can be utilised on any published RCT, providing a diversity 'quality measure' that can be considered overall, or split into female, age, and ethnicity subgroup scores. Scores may then be compared to an acceptable 'benchmark', or directly compared with other trials and/or organisations, highlighting the efforts that organisations are, or are not, making to ensure their clinical trials are generalisable. As part of its development, retrospective application of the FIS on 69 RCTs (leading to FDA approval of 59 novel therapeutics between 2012–2017) showed that trials often displayed good transparency (mostly age and gender, with fewer studies noting ethnicities), but poor demographic representation, consistent with previous findings. Although the score highlights and considers diversity of trial populations after publication, this is performed retrospectively, and does not play a role in improving inclusivity prospectively.[8,103]

Similarly, organisations in the USA, such as the National Academies of Sciences, Engineering, and Medicine, are calling on journal editors and publishers to consider trial representation and inclusivity in all submissions.[1] However, changes must be considered far earlier than this, hence the proposal of a Diversity, Equity and Inclusion Clinical Trial Life Cycle (DEICTLC), produced

by Versavel et al.[1] Somewhat similar to the NIHR-INCLUDE project, the DEICTLC outlines each stage of trials from planning to close, with a useful checklist of actions that can be undertaken at each stage to maximise inclusion of underserved groups. Though the DEICTLC is in its infancy, and more evidence around its use in real-world practice is required, it shows great potential as an aid for study sponsors. In the UK specifically, organisations such as MedCity have themselves released guidance on trial inclusivity, with recommendations largely echoing those previously noted above. They also call for official UK organisations such as the Association of the British Pharmaceutical Industry (ABPI) and the Prescription Medicines Code of Practice Authority (PMCPA) to formulate code of practice regulations for trial sponsors, formalising guidance which will enhance community outreach and engagement.[104]

CONCLUSION

Though steps are being made towards improving clinical trial EDI, there remains significant room for improvement, particularly in Europe. Using a combination of general and targeted approaches, academic and commercial organisations must strive to implement innovative solutions at all stages of clinical trials, to recognise and act on the disparities underserved groups experience. Only when these have been addressed, can we say our clinical trials are truly representative of the populations they serve.

References

1. Versavel S et al. Diversity, equity, and inclusion in clinical trials: a practical guide from the perspective of a trial sponsor. Contemp Clin Trials. 2023;126:107092.
2. Bøttern J et al. Sex, racial, and ethnic diversity in clinical trials. Clin Transl Sci. 2023;16(6):937-45.
3. Delon C et al. Differences in cancer incidence by broad ethnic group in England, 2013-2017. Br J Cancer. 2022;126(12):1765-73.
4. Cancer Research UK. Cancer incidence statistics. 2023. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-One. Last accessed: 17 September 2023.
5. Gray DM et al. Diversity in clinical trials: an opportunity and imperative for community engagement. Lancet Gastroenterol Hepatol. 2021;6(8):605-7.
6. Centers for Disease Control and Prevention (CDC). What is health equity? | Health equity. 2023. Available at: https://www.cdc.gov/healthequity/whatis/index.html. Last accessed: 3 November 2023.
7. The United States Food and Drug Administration (FDA). Diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials; draft guidance for industry. 2022. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations. Last accessed: 10 August 2023.
8. Varma T, Miller JE. Ranking pharmaceutical companies on clinical trial diversity. BMJ. 2023;380:334.
9. Cambridge Dictionary. Race | English meaning. 2023. Available at: https://dictionary.cambridge.org/dictionary/english/race. Last accessed: 3 November 2023.
10. Cambridge Dictionary. Ethnic minority | English meaning. 2023. Available at: https://dictionary.cambridge.org/dictionary/english/ethnic-minority. Last accessed: 3 November 2023.
11. Merriam-Webster. Ethnic definition & meaning. 2023. Available at: https://www.merriam-webster.com/dictionary/ethnic. Last accessed: 3 November 2023.
12. The National Institute for Health and Care Research (NIHR). Randomised controlled trial participants: diversity data report. 2022. Available at: https://www.nihr.ac.uk/documents/randomised-controlled-trial-participants-diversity-data-report/31969#the-results-of-this-analysis-align-with-the-results-of-the-2011-census-does-this-mean-there-is-no-focus-needed-on-diversifying-rct-participants Last accessed: 2 August 2023.
13. Smith Z et al. Quantifying diversity and representation in pivotal trials leading to marketing authorization in Europe. Ther Innov Regul Sci. 2022;56(5):795-804.
14. Van Poppel H et al. European cancer organisation's inequalities network: putting cancer inequalities on the European policy map. JCO Glob Oncol. 2022;8(8):e2200233.
15. The Lancet Oncology. Racial disparities in cancer care: can we close the gap? Lancet Oncol. 2021;22(12):1643.
16. Schwartz AL et al. Why diverse clinical trial participation matters. N Engl J Med. 2023;388(14):1252-4.
17. Scharf DP et al. More than Tuskegee: understanding mistrust about research participation. J Health Care Poor Underserved. 2010;21(3):879-97.
18. Boulware LE et al. Race and trust in the health care system. Public Health Rep. 2003;118(4):358-65.
19. Schwarz K et al. The unspoken benefit of participation in a clinical trial. Clin Med. 2021;21(6):e645-7.
20. Majumdar SR et al. Better outcomes for patients treated at hospitals that participate in clinical trials. Arch Intern Med. 2008;168(6):657-62.
21. Braunholtz DA et al. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J Clin Epidemiol. 2001;54(3):217-24.
22. Krzyzanowska MK et al. How may clinical research improve healthcare outcomes? Ann Oncol. 2011;22(Suppl 7):10-5.
23. Cancer Research UK. The pros and cons of taking part in a clinical trial. 2022. Available at: https://www.

cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-you-should-be-told-about-a-clinical-trial/advantages-and-drawbacks. Last accessed: 3 November 2023.

24. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res. 2009;15(15):4806-14.
25. Bauer KR et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer registry. Cancer. 2007;109(9):1721-8.
26. Prakash O et al. Racial disparities in triple negative breast cancer: a review of the role of biologic and non-biologic factors. Front Public Health. 2020;8:576964.
27. Schmid P et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Eng J Med. 2022;386(6):556-67.
28. Schmid P et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810-21.
29. The NHS Accelerated Access Collaborative. Increasing diversity in research participation: a good practice guide for engaging with underrepresented groups. 2023. Available at: https://www.england.nhs.uk/aac/publication/increasing-diversity-in-research-participation/. Last accessed: 2 August 2023.
30. Bodicoat DH et al. Promoting inclusion in clinical trials - a rapid review of the literature and recommendations for action. Trials. 2021;22(1):1-11.
31. Hughson JA et al. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016;17(1):263.
32. Symonds RP et al. Recruitment of ethnic minorities into cancer clinical trials: experience from the front lines. Br J Cancer. 2012;107(7):1017-21.
33. Hussain-Gambles M et al. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. Health Soc Care Community. 2004;12(5):382-8.
34. The National Institute for Health and Care Research (NIHC). Improving inclusion of under-served groups in clinical research: guidance from INCLUDE project. 2020. Available at: https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435#examples-of-underserved-groups. Last accessed: 3 August 2023.
35. Roy M et al. Limited English proficiency and disparities in health care engagement among patients with breast cancer. JCO Oncol Pract. 2021;17(12):e1837-45.
36. Cision PR Newswire. Bioethics International publishes new index to score pharma companies on clinical trial diversity in BMJ Medicine. Available at: https://www.prnewswire.com/news-releases/bioethics-international-publishes-new-index-to-score-pharma-companies-on-clinical-trial-diversity-in-bmj-medicine-301713665.html. Last accessed 2 August 2023.
37. Centers for Disease Control and Prevention (CDC). What is health literacy? 2023. Available at: https://www.cdc.gov/healthliteracy/learn/index.html. Last accessed: 2 August 2023.
38. O'Sullivan L et al. Readability and understandability of clinical research patient information leaflets and consent forms in Ireland and the UK: a retrospective quantitative analysis. BMJ Open. 2020;10:e037994.
39. McKee MM, Paasche-Orlow MK. Health literacy and the disenfranchised: the importance of collaboration between limited English proficiency and health literacy researchers. J Health Commun. 2012;17(Suppl 3):7.
40. Clark LT et al. Increasing diversity in clinical trials: overcoming critical barriers. Curr Probl Cardiol. 2019;44(5):148-72.
41. Anderson ML et al. Barriers and facilitators to deaf trauma survivors' help-seeking behavior: lessons for behavioral clinical trials research. J Deaf Stud Educ. 2017;22(1):118-30.
42. Singh GK, Siahpush M. Widening rural-urban disparities in life expectancy, U.S., 1969-2009. Am J Prev Med. 2014;46(2):e19-29.
43. Campbell NC et al. Rural and urban differences in stage at diagnosis of colorectal and lung cancers. Br J Cancer. 2001;84(7):910-4.
44. Launoy G et al. Influence of rural environment on diagnosis, treatment, and prognosis of colorectal cancer. J Epidemiol Community Health. 1992;46(4):365-7.
45. Virani S et al. Barriers to recruitment of rural patients in cancer clinical trials. J Oncol Pract. 2011;7(3):172-7.
46. Baquet CR et al. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. Cancer Detect Prev. 2006;30(1):24-33.
47. Asher N et al. Oncologic patients' misconceptions may impede enrollment into clinical trials: a cross-sectional study. BMC Med Res Methodol. 2022;22(1):5.
48. The Institute of Cancer Research (ICR). Clinical trials in cancer - barriers in access to clinical trials, especially in light of the Covid-19 pandemic. 2021. Available at: https://www.icr.ac.uk/media/docs/default-source/corporate-docs-accounts-and-annual-reports/policy-statements/clinical-trials-in-cancer.pdf?sfvrsn=d2a92b69_8. Last accessed: 2 August 2023.
49. Shack L et al. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. BMC Cancer. 2008;8(1):271.
50. O'Brien TE. Health care disparity: an overlooked problem in phase I oncology trials. J Clin Oncol. 2007;25(21):3182-3.
51. Agrawal M et al. Patients' decision-making process regarding participation in phase I oncology research. J Clin Oncol. 2006;24(27):4479-84.
52. The King's Fund. What are health inequalities? 2022. Available at: https://www.kingsfund.org.uk/publications/what-are-health-inequalities. Last accessed: 3 November 2023.
53. Office for National Statistics (ONS). Socioeconomic inequalities in avoidable mortality, England and Wales. 2018. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/articles/measuringsocioeconomicinequalitiesinavoidablemortalityinenglandandwales/2001to2016. Last accessed: 5 November 2023.
54. Noor AM et al. Effect of patient socioeconomic status on access to early-phase cancer trials. J Clin Oncol. 2013;31(2):224-30.
55. Bruner DW et al. Reducing cancer disparities for minorities: a multidisciplinary research agenda to improve patient access to health systems, clinical trials, and effective cancer therapy. J Clin Oncol. 2006;24(14):2209-15.
56. Brown M, Moyer A. Predictors of awareness of clinical trials and feelings about the use of medical information for research in a nationally representative US sample.

2010;15(3):223-36.

57. Langford A et al. Clinical trial awareness among racial/ethnic minorities in HINTS 2007: sociodemographic, attitudinal, and knowledge correlates. 2010;15(Suppl 3):92-101.
58. Lejeune C et al. Socio-economic disparities in access to treatment and their impact on colorectal cancer survival. Int J Epidemiol. 2010;39(3):710-7.
59. Sharrocks K et al. The impact of socioeconomic status on access to cancer clinical trials. Br J Cancer. 2014;111(9):1684-7.
60. Huey RW et al. Patient-reported out-of-pocket costs and financial toxicity during early-phase oncology clinical trials. Oncologist. 2021;26(7):588-96.
61. Skea ZC et al. Exploring non-retention in clinical trials: a meta-ethnographic synthesis of studies reporting participant reasons for drop out. BMJ Open. 2019;9(6):e021959.
62. Ford JG et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112(2):228-242.
63. Wang J, Geng L. Effects of socioeconomic status on physical and psychological health: lifestyle as a mediator. Int J Environ Res Public Health. 2019;16(2):281.
64. Sedrak MS et al. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. CA Cancer J Clin. 2021;71(1):78-92.
65. Huang LW, Wang S. Cancer clinical trial enrollment in older vs younger adults. JAMA Netw Open. 2022;5(10):e2235718
66. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. Perspect Clin Res. 2015;6(4):184-9.
67. European Organisation for Research and Treatment of Cancer (EORTC). Oldera. 2022. Available at: https://www.eortc.org/research_field/older-adults/. Last accessed: 5 November 2023.
68. Société Internationale d'Oncologie Gériatrique. About SIOG. 2021. Available at: https://siog.org/about-us/the-society/about-siog/. Last accessed: 5 November 2023.
69. Roberson NL. Clinical trial participation viewpoints from racial/ethnic groups. Cancer. 1994;74(Suppl 9):2678-91.
70. Patel SN et al. Are ethnic and racial minority women less likely to participate in clinical trials? Gynecol Oncol. 2020;157(2):323-8.
71. Katz RV et al. Exploring the "legacy" of the Tuskegee Syphilis Study: a follow-up study from the Tuskegee Legacy Project. J Natl Med Assoc. 2009;101(2):179-83.
72. Stubbe DE. Practicing cultural competence and cultural humility in the care of diverse patients. Focus (AM Psychiatr Publ). 2020;18(1):49-51.
73. Nolan TS et al. Use of video education interventions to increase racial and ethnic diversity in cancer clinical trials: a systematic review. Worldviews Evid Based Nurs. 2021;18(5):302-9.
74. Trial Forge. The INCLUDE Ethnicity Framework. Available at: https://www.trialforge.org/trial-forge-centre/include/. Last accessed: 3 August 2023.
75. UK Research and Innovation (UKRI). Expectations for equality, diversity and inclusion. 2023. Available at: https://www.ukri.org/what-we-do/supporting-healthy-research-and-innovation-culture/equality-diversity-and-inclusion/epsrc/expectations-for-equality-diversity-and-inclusion/. Last accessed: 2 August 2023.
76. GOV.UK. The future of UK clinical research delivery: 2021 to 2022 implementation plan. 2021. Available at: https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery-2021-to-2022-implementation-plan/the-future-of-uk-clinical-research-delivery-2021-to-2022-implementation-plan. Last accessed: 2 August 2023.
77. Egality. Improving diversity in health research and trials, a conversation with medical research charities. 2021. Available at: https://slginvolvement.org.uk/wp-content/uploads/2021/03/Egality-Improving-diversity-in-health-research-and-trials-public.pdf. Last accessed: 2 August 2023.
78. European Medicines Agency (EMA). ICH guideline E8(R1) step 5 on general considerations for clinical studies. 2021. Available at: https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies-scientific-guideline#:~:text=The%20ICH%20guideline%20'General%20considerations,consideration%20of%20quality%20in%20the. Last accessed: 2 August 2023.
79. European Medicines Agency (EMA). ICH E6 (R3) guideline on good clinical practice (GCP) step 2b. 2023. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6-r3-guideline-good-clinical-practice-gcp-step-2b_en.pdf. Last accessed: 2 August 2023.
80. GOV.UK. MHRA to streamline clinical trial approvals in biggest overhaul of trial regulation in 20 years. 2023. Available at: https://www.gov.uk/government/news/mhra-to-streamline-clinical-trial-approvals-in-biggest-overhaul-of-trial-regulation-in-20-years. Last accessed: 2 August 2023.
81. Fain KM et al. Race and ethnicity reporting for clinical trials in ClinicalTrials.gov and publications. Contemp Clin Trials. 2021;101:106237.
82. Willis A et al. Improving diversity in research and trial participation: the challenges of language. Lancet Public Health. 2021;6(7):e445-6.
83. Weiss BD. Health literacy and patient safety: help patients understand. Manual for clinicians. 2nd ed. | PSNet. Available at: https://psnet.ahrq.gov/issue/health-literacy-and-patient-safety-help-patients-understand-manual-clinicians-2nd-ed. Last accessed: 17 September 2023.
84. Kushalnagar P et al. Barriers and facilitators to the inclusion of deaf people in clinical trials. Clin Trials. 2023;20(5):576-80.
85. Bharucha AE et al. Participation of rural patients in clinical trials at a multisite academic medical center. J Clin Transl Sci. 2021;5(1):e190.
86. Friedman DB et al. A qualitative study of recruitment barriers, motivators, and community-based strategies for increasing clinical trials participation among rural and urban populations. AM J Health Promot. 2015;29(5):332-8.
87. Mudaranthakam DP et al. Barriers to clinical trial participation: comparative study between rural and urban participants. JMIR Cancer 2022;8(2):e33240.
88. Niranjan SJ et al. Perceived institutional barriers among clinical and research professionals: minority participation in oncology clinical trials. JCO Oncol Pract. 2021;17(5):e666-75.
89. University of Lincoln. LIIRH | research. Available at: https://www.lincoln.ac.uk/collegeofsocialscience/research/liirh/. Last accessed: 2 August 2023.
90. Nelson D. Implementing the European code of cancer practice in rural and remote communities. European School of Oncology (ESO). 2022. Available at: https://eprints.lincoln.ac.uk/id/eprint/50139/. Last accessed: 2 August 2023.

91. Trial Forge. The INCLUDE socioeconomic disadvantage framework. 2023. Available at: https://www.trialforge.org/trial-forge-centre/socioeconomic-disadvantage-framework/. Last accessed: 3 August 2023.
92. European Medicines Agency (EMA). ICH E7 studies in support of special populations: geriatrics - scientific guideline. 2010. Available at: https://www.ema.europa.eu/en/ich-e7-studies-support-special-populations-geriatrics-scientific-guideline. Last accessed: 2 September 2023.
93. Kaplan W, Laing R.; World Health Organization (WHO). Priority medicines for Europe and the world. 2004. Available at: https://apps.who.int/iris/handle/10665/68769. Last accessed: 2 September 2023.
94. Committee for Human Medicinal Products (CHMP). Committee for Human Medicinal Products (CHMP) adequacy of guidance on the elderly regarding medicinal products for human use. 2006. Available at: http://www.emea.europa.eu. Last accessed: 2 September 2023.
95. Hurria A et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32(24):2587-94.
96. Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. 2014;21(3):209-14.
97. European Medicines Agency (EMA). Clinical trials in human medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines. Last accessed: 10 August 2023.
98. Bristol Myers Squibb (BMS). Fulfilling our role in diversifying clinical trials. Available at: https://www.bms.com/life-and-science/news-and-perspectives/fulfilling-out-role-in-increasing-clinical-trial-diversity.html. Last accessed: 10 August 2023.
99. Eli Lilly and Company. Diversity in clinical trials. Available at: https://www.lilly.com/clinical-research/clinical-trial-diversity. Last accessed: 10 August 2023.
100. Pfizer. Diversity in our clinical trials. Available at: https://www.pfizer.com/science/clinical-trials/diversity. Last accessed: 10 August 2023.
101. Sanofi. Diversity in clinical trials. Available at: https://www.sanofi.com/en/our-science/clinical-trials-and-results/diversity-in-clinical-trials. Last accessed: 10 August 2023.
102. Glaxosmithkline (GSK). Diversity in clinical trials. Available at: https://www.gsk.com/en-gb/innovation/trials/diversity-in-clinical-trials/. Last accessed: 10 August 2023.
103. Varma T et al. Metrics, baseline scores, and a tool to improve sponsor performance on clinical trial diversity: retrospective cross sectional study. BMJ Medicine. 2023;2(1):e000395.
104. MedCity. Why diversity in clinical trials is essential to the future of UK life sciences. 2023. Available at: https://www.medcityhq.com/2023/03/29/why-diversity-in-clinical-trials-is-essential-to-the-future-of-uk-life-sciences/. Last accessed: 2 September 2023.