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Diversity in decentralized clinical trials: prioritizing inclusion of underrepresented groups

Tessa I. van Rijssel[1,2*], Johannes J. M. van Delden[1], Bart Lagerwaard[1], Mira G. P. Zuidgeest[1], Ghislaine J. M. W. van Thiel[1] and on behalf of the Trials@Home consortium[3]

Abstract

Background The importance of more diversity of study populations in clinical trials is currently widely acknowledged. Decentralized clinical trial (DCT) approaches are presented as a potential means to broaden diversity by eliminating several barriers to participation. However, the precise meaning of, and objectives related to diversity in DCTs remain unclear. Diversity runs the risk of becoming a 'buzzword': widely acknowledged to be important, yet prone to multiple interpretations and challenging to implement in practice. We argue that the aim of increasing diversity in clinical trials requires clear and well-substantiated specifications.

Methods We analyze the concept of diversity and the ethical requirements surrounding fair participant selection within the context of clinical research, in order to further specify and operationalize the aim of increasing diversity in the context of DCTs.

Results Through analyzing the concept of diversity and ethical requirements for fair participant selection, we propose that diversity should be specified in a way that improves the position of the groups that are currently most underrepresented in the research context. In practice, this entails that, in order to contribute to diversity, the selection of participants should prioritize (i) gaining scientific knowledge on groups for which this is lacking, and (ii) inclusion of underrepresented groups in research when appropriate considering a study's objectives, and risks and benefits.

Conclusions Our analysis facilitates translating the aim of increasing diversity with DCTs to more specific and actionable objectives for recruitment and inclusion. Moreover, it contributes to a further specification of the concept of diversity and fair participant selection in research contexts.

Keywords Diversity, Research ethics, Fair participant selection, Decentralized clinical trials, DCTs

Background

Many populations remain excluded and underrepresented in clinical trials, such as women, children, elderly patients, racial- and ethnic minorities, people with comorbidities or comedications, and individuals with lower socio-economic status (SES) or living in rural areas [1–4]. The often false assumption that knowledge based on homogeneous populations is sufficiently generalizable to a heterogeneous reality has resulted in a lack of knowledge on many of these groups. Moreover, initial

*Correspondence:
Tessa I. van Rijssel
t.i.vanrijssel@umcutrecht.nl
[1] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of IQ Health, Radboud University Medical Center, Nijmegen, the Netherlands
[3] https://www.trialsathome.com

regulatory oversight prioritized protection, and therefore exclusion, of groups considered vulnerable [5], as for example highlighted in the Belmont Report [6]. However, this protectionist approach has been criticized in the past decades, as categorial exclusion of groups has disadvantages and research can also be potentially beneficial for participants themselves. Current ethical guidelines and an increasing amount of literature emphasize therefore the importance of including more diverse populations in research [7–9].

Decentralized clinical trial (DCT) approaches hold the promise of increasing the diversity of study populations. DCTs are a novel approach for conducting trials in which trial activities take place in (the vicinity of) participants immediate surroundings, rather than at a clinical site. This approach uses digital (health) technologies and other innovations to facilitate data collection [10]. DCTs potentially improve the conduct of clinical trials in multiple ways, including increasing accessibility for a wider demographic by eliminating geographical and logistical obstacles that often hinder participation in clinical trials [11–15]. DCTs arguably remove barriers to participation for several groups, such as patients living further from research sites, patients with limited mobility, patients who have too busy lives to visit trial sites, elderly patients, patients with comorbidities, and racial- and ethnic minorities [12, 16]. The potential broader inclusion is often associated with potentially improving the generalizability of results to real-life settings [11, 14, 15, 17].

However, there is a lack of clarity regarding the precise objectives of increasing diversity and the criteria for defining adequate representation in clinical trials [18]. Diversity can refer to a wide range of differences and characteristics in study populations, and the importance of diversity, from an ethical perspective, extends beyond enhancing generalizability. As a result, diversity has the risk of becoming a 'buzzword' that is widely acknowledged to be important, but at the same time susceptible to multiple interpretations and difficult to translate into practice [19]. A lack of further conceptualization of clinical trial diversity will hinder efforts to improve diversity to have the intended outcomes. For example, focusing on a single aspect of diversity with DCTs, such as race or ethnicity, has unintentionally led to a lack of diversity related to other aspects, such as gender, education, or digital literacy [20].

To overcome these challenges and promote meaningful use of the concept, we argue for further specification of the concept of diversity as well as reflection on its relevance and potential in the context of DCTs. This paper contributes to the specification and operationalization of diversity in DCTs, through an analysis of the concept of diversity, and reflection on ethical requirements for fair participant selection. While our analysis may apply to clinical trial diversity in general at certain points, its relevance is particularly significant for DCTs. Given that DCTs explicitly aim and promise to increase diversity, it is important to provide additional guidance on how to achieve this within the DCT context.

Concept of diversity

Diversity is susceptible to multiple interpretations [21–23]. First, the term diversity does not specify which characteristics or variety among individuals are relevant in a given context. Much of the recent literature on diversity in clinical research is focused on ethnicity, while this is not the only relevant aspect of diversity in clinical research [24]. At the same time, the groups that DCTs arguably include more easily (e.g., people living further away from research sites, elderly people, and ethnic minorities) are based on many different characteristics. It is thus often unclear or ambiguous to what characteristics the term diversity refers to. While tools like the PROGRESS-plus guidelines [25] identify specific groups and characteristics to consider, they remain quite broad and leave room for context-specific features. This wide scope can make it challenging to apply and specify these guidelines and account for diversity in specific studies. This aspect of diversity is further complicated by difficulty in delineating and categorizing subpopulations in general [26]. All individuals possess a variety of different characteristics and cannot be classified in separate homogeneous groups. This phenomenon is also referred to by the term intersectionality. Intersectionality emphasizes how many different factors, such as class, gender, race, and sexuality interact and shape an individual's experience [27]. In line with this, a wide variety of factors and characteristics shape an individual's health and can thus influence treatment outcomes, as reflected in the wide scope of the PROGRESS-plus characteristics [25]. The intersectional view on diversity complicates the operationalization of the concept in the context of clinical research. Intersectionality emphasizes that classification of individuals in homogeneous groups is not possible due to the wide variety of factors that influence an individual's health outcomes. Yet, clinical trials require the classification of participants into a limited number of subgroups to maintain statistical power. Subgroups are implicitly considered to be fixed, and a single cause is suggested for subgroup differences. This creates a tension with intersectionality and reduces diversity in a way, as it may not be able to acknowledge heterogeneity within groups. Considering these features of clinical research, it may be necessary to select particular aspects of diversity to focus on in the context of research.

Second, there are different understandings of when a group can be considered diverse [22]. For example, an egalitarian understanding of diversity presupposes that a group is diverse when all relevant characteristics are present equally within a group [22]. Alternatively, representative diversity implies that a group is diverse when all characteristics are distributed analogous to a reference population [22]. An egalitarian approach to diversity would, for instance, mean that a sample includes an equal number of individuals from each relevant ethnicity. In contrast, a representative approach to diversity would ensure that each ethnicity is included in the same proportion as in the general population of, for example, a country. Finally, a normic understanding determines the level of diversity in a group based on the extent to which the relevant characteristics diverge from a non-diverse norm in a reference population. This non-diverse norm can be determined based on the majority in a reference population, or due to social status (e.g., being white or male) [22]. These different understandings of diversity are relevant to distinguish because they require distinct operationalizations in practice, such as in determining how many individuals from each relevant group should be included. Furthermore, these possible interpretations of diversity are linked to different assumptions of why diversity is important in a given context. For instance, normic understandings prioritize minority group representation, while egalitarianism deems characteristics distribution in a reference population irrelevant [22]. Therefore, it is important to consider why diversity is relevant in specific contexts, such as the context of DCTs, and the research contexts in which they are put to use.

Diversity is thus an ambiguous concept that is inevitably in need of further specification. In some cases, it may be necessary to select particular aspects of diversity to focus on. This is especially the case when diversity is addressed through conducting subgroup analyses. Such analyses are necessary to gain knowledge on potential differences between (minority) groups. When data of a diverse group is combined within one sample, differences between smaller subgroups can be overshadowed by the majority. For instance, while a new treatment might seem effective overall, its effectiveness could vary significantly between younger and older participants. However, without subgroup analyses, the responses of a specific age group will be averaged with the responses of the whole group. In the next section of this paper, we analyze the ethical requirements for fair participant selection to give further guidance on which aspects of diversity should be prioritized in specific research contexts in which DCTs may be employed.

Fair participant selection

Fair participant selection is a requirement for ethical research and involves selecting participants in a manner that ensures fair distribution of research benefits and burdens [7, 28]. The CIOMS International Ethical Guidelines for Health-related Research Involving Humans require that participants should be invited based on scientific reasons, and that the exclusion of specific groups must be justified [7]. Furthermore, groups or individuals that are unlikely to benefit from the knowledge gained, but face increased risks, should be excluded [7]. Finally, underrepresented groups should be given appropriate access to participate, as knowledge of these groups can benefit future patients from these groups [7]. This latter requirement is also highlighted in the Declaration of Helsinki [29].

Fair participant selection encompasses fair sharing of multiple types of benefits and burdens [30]. First, the *scientific benefits* of the study must be shared fairly by generating knowledge that is sufficiently generalizable and useful to the entire population [30]. Secondly, participating in research may have *individual benefits*, such as receiving new or improved treatments, which should be distributed fairly. This means that people should not be excluded unfairly and that reasonable efforts should be made to enhance people's ability to participate [30]. Thirdly, the *risks and burdens* of research need to be shared equally, which involves selecting participants that are best able to bear the burdens of research, and excluding participants facing unacceptably high risks [30]. Potential risks and harms to non-participants, such as the risks related to studies on infectious diseases, but also the risks of causing stigmatization or discrimination by doing research with specific groups, need to be considered here as well [30]. These different considerations can sometimes create conflicting demands [30]. For example, ensuring sufficient generalizability may require including certain groups in research, even when they face additional risks, such as pregnant individuals [31]. This necessitates careful consideration in specific cases [30].

The aim of promoting diversity in clinical research is thus grounded in reaching a fair sharing of the benefits and burdens of research. At present, these benefits and burdens are not shared fairly in at least two ways. First, the groups that participate in research traditionally consisted of mainly relatively healthy, young or middle-aged, white men [32], so most scientific knowledge is based on this group. For several underrepresented groups, sufficient scientific knowledge on the safety and effectiveness of treatments may be lacking. This is specifically the case for underrepresented groups that have medically relevant differences from majority groups. For example, sex differences in cardiovascular diseases have led

to health disparities due to the historical exclusion of women in cardiovascular research [33]. Some groups, such as racial/ethnic minorities and older individuals are still underrepresented in current research [1]. Both historical and current underrepresented groups in research risk facing health disparities due to knowledge gaps. Second, overrepresented groups in research also receive most individual benefits of participating in research, such as receiving new or improved treatments. This aspect of unfair benefit and burden sharing is further exacerbated by the fact that for earlier phase studies, there are indications that racial- and ethnic minorities and individuals with lower SES are overrepresented. These studies generally involve the least direct benefits and pose relatively more risks and burdens. Some populations, such as racial- and ethnic minorities and individuals with a lower SES, are overrepresented in these studies while more often underrepresented in later-phase studies with generally more direct benefits [34, 35].

While guidelines emphasize the importance of fair participant selection, the concept of fairness remains unspecified, which makes these guidelines difficult to operationalize. It is to a certain extent unclear what requirements for fair participant selection entail in practice for diversity in individual studies. There is less specific guidance compared to most other ethical requirements for research [9]. Moreover, the overarching goal to reach a fair sharing of benefits and burdens in research is difficult to translate into diversity and inclusion requirements for individual studies. As we have argued, it may in some cases be necessary to select a particular aspect of diversity to focus on. In light of redressing historical inequalities in research described above, and to contribute to a fairer sharing of benefits and burdens, we propose that increasing diversity in research should be specified in a way that prioritizes improving the position of currently most underrepresented groups. Prioritizing groups that are worst off is a more commonly recommended approach in the field of medical ethics [36, 37]. In the context of DCTs, this would imply that groups should be selected (e.g., through eligibility criteria, trial designs, and recruitment methods) in a way that prioritizes (i) gaining knowledge on groups for which knowledge is lacking in specific research contexts or therapeutic areas, and (ii) inclusion of underrepresented groups in research with sufficient expected direct benefit.

Implications for clinical trials and opportunities for DCTS

We will give further direction on the practical implementation for increasing diversity in DCTs. It should be noted here that we acknowledge that DCTs do not offer a quick solution for rectifying existing inequalities rooted in complex histories. However, DCTs potentially contribute to increasing diversity in clinical research, and we believe our approach can offer guidance for addressing diversity in a more meaningful and valuable way.

Prioritizing gaining knowledge on underrepresented groups

The primary aim of conducting clinical research is to gain knowledge or develop novel treatments that are sufficiently generalizable or useful to indicated groups of those treatments. Therefore, scientific reasons should primarily guide participant selection [7, 28, 30]. It is commonly argued that study populations should ideally be representative of the population with the specific treatment indication in most or all aspects of diversity to ensure generalizability [38]. It should be noted here that the precise characteristics of this population are often not so well known, as this information is not collected in practice. Beyond the influence on diversity, DCTs can also contribute to generalizability through collecting data in patients' usual circumstances, generating more real-world evidence [12]. If the aim of increasing diversity is further specified in a way that prioritizes gaining knowledge on underrepresented groups to fill existing knowledge gaps, as we suggested, this would have additional implications. Prioritizing the inclusion of underrepresented groups in studies, such as women, racial or ethnic minorities, individuals with comorbidities, and pregnant individuals, would enhance scientific knowledge and enable the development of tailored treatments for these populations. In order to actually gain knowledge on specific groups, it is necessary to conduct subgroup analyses, which have specific methodological and statistical implications and requirements [39, 40].

In specifying which groups would require subgroup analyses, several other aspects should be considered. The characteristics that are often used to define underrepresented groups are not necessarily medically or biologically relevant [41]. In line with this, evidence suggests that variance in eligibility criteria or baseline characteristics does not necessarily impact generalizability [42]. This is because diversity only affects generalizability through characteristics that modify the treatment effect [38]. Thereofore, it differs per study or therapeutic area what "representative" actually is. Modifiers of treatment effects can range from gender, age, genetic variations, and comorbidities to treatment adherence and environmental- and lifestyle characteristics.

In addition, underrepresented groups are commonly described by concepts such as ethnicity, race, gender, or SES. Social categories or identities like these are regularly proxies for social, cultural or environmental factors [43]. Using these concepts in research may locate possible

(health-related) differences too much in individuals and consider these as purely biological or "fixed". Moreover, studies suggest that these types of categorizations in medical research vary significantly in terms of the criteria used to define them [44, 45]. Using these concepts (especially in an inconsistent way) can have unintentional harmful and stigmatizing effects, such as constructing and reinforcing fixed categories, and suggesting simplistic or inaccurate explanations for differences between groups, while disguising social or cultural influences [43–46]. For example, presumed racial or gender differences can cause wrong diagnoses or treatments once applied in healthcare contexts, when heterogeneity within groups is not considered [47], or may even legitimize discriminatory thinking or treatment [43]. Therefore, critical assessment is needed regarding which variables are used and how groups are classified. In some cases, it may be better to use other (socioeconomic) variables, instead of concepts such as ethnicity [32, 44, 45, 48].

We propose that if there are reasonable indications that a characteristic of an underrepresented group may serve as a modifier of the treatment effect, these groups should be included sufficiently for subgroup analyses. On the one hand, only investigating subgroups based on prior indications may lead to overlooking relevant differences between groups. On the other hand, repeatedly investigating (too small) subgroups can lead to observing differences that do not exist in the general population [38], or to harmful effects of making classifications described in the previous paragraph. Outcomes of subgroup analyses quantify differences between outcomes but do not reveal the causal pathways or the interaction between different factors – which are not necessarily biological [49]. Therefore, researchers should justify the groups that are included for subgroup analyses, include sufficient participants, and interpret results carefully.

Prioritizing inclusion of underrepresented groups

As stated before, prioritizing the inclusion of underrepresented groups in research is not only relevant to gain scientific knowledge relating to these groups but also to ensuring a fair distribution of individual research benefits. Currently, many groups are underrepresented in research that has potential benefits for participants such as receiving new or improved treatments.

To reach a fair sharing of these benefits and burdens overall, it is however not relevant to have a representative form of diversity in every single study. Focusing on the representation of certain groups could even lead to forms of 'tokenism' if existing barriers to participation remain unaddressed. Therefore, the requirement of fair distribution of these benefits is generally specified as fair opportunity to participate in research, instead of striving for forms of representative diversity in individual studies. Fair opportunity implies that all potential participants who meet the scientifically established eligibility criteria should have a fair opportunity to participate in potentially beneficial research [30, 50].

It is however not clear what fair opportunity entails in practice, as there are many barriers to participation. Groups can be excluded through eligibility criteria, such as people with common comorbidities or comedications, to enhance internal validity. However, underrepresented groups often face various other barriers, including practical ones like geographical distance or time and resource constraints, but also structural barriers, such as a lack of awareness of clinical trials, lack of trust and fear of stigma, or consequences of systemic issues such as poverty, racism, and discrimination [4, 24, 51, 52]. Fair opportunity may only imply that the eligibility criteria do not exclude groups unjustly (i.e., formal equality of opportunity), but it may also imply that researchers should make additional efforts to take away social, geographical, economic, or other types of barriers to participation (i.e., fair equality of opportunity) [30, 50]. A precise interpretation of fair opportunity is difficult to determine, due to the existence of various types of barriers. These barriers may stem from participants themselves (e.g., lack of trust), from the researcher (e.g., bias), or can be more systemic in nature. This raises complex questions about whether researchers need to address all types of barriers, and whether it is always realistic to expect them to do so, especially in relation to systemic barriers. Additionally, it may be worth considering whether it is always desirable to overcome barriers to participation stemming from participants' personal preferences or reluctance to participate in research.

The way DCTs may improve diversity contributes to fair opportunity in the sense of fair equality of opportunity, as it aims to decrease various barriers to participation. DCTs are potentially more accessible for populations living further away from research sites [12, 16], and patients for whom it is more difficult to travel or who carry certain additional burdens of research participation, such as elderly patients or patients with certain comorbidities [12]. Online recruitment methods, commonly applied in DCTs, can also broaden inclusion by not solely relying on physician referrals. This has been successful in including underrepresented populations [53], such as racial and ethnic minorities [16]. Furthermore, within the digital context of DCTs, there is the potential to provide trial information, procedures, and activities in diverse formats and languages, to promoting better comprehension [54–56]. Lastly, the increased sense of anonymity of participating in DCTs

compared to regular trials could help inclusion for diseases with stigma attached to them (e.g., HIV).

Yet, obviously, adoption of DCTs will not directly take away social barriers and could in some cases, regarding use of digital devices and internet, exacerbate social barriers and systemic issues. This could cause an underrepresentation of less digitally literate groups, but also patients with lower SES [57]. There are indications that these groups are already underrepresented in clinical trials [58, 59]. DCTs' aim to increase diversity should, according to our analysis, imply prioritizing inclusion of currently underrepresented and disadvantaged groups. Therefore, researchers should devote additional attention to also include these groups in DCTs, as there is a risk that this trial approach is especially accessible for groups who are already advantaged in certain ways. Researchers could for example consider implicit participation prerequisites (e.g., owning devices, digital literacy) and ensure sufficient support for participants in fulfilling study tasks and handling technologies and devices. Hence, with the increasing implementation of DCTs [60], researchers who use decentralized approaches in their trials are not exempt from additional efforts to take away barriers to participation [61, 62].

To summarize, when research is expected to provide scientific benefits for underrepresented groups, and direct benefits for participants – which means that a study offers sufficient individual direct benefit to participants in relation to the expected burdens – fair opportunity can be enhanced through the eligibility criteria, recruitment methods, or by addressing other barriers, for example using decentralized approaches. At the same time, in research with few direct benefits but more risks or burdens, such as earlier phase studies, increasing access for certain populations may not be desirable. Some groups that are typically seen as underrepresented in research, are not necessarily underrepresented in these types of studies [34, 35]. Taking away barriers through decentralization may aggravate the unfair sharing of benefits and burdens of research in these cases. Similarly, groups facing increased risks in a specific study may warrant exclusion [7, 30]. Nonetheless, researchers should remain critical here, in evaluating whether exclusion grounded in protectionism is justified. This form of protectionism has proven to disadvantage groups in the long run, through creating knowledge gaps. Thus, it should be considered whether taking away barriers for underrepresented groups is desirable, by assessing whether the potential benefits that specific groups may gain from the knowledge acquired in the study can justify burdens for these groups.

Discussion

Addressing diversity with DCTs requires clear and well-substantiated objectives, and these should be adapted to the specific context in which they are employed. We propose that diversity should be specified in a way that especially improves the position of the most underrepresented groups. In practice, this would imply that researchers should first identify groups that are relevant to study, based on existing evidence or other indications. These groups may differ for each research context or therapeutic area, but should in any case be included sufficiently to draw conclusions for that group. Next, the inclusion of underrepresented groups should be prioritized through addressing barriers to participation, when appropriate in light of the studies' risks and benefits, for example trough decentralized approaches.

Current ethical guidelines relating to fair participant selection state that "appropriate access" should be given to underrepresented groups [7]. Our analysis implies that, for groups on which knowledge is currently lacking (e.g., due to historical exclusion or underrepresentation) appropriate access should be interpreted as explicitly *prioritizing* the inclusion of these groups above other groups. Moreover, while some ethical guidelines solely require that eligibility criteria are justified [7], this alone has not necessarily resulted in greater diversity within studies, as numerous barriers persist. DCTs could contribute further to prioritizing the inclusion of underrepresented groups by addressing other barriers to participation. At the same time, many existing barriers and inequalities, especially those related to more systemic issues such as poverty, racism, and discrimination, require effort beyond using decentralized approaches [61, 62]. Researcher may need to devote additional attention to these barriers in the context of DCTs, compared to regular trials, in order to optimize DCTs' potential for diversity.

Finally, our analysis also reveals difficulties in specifying certain aspects of fair participant selection for individual studies. This problem can be understood in the context of how clinical research is regulated. Implicitly, research is understood as a transaction between researchers and participants, regulated by research ethics committees (RECs) [63, 64]. As a result, guidelines focus on the ethics of the researcher-participant relationship, and issues such as informed consent and favorable risk-benefit ratio have been specified in depth. However, issues relating to justice are less developed and more difficult to address in practice from this point of view [63, 64]. Further development of guidelines for fair participant selection may require a shift from a focus on the participant-researcher relation in individual studies, towards looking beyond individual studies to the research practice as a whole.

Conclusions

Decentralized approaches potentially serve as valuable tools in enhancing diversity in research. To fulfil the potential of DCTs, the eligibility criteria, trial design, and recruitment methods should be specified in a way that prioritizes including and improving the position of underrepresented groups, within a specific research context. A lack of a clear and well-substantiated specification in the context of clinical trials can result in diversity efforts missing its mark, potentially leading to forms of tokenism, unfair distribution of burdens, and stigmatization of minority groups. Further development of guidance on fair participant selection is needed as well, to facilitate the translation of ethical requirements into specific objectives for individual studies, and, subsequently, for contributing to improving diversity in clinical trials in a valuable way.

Abbreviations

DCT Decentralized clinical trial
REC Research ethics committee
SES Socio-economic status

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Authors' contributions

TR conceptualized and drafted the paper. TR, GT, and JD contributed to the conceptualization and analysis of the paper. All authors contributed to writing and critically reviewing the manuscript, and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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