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CLINICAL VIEWPOINT

Development of decision-making considerations to support equitable patient selection in paediatric haemophilia trials

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Assessment of medical need, potential support needs, and safety considerations form the basis of criteria for discussions around how to make enrolment in paediatric haemophilia clinical trials more equitable

Background: Clinical trials for investigational haemophilia treatments such as gene therapy offer a potentially life-changing opportunity to those who are selected for enrolment. However, the number of enrolment slots available for these trials is often greatly exceeded by the number of eligible patients. Many of the strategies that are commonly used to select candidates for participation can be highly unsystematic, inequitable, and subjective. A more rigorous set of criteria is therefore needed to evaluate each candidate's suitability for trial participation in order to eliminate bias in selection and fulfill the ethical principle of justice. **Aims:** To review current knowledge and issues in patient selection for paediatric haemophilia clinical trials with competitive availability, and to develop a more objective standard

for decision-making that takes into account the needs of all involved parties. **Methods:** A literature search on the ethics of trial participant selection and the practice of fairly distributing limited medical resources was conducted to identify previous literature and best practices in the area. A list of essential decision-making considerations was then designed to guide the selection of paediatric participants for haemophilia therapy trials through iterative group discussions between a diverse team of health professionals at McMaster Children's Hospital, Hamilton, ON, Canada. **Results:** Current practices in resolving this ethical issue are highly heterogenous, although there are some common themes and recommendations. The three main criteria supported by the team and the literature search for inclusion in the considerations were: medical need, need for support, and potential safety considerations for the patient. Three measures for evaluating each criterion were developed and added for consideration during the decision-making process. The role of patient selection in meeting the scientific aims of the trial was also considered. **Conclusion:** Attempting to create an equitable, systematic decision-making procedure for clinical trial participant selection involves a wide variety of competing values and ethical considerations, and discrepancies between recommendations are commonplace. The criteria presented here are intended to be used as a guideline to assist the equitable selection of paediatric patients for participation in haemophilia clinical trials with highly limited enrolment, although it may have some applicability to other areas of clinical research or therapeutic areas concerned with the allocation of scarce medical resources. Next steps should involve speaking with patients, community members and other stakeholders in order to include their perspectives.

Keywords: *Clinical decision-making, Haemophilia, Paediatric, Health equity, Research ethics*

Current haemophilia prophylaxis strategies mainly consist of frequent factor infusions to replace the missing factor, with additional on-demand treatment given as necessary during bleeding episodes [1]. However, there is currently no long-term treatment for hemophilia, and infusion therapy can be a costly, time-consuming endeavour [2]. New experimental treatments that could potentially provide life-changing benefits for patients with hemophilia, such as gene therapy, are being investigated. Although gene therapy is not yet available for paediatric patients, it is on the horizon, and other novel agents with comparable selectivity are being investigated in paediatrics. Enrolment for these trials is highly limited due to the costliness of the studies and the need to register only as many participants as are necessary to ensure statistically significant results. Consequently, participant selection is extremely competitive, and there are often many more eligible candidates for these clinical trials than there are opportunities for enrolment. It thus becomes essential for clinicians to select their subjects carefully when given the rare opportunity to register their patients in such a trial, and to have discussions about the patient selection process ahead of the arrival of new investigational therapies in paediatric patients with haemophilia.

There are already many methods in place for selecting patients for potential enrolment in trials. Strategies such as random selection, 'first come, first served', or the principal investigator using their own judgement to select participants are amongst the most common procedures for conducting subject selection. However, these strategies may also be highly subjective as there can be significant discrepancies in each investigator's judgement, their knowledge of facilitators and barriers to the patient's participation, and patient and investigator priorities when it comes to allocating treatments. Furthermore, approaches such as 'first come, first served' may not be equitable, since individuals with greater wealth, connections, or social capital may be able to access and enrol in trials earlier [3]. These enrolment decisions could have implications for the generalisability of the research findings and their ethical underpinnings. A more systematic decision-making process that considers the full scope of each research project, as well as any facilitators and barriers to participant participation, is required.

Of particular concern regarding the four ethical pillars of beneficence, non-maleficence, autonomy, and justice in medicine is the issue of equitable subject enrolment and the unfair exclusion or inclusion of certain groups when selecting participants for enrolment in clinical trials [4]. For instance, socioeconomic, linguistic, or logistical barriers may unfairly preclude a patient from participation in a competitive selection process [5,6]. It is also important to weigh up the risks and benefits of participation to the individual and their community. Including certain groups of participants may mean putting their health at needless risk, especially if they are members of a marginalised population; but excluding certain groups of participants may mean impeding generalisability and

missing out on important safety data [5,7]. Ideally, fair subject selection should take into account inclusion, opportunity, burden-sharing, and assumption of third-party risks (risks faced by non-participants in the trial, such as members of the participant's community) amongst all candidates in a holistic, rigorous way [8].

LITERATURE SEARCH

In order to identify gaps in our knowledge of equitable enrolment processes, a preliminary literature search was conducted using the Google Scholar and MEDLINE databases for information on competitive participant selection using keywords such as 'participant selection', 'competitive selection', 'fair subject selection', 'resource allocation', and 'selection bias' in combination with the term 'clinical trial' for articles published between January 1960 and July 2021. Inclusion criteria consisted of any English language article that provided trial participant selection guidelines or examined challenges in maintaining equity of opportunity when distributing limited resources, whether in the allocation of clinical trials or other therapies. Articles about clinical trial recruitment were excluded as our concern was not with increasing enrolment in trials, but rather selecting between participants who were already deemed eligible for enrolment. In our experience, recruitment has typically not been a challenge amongst paediatric haemophilia patients, and there are limited avenues for increasing enrolment within this population because certain essential qualifying criteria (such as body weight or previously untreated status) cannot be altered by clinicians.

After screening, we found 11 relevant articles (Appendix), many of which outlined guidelines for fair subject selection, but few of which had attempted to implement the recommendations and discuss the outcomes. No articles concerning enrolment in haemophilia trials were found, but two articles were identified that discussed participant selection in cystic fibrosis clinical trials with competitive enrolment [6,10]. One article specifically examined challenges in equitable subject selection for COVID-19 therapy trials [3].

The literature review revealed that current practices for formulating enrolment processes are highly heterogenous, although there are some overarching themes. Recent literature on COVID-19 therapy allocation proved to be especially helpful in our search, as the pandemic provided a prominent example of how to distribute limited medical resources amongst an extremely large group of eligible people with competing and diverse interests.

Of the strategies proposed and reviewed in the literature search, 'first come, first served' was a tactic that was generally not recommended, as it unfairly advantages those who can access or learn about treatments more quickly, and neither attempts to maximise benefits nor minimise harms with what limited resources are available [3,12,14]. Several of the articles reviewed explicitly stated the need to prioritise vulnerable patients or those with a medical need, indicating that protecting at-risk patients is a common priority [3,11-15]. However, this may not necessarily be a consideration that carries over to clinical trials, as clinical trials have scientific aims to fulfil that scenarios involving resource allocation do not. Prioritising only those with the greatest medical need for trial enrolment may therefore adversely influence the generalisability and quality of the results one can obtain from the trial – a factor that needs to be taken into consideration during the decision-making process.

Another frequent concern was the importance of reducing healthcare disparities and overcoming barriers such as personal biases or prejudices, geographic limitations, or language in equitable subject selection [3,7-12]. Amongst articles that did not limit their scope to the distribution of a particular resource or patient population, preventing the unjustified inclusion or exclusion of certain populations was a popular aim, except in cases where the participant or their community would be put at unacceptable risk, suggesting that patient safety was critical [7-9]. A small number of articles concerning resource allocation during the COVID-19 pandemic encouraged the prioritisation of participants based on 'instrumental value' to some degree – although the value of any individual is difficult to determine or translate to a clinical trial setting for a disease such as haemophilia, and invites its own ethical questions [12-14].

Regarding the major realms of disagreement, random selection was a somewhat controversial method of decision-making. While random selection was lauded for its impartiality and received positive feedback for its usage in Dobra et al.'s algorithm for patient selection in competitive cystic fibrosis trials [6], it has also been said to not meaningfully reduce morbidity or mortality, provide any economic or social benefit, or reduce health disparities [12]. In addition, many articles seem to lay out criteria or recommend selection processes that random chance is inadequate in fulfilling alone [3,8,9,12-15]. Furthermore, although a considerable number of articles examined in the literature search made an effort to take into account the conflicts

that may arise when attempting to satisfy multiple criteria during decision-making, each recommended a different order of priority [6,9,11,12,14,15]. One article did not recommend that the interplay between criteria be taken into account at all, arguing that attempting to consider such complex interactions would make the processes too inconsistent or difficult to implement, and instead suggested following a linear, rigid sequence of priority [13]. Again, we see that any effort to weigh these ethical principles against each other proves to be troublesome, providing another example of a pertinent ethical challenge that researchers face.

Lastly, in attempting to develop and implement a decision-making protocol that balances these competing priorities, four articles specifically recommended assembling a diverse team of stakeholders and using iterative deliberations to create a shared set of values and ethical principles to inform patient selection [3,6,14,15]. Of these articles, one recommended using a blinded scoring system to reduce bias and introduce a quantitative aspect to the selection process [3]; one team came to the conclusion of using randomisation [6]; one used a scoring system to develop solutions but left the relative weightings of each criterion up to individual judgement [15]; and one suggested that multiple approaches should be used and that researchers' personal ethical and clinical reasoning would be required to evaluate trade-offs between conflicting priorities [14].

Although this literature search revealed a great deal of knowledge on how clinicians may go about developing more equitable trial selection processes, there is a general dearth of information and recommendations for resolving this ethical issue, the importance of which researchers have only recently begun to acknowledge.

In light of this literature search, our objective was to develop a list of preliminary decision-making criteria to describe a more objective process for selecting paediatric patients for participation in therapeutic haemophilia trials with competitive enrolment, in hopes of making participation opportunities more equitable.

METHOD

The criteria for these considerations were developed through discussions amongst our team of interdisciplinary clinical and allied health professionals, followed by iterative sessions of revision and deliberation, drawing primarily upon the ethical foundations outlined by the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans [16].

Iterative Step 1: Assessment of medical need

Our first meeting identified medical need as one essential factor to consider in participant selection, as medical need is generally accepted as one of the most important benchmarks for clinical decision-making [15-16]. In this respect, we used standard indicators of severity in paediatric patients with haemophilia to assess this criteria, such as the effectiveness of the patient's current treatment, required frequency of infusions, and the severity and frequency of haemophilia-related complications such as breakthrough bleeding, joint damage, and previous bleeds (Table 1) [17-19]. Evaluating these factors may allow researchers to allocate the opportunity for patients to receive new therapeutic interventions through a clinical trial to those whose current treatment options may not be optimally meeting their needs. However, our team also recognises the importance of weighing this criterion carefully in light of other considerations. While medical need is important in ensuring the ethical pillar of justice and beneficence are met, enrolling only those with the greatest medical need may lead to inequitable patient selection and impede generalisability in its own respect. Clinical judgement will be required to navigate such decisions.

Table 1. Decision-making matrix to support equitable potential participant selection – Assessment of medical need

ITEM NUMBER	ITEM DESCRIPTION
1	Efficacy of current intervention (potential unmet medical need)
a	Presence of breakthrough bleeds in the last 12 months
b	Frequency of infusion in the last 12 months
c	Joint health and historical and/or current joints identified

Iterative Step 2: Assessment of potential need for support

As a result of the discussion in Step 1, other systemic barriers to participation such as the patient's potential requirements for additional support were identified. These included obstacles such as transportation to the treatment centre, challenges with at-home infusions, or the need for assistance in accessing supplies or the shipment of the investigational product (Table 2) [20,21]. Taking these accessibility barriers into account in a systematic way may assist clinicians in making equitable decisions during the selection process.

Table 2. Decision-making matrix to support equitable potential participant selection – Assessment of potential need for support

ITEM NUMBER	ITEM DESCRIPTION
2	Potential need for support
a	Challenges with transportation to site for care
b	Difficulty managing intravenous infusions of factor independently
c	Challenges with venous access in the home (home care)

Iterative Step 3: Participant safety considerations and identification of possible risk

Finally, we considered the issue of patient adherence and engagement, which is critical in minimising risk to the patient. Because the safety and efficacy of these experimental therapies are not yet known, it is imperative that the participants are able to adhere to therapeutic protocol to facilitate safety and analysis of efficacy [22]. This means researchers should consider any barriers that may affect the patient's ability to engage in the study protocol, such as their ability to attend appointments, perform infusions at home, and document infusions in their patient diary (Table 3).

Table 3. Decision-making matrix to support equitable potential participant selection – Participant safety considerations and identification of possible risk

ITEM NUMBER	ITEM DESCRIPTION
3	Safety considerations and possible barriers towards complying with care plan
a	Family ability to infuse according to current treatment plan as measured by documentation of home care infusions
b	Family ability to attend clinic review appointments as per the standard of care plan for haemophilia follow up
c	Family ability to document home care infusions in patient diary as per standard of care for haemophilia

DISCUSSION

Creating a selection process for competitive clinical trial enrolment is undoubtedly a difficult undertaking that involves balancing many diverse, competing factors. We sought to create a list of considerations that could be used as a guideline when there were many eligible candidates that could be offered the opportunity to participate in a competitive clinical trial for paediatric patients with haemophilia. Although the principles of these considerations may be applied to other situations in clinical settings where equitable resource distribution is an issue, each therapeutic area will differ, and users are therefore advised to tailor the criteria to best suit their specific requirements. Haemophilia is a unique therapeutic area in that there may be more potentially eligible patients who express interest in participation in clinical trials than there are opportunities to enrol. Larger studies in other therapeutic areas may find other methods of participant selection more appropriate to mitigate bias and ensure fair opportunity.

The criteria presented provide a potentially more objective process for facilitating equitable patient selection in clinical trials with limited enrolment availability by urging clinicians to intentionally consider factors such as medical need, systemic barriers, and patient engagement during the selection process. By developing a comprehensive list of the considerations involved in competitive participant selection, we hope that this tool will enable clinicians to recognise and discuss potential sources of bias more readily. Traditionally, factors such as language barriers or a therapeutic team's lack of cultural competence have proven to be obstacles to clinical trial recruitment. These may emerge as issues if clinicians preemptively and unjustly exclude patients on this basis without awareness of the possible biases involved. Encouraging deliberate conversations around the factors involved in enrolment processes may therefore enhance equitable decision-making [23].

In our experience, these considerations have proven to be an effective framework for discussion amongst a multidisciplinary team through encouraging a variety of professionals – including social workers, physiotherapists, nurses, and physicians – to provide insight into their areas of specialty and facilitating a more holistic decision-making process overall. However, as the criteria are still being trialled, we encourage other clinicians to modify them to meet their needs as they see fit.

In light of these criteria, our team also recognises that clinical trials serve not only a therapeutic purpose, but a scientific one. As such, one final factor to consider when selecting amongst patients is whether their participation will be conducive to the study's investigational aims. Our main concern is that the patients selected should be appropriately representative of the therapy's target population to ensure generalisability. In selecting patients who may

meet the considerations described here, a clinician may skew the trial population towards those who they believe may be more 'deserving' of the opportunity or more successful in a trial – such as those with greater medical need, or those who require less support. As such, patient selection must also take into consideration which demographics may be systematically excluded in trying to optimise these factors. It is imperative that the scientific goals of the study are assessed before considering any other criteria for competitive selection.

There are situations where these considerations may come into conflict with each other. For instance, Iterative Step 1 may lead clinicians to conclude that patients with poor adherence be recommended for trial enrolment due to their greater medical need, while Iterative Steps 2 and 3 suggest that patients with fewer support needs and greater adherence could have a greater chance of success. As evidenced by the literature search, this area of ethical consideration is rich in disagreements on how to weigh such criteria against each other. As a guideline, our team recommends weighing the considerations developed in each step equally, unless there is a need to adjust them based on the scientific aims of the study. Although this reliance on individual judgement could result in some decision-making discrepancies between each team, it permits these considerations to be flexible enough to meet a wide variety of needs. For this reason, we elected to avoid assigning any scoring system to the criteria to avoid inhibiting decision-making.

Issues involved with negotiating the intersectionality of aspects such as race and gender have not been considered here. Our team recognises the role that inherent biases and systemic barriers play in clinical decision making and initial consultations were held with equity and diversity specialists at McMaster Children's Hospital to help clarify the ways in which these circumstances may affect patient selection. Although this information was not included in our initial set of matrix criteria, future steps should involve incorporating the voices of patients and communities, as well as consultations with greater numbers of stakeholders, in order to better understand the role that social determinants of health play in influencing participant selection.

Finally, although historically we have not found enrolment to be an issue within our population of interest, we recognise that the task of increasing enrolment in clinical trials as a whole and selecting between eligible patients who are already enrolled share common ethical concepts. As such, our exclusion of articles discussing enrolment introduces limitations to our literature search. These articles could possibly provide insight into additional barriers towards trial participation or reveal patient perspectives on the burden of clinical research, and are recommended as an area of future investigation. Ultimately, we hope that these criteria serve as a starting point for stimulating team discussions around how to make the competitive clinical trial enrolment process more representative, equitable, and rigorous.

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APPENDIX

Results of literature search on the ethics of trial participant selection and the practice of fairly distributing limited medical resources

AUTHOR	RESOURCE TO BE ALLOCATED	RELEVANT FINDINGS
Jansen et al. [3]	Investigational COVID-19 therapies	• **Recommended selection methods:** Random selection or prioritising patients who are most vulnerable • 'First come, first served' may not be equitable as patients with connections may learn about and join trials earlier • Allocation method may be arrived at through stakeholder discussions • **Health inequities:** Implicit bias and structural barriers to participation should be identified and minimised, possibly with the use of a blinded scoring system
Dobra et al. [6]	Investigational cystic fibrosis treatments	• Allocation method determined through group discussions and consultations • **Recommended selection methods:** Regardless of participation in early-phase trials, patients who could give consent and met inclusion criteria were put into a random selection algorithm, then contacted in that random order until recruitment slots were filled • **Implementation and outcomes:** Regardless of outcome, participants/caregivers reported that the use of random chance was fair
Weijer [7]	N/A	• **Recommended selection methods:** Does not necessarily require resources to be evenly distributed, but that they be distributed without coercion or domination • **Health inequities:** Marginalised groups (including women, the elderly, people with a history of drug use, or people with HIV) should not be unnecessarily excluded from clinical trials if they otherwise fit
MacKay & Saylor [8]	N/A	• **Recommended selection methods:** Main factors to consider are fair inclusion of participants, fair burden-sharing and risk assumption amongst subjects, fair opportunity for a subject to participate in research that may benefit them, and fair distribution of risks to third parties and surrounding community members • **Health inequities:** Benefits and risks of the research should be distributed fairly • **Interacting priorities:** Fair inclusion is prioritised over fair opportunity and fair burden-sharing. Fair distribution of third-party risks should be prioritised over fair inclusion, fair opportunity, or fair burden-sharing, except in cases where including a subject puts them at unacceptable risk
Emanuel et al. [9]	N/A	• **Recommended selection methods:** Should mainly consider the scientific goals of the research, with the exclusion of any patient/group being scientifically or medically justified • Subjects should be selected to minimise risks and maximise benefits to individuals and to society • **Health inequities:** Those who bear the risks of the research should have access to benefits of the research, while those who are likely to benefit should share some of the risks
Strassle [10]	Investigational cystic fibrosis treatments	• **Health inequities:** In response to Dobra et al. [6], the author suggests using the national registry of patients with cystic fibrosis to select participants, as geographic proximity to a cystic fibrosis treatment centre could be a barrier to participating in a clinical trial even though many cystic fibrosis patients show a willingness and ability to travel for treatment
MacKay [11]	N/A	• **Recommended selection methods:** Participants should not be excluded or treated differently simply because they may face greater risks than others during the trial, unless their inclusion places them at undue harm or will not help facilitate the scientific goals of the study • **Interacting priorities:** Deliberately excluding those at greater risk under the principle of beneficence contradicts the principle of justice, while attempting to solely maximise good and minimise bad outcomes may lead to counterintuitive selection processes

AUTHOR	RESOURCE TO BE ALLOCATED	RELEVANT FINDINGS
Gupta & Morain [12]	COVID-19 vaccines	• **Recommended selection methods:** Prioritisation of the most vulnerable, prioritisation of those who would gain the greatest number of life-years, prioritisation of those with 'instrumental value' [12] such as essential workers, prioritisation based on random lottery, 'first come, first served', or prioritisation based on minimising outbreaks • Random lottery or 'first come, first served' is not recommended because this strategy is inequitable and unlikely to reduce morbidity, mortality, or health disparities • **Interacting priorities:** Conflicts and synergies may arise when one of the above distribution methods is chosen. Those at the intersection of any one of the above groups should be vaccinated first, with further decisions being made based on empirical data
Henn [13]	COVID-19 vaccines	• **Recommended selection methods:** The suggested ranking of priority for distribution is healthcare professionals in immediate patient care, followed by recipients of organ transplants undergoing immunosuppressive therapy, and then all other people ordered from oldest to youngest regardless of medical insurance • This order is based on the principle that "those who are most needed come first, followed by those most in need." [13] • **Interacting priorities:** Interacting priorities were not considered, as "any granularity in the criteria would render them less transparent and actionable." [13]
Rawlings et al. [14]	Scarce medical resources during the COVID-19 pandemic	• **Recommended selection methods:** Prioritising the number of lives saved or life years gained, prioritising the most vulnerable groups, prioritising instrumental personnel, or by random lottery • 'First come, first served' is not advised as it prioritises those who can access resources quickly and makes no attempt to maximise benefits • Developing a 'clinical triage team' to form an allocation framework may be advisable • **Interacting priorities:** Multiple tactics should be used, and some trade-offs may be necessary as determined by the clinician's own reasoning • Decision-making should always consider the four fundamental principles of beneficence, non-maleficence, autonomy, and justice
Guidolin et al. [15]	Medical resources, treatment, equipment, and staff during the COVID-19 pandemic	• **Suggested methods of selection:** Decision-making criteria were formed through iterative discussions with a team of diverse professionals. A semi-quantitative score-assigning method was used to evaluate possible solutions, but each criterion's comparative importance was left up to clinicians' judgement • Ethical criteria considered included the four pillars, [4] alongside medical criteria such as medical need, availability of alternative treatments, and wait times • **Implementation and outcomes:** Ethical concerns in the decision-making method or the decisions made were revised once noticed • Involving a multidisciplinary team was important in order to obtain a range of perspectives