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Title: Heterogeneity in access to clinical trials for innovative hemophilia treatments: a call for global equity

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To the Editor,

Hemophilia is a rare inherited bleeding disorder caused by deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Prophylactic replacement therapy with clotting factor concentrates remains the standard of care for individuals with severe hemophilia (1). Although this approach has substantially improved patient quality of life, important limitations persist, including inhibitor risk, the burden of frequent intravenous administration, and incomplete protection from bleeding, which may contribute to progressive joint damage (2).

Over the past decade, the therapeutic landscape has evolved. Extended half-life (EHL) concentrates, non-replacement agents, and gene therapies offer the potential for more effective and less burdensome prophylaxis (3, 4). These innovations may improve adherence, increase treatment autonomy, and reduce the physical and psychosocial impact of long-term prophylaxis (5). However, their successful integration into routine care depends not only on regulatory approval and reimbursement but also on equitable access to the clinical trials that underpin their development.

A growing body of literature has highlighted disparities in global participation in hemophilia clinical trials. Recent analyses demonstrate that trial sites remain disproportionately located in high-income countries, with limited representation of lower-income regions (6). While these observations are well recognized, an updated understanding of how such inequities manifest across trial phases and geographic settings is needed to inform strategies that promote more inclusive research.

To provide a contemporary perspective on the distribution of hemophilia clinical trials, we performed a search on ClinicalTrials.gov website (updated on 12 August 2026) and identified 66 active interventional studies (53 recruiting and 13 not-yet-recruiting) specifically involving individuals with congenital hemophilia A or B. Of the 66 studies, 8 were phase 1, 6 phase 1/2, 2 phase 2, 2 phase 2/3, 21 phase 3, and 12 phase 4 studies. Phase classification was not applicable for 15 studies. Countries were classified according to the World Bank FY2027 income classification, as low-income countries (LICs); lower-middle-income countries (LMICs); upper-middle-income countries (UMICs); and high-income countries (HICs). This analysis was based on publicly available information retrieved from ClinicalTrials.gov and did not involve direct participation of human subjects or access to identifiable personal data. Formal approval by an Institutional Review Board

or Ethics Committee and informed consent were not required. The study was conducted in accordance with the ethical and regulatory requirements applicable in Italy.

Across the 66 eligible studies, the combined registered enrollment was 4,130 participants, with a median of 30 participants per study (interquartile range, 16.3–70; range, 4–451). Industry was the lead sponsor for 35 studies (53.0%). Fifty-one studies (77.3%) evaluated a therapeutic product, whereas 15 studies (22.7%) evaluated non-pharmacological or other interventional aspects of hemophilia care.

Trial activity varied markedly across regions. Among the 60 studies for which location data were available, 654 unique listed trial sites were identified across 55 countries. Of these sites, 463 (70.8%) were located in HICs, 170 (26.0%) in UMICs, and 21 (3.2%) in LMICs. No trial sites were identified in LICs (Figure 1). The largest numbers of sites were located in the United States (n=105), China (n=98), Italy (n=44), Türkiye (n=41), Spain (n=36), the United Kingdom (n=31), Japan (n=30), and France (n=28). By contrast, LMICs representation was limited to India (n=18), Bangladesh (n=1), Egypt (n=1), and Pakistan (n=1). These findings are consistent with previous cross-sectional analyses demonstrating persistent geographic inequities in access to hemophilia drug trials (6).

Global disparities in health expenditure further contribute to unequal access. Out-of-pocket costs account for approximately 18.4% of total health spending in HICs, compared with 26.6% in UMICs and more than 40% in LMICs. Although HICs represent only 16% of the world's population, they account for more than one-third (34.9%) of diagnosed hemophilia cases and over half (54.8%) of global clotting factor use (7). In contrast, countries with the largest population shares receive a disproportionately small fraction of available factor supplies. Such imbalances may limit both clinical trial participation and the generalizability of trial outcomes.

A multilevel interplay of structural, regulatory, and patient-level barriers continues to drive inequities in access to hemophilia clinical trials. Trial access may be constrained at several stages. At the study-planning level, country and site selection by sponsors and contract research organizations may favour experienced, well-resourced centres with established research infrastructure and predictable recruitment capacity, contributing to the concentration of trials in urban tertiary institutions. At the participating-centre level, referral pathways, screening practices, patient identification, and local awareness of trial opportunities may further influence recruitment. Consequently, patients living in rural or otherwise underserved regions face substantial logistical barriers to participation.

Socioeconomic constraints also play a significant role. Travel costs, limited employment flexibility, and inadequate insurance coverage for trial-related expenses may discourage participation among individuals with disadvantaged backgrounds (8). In many LICs, the absence of specialized hemophilia treatment centres and digital health infrastructure further restricts opportunities for trial enrolment. (9)

Regulatory processes can introduce additional delays. Variability in ethics approval requirements and the limited capacity of regulatory authorities in resource-constrained settings may prolong trial initiation timelines, thereby reducing the feasibility of conducting multicentre studies in these regions.

Biological and trial design considerations may also contribute to exclusion. For example, gene therapy trials frequently exclude individuals with pre-existing antibodies to adeno-associated virus (AAV) vectors, liver dysfunction, or milder disease phenotypes (10, 11). These criteria may disproportionately affect populations in settings where comorbid conditions are more prevalent or where access to early diagnosis and prophylaxis is limited.

Persistent underrepresentation of specific demographic groups remains another important concern. Evidence suggests that women and girls, as well as certain racial and ethnic minority populations (i.e. Black and Hispanic patients), remain underrepresented in hemophilia clinical trials despite potentially distinct disease experiences and treatment needs (12). Among the 66 studies analyzed, 23 (34.8%) permitted female participation, including one study specifically focused on women and girls with hemophilia A. However, none of the female-eligible studies explicitly listed heavy menstrual bleeding, pregnancy-related bleeding, or postpartum hemorrhage among their primary or secondary outcomes. Meaningful inclusion of women and girls should therefore extend beyond eligibility to incorporate outcomes relevant to their specific bleeding and reproductive health needs. Without deliberate efforts to broaden both participation and outcome assessment, emerging therapies risk reinforcing existing health inequities.

Ethical and practical considerations in global trial design extend beyond study conduct to encompass equitable access to the benefits of research. Conducting clinical trials in lower-income settings raises complex ethical questions, as participants may contribute to the generation of evidence supporting novel therapies yet remain unable to access these treatments after trial completion because of financial or infrastructure constraints (13).

Addressing these issues requires careful consideration of post-trial policies, local capacity building, and sustainable treatment delivery models.

Clinical heterogeneity (i.e., variability in disease presentation and progression) should also be incorporated into trial design. Bleeding risk is influenced by multiple factors, including hemophilia type and severity, treatment history, inhibitor status, and lifestyle characteristics such as physical activity and treatment adherence (14). Trials that fail to capture this diversity may produce findings that are difficult to generalize to real-world populations.

Emerging strategies to improve equity in hemophilia clinical trials increasingly emphasize the integration of diversity, equity, and inclusion principles throughout the research process. Recent initiatives recommend broadening eligibility criteria, implementing decentralized and hybrid trial models, strengthening community engagement, and improving the dissemination of trial information to underserved populations. Collectively, these approaches aim to reduce barriers to participation, enhance the representativeness of enrolled populations, and ensure that the benefits of therapeutic innovation are more equitably distributed. (15)

Decentralized approaches, such as telehealth assessments, mobile hemophilia treatment services, and satellite trial sites, may help extend participation opportunities to patients in geographically remote areas(15). Providing financial and logistical support for trial participation, including coverage of travel and accommodation costs, represents another potential strategy for reducing socioeconomic barriers (4, 11). Educational initiatives targeting patients, clinicians, nurses, research coordinators, research assistants, and other participating trial staff are also needed to strengthen disease- and trial-specific knowledge, improve awareness of ongoing studies, and facilitate more equitable recruitment and retention.

International organizations such as the World Federation of Hemophilia and the International Society on Thrombosis and Haemostasis could also play an important convening and standard-setting role by bringing together patient organizations, investigators, sponsors, regulators, and policymakers. Consensus guidance could promote more equitable country and site selection, establish transparent expectations for geographic representation, support trial readiness and research-capacity development in underserved regions, and encourage planning for sustainable post-trial access to effective therapies.

Research priorities and future directions should focus on addressing the persistent knowledge gaps surrounding equitable participation in hemophilia clinical trials. Despite increasing recognition of disparities in clinical trial participation, systematic data remain limited regarding how hemophilia treatment centres worldwide engage in clinical research and the specific structural, regulatory, institutional, and patient-level barriers that constrain participation across different healthcare systems. Generating such evidence will be essential to inform targeted interventions, guide policy development, and promote more equitable access to clinical research globally. Future studies should also quantify geographic accessibility, including travel distance and travel time to participating trial centres, and determine whether these factors influence screening, enrolment, retention, protocol adherence, treatment burden, and patient-reported outcomes.

To address this need, the International Prophylaxis Study Group (IPSG) Access Expert Working Group is developing a global survey of hemophilia treatment centres. This initiative aims to generate empirical evidence on patterns of trial involvement, infrastructure capacity, and perceived barriers to participation. Such data may inform the development of scalable strategies to promote equitable access to innovative therapies.

In conclusion, substantial inequities persist in global access to hemophilia clinical trials. These disparities reflect a complex interplay of structural, socioeconomic, regulatory, and biological factors. Ensuring that emerging therapies benefit diverse patient populations will require intentional efforts to design inclusive trials, expand research capacity in underserved regions, and implement policies that support equitable participation. A coordinated international approach involving patient organizations, professional societies, investigators, industry sponsors, regulators, and policymakers, supported by contemporary evidence and sustained stakeholder engagement, is essential to achieving this goal.

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Figure 1. Global distribution of sites involved in 66 eligible active interventional studies in congenital hemophilia A and B identified in ClinicalTrials.gov as of 12 August 2026, stratified according to the World Bank FY2027 country income classification.

