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Editorial
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A Lack of Diversity, Equity, and Inclusion in Clinical Research Has Direct Impact on Patient Care

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Diversity, equity, and inclusion (DEI) in research is important. This is the case not only because it is simply the right thing to do but also because DEI fosters collaboration, empathy, and psychological safety between scientists and clinicians as well as in our attitudes to and relations with patients. Inclusion of patient samples from diverse populations is critical to ensure that the full range of biological variabilities are represented in basic and clinical research.

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One important aspect is to ensure the possibilities of all researchers to use their talents to the fullest without structural limitations. Another is the broader societal benefit. Without policies that promote DEI values in access to academic positions, research funding, and mentorship regardless of, for example, ethnicity, religion, nationality, disabilities, sexuality, and gender, the complex challenges of today's health care cannot be solved in a way that reflects the needs of the entire society in its complexity—minorities as well as majorities. There are no instant solutions, but all change starts with awareness.

The European Hematology Association (EHA) has established a DEI task force with the goal to identify and address existing barriers to DEI in research within the hematology community such as those related to gender, ethnicity, and geographical disparities. Our motivation is based on the conviction that a broad representation of committed and talented people in our community will foster stronger research, more relevant educational activities, and better career tracks/opportunities in European hematology. However, developing better care for patients with hematological diseases is what EHA stands for and is at the heart of all EHA's activities. We believe that a stronger focus on DEI values in all aspects of research will not only benefit scientists but also have a much wider positive impact on patient care. Recognizing the multiple ways that lack of DEI values in research can have direct and indirect impacts on patient care is a first critical step toward accelerating the implementation of DEI principles in our research communities. Fewer options to participate in research with inevitably greater difficulty in accessing novel therapies or diagnostic tests are clear examples of lack of inclusion from the patient perspective. Indirect impact on patient care also occurs, as the knowledge and experience gained through diverse, multicultural active clinical trial participation will not only benefit trial participants but also leave better opportunities for sharing and discussing difficult patient cases within expert networks.

UNEQUAL ACCESS TO CLINICAL TRIALS

Unequal access to clinical trials is a major obstacle to offering patients equal treatment opportunities. The median clinical development time for novel drugs is already close to 10 years.[1] Not all novel therapies are successful, but some fundamentally change the survival outcomes for patients. For example, the

use of BCL2 inhibitors in chronic lymphocytic leukemia[2] and acute myeloid leukemia[3] has led to tolerable, highly efficacious treatment regimens for patients with difficult-to-treat diseases. New classes of therapies, including chimeric antigen receptor T-cell therapy, have changed the treatment paradigm for many relapsed/refractory lymphomas completely. Patients without any previous good treatment options can now achieve long-term survival and possibly cure.[4] The development of gene therapies for patients with inherited blood disorders such as sickle cell disease can dramatically improve quality of life for patients and their families.[5,6] After pivotal studies and regulatory approval by the European Medicines Agency (EMA), health technology assessments and pricing negotiations further delay patient access to novel drugs. The median time from marketing authorization to inclusion in reimbursement lists in selected European countries is 227 days. Of note, this is for drugs that actually do get reimbursed; in reality far from all EMA approved, effective drugs eventually become available to patients in all countries.[7] During the long development phase, subsequent regulatory reviews, and final reimbursement negotiations, potentially transformative therapies will only be available to patients that have access to clinical trials (with the exception of typically limited compassionate use programs). Therefore, we should strive for a situation where patients have more equal opportunities to be considered for enrollment in trials, possibly with trial adaptations to permit wider access.

Unequal access to trial participation can be caused by several factors. The country of residence is a major determinant of trial availability. Patients with cancer from higher-income countries have more access to trials than patients from middle-income countries, with West European countries dominating the top 10 in access to clinical trials in 2015–2019.[8] Access inequalities by national income are evident for industry sponsored trials, in which innovative drugs are typically tested for the first time.[8] The number of trials registered in 2005-2019 was substantially higher, and distances to trial sites for citizens were lower in high-income countries. Although a recent cross-sectional study suggested that some lower and upper middle-income countries contribute substantially to the enrollment in global randomized clinical trials led by high-income countries, the subset of trials led by high-income countries that actively recruited in low-resource settings were more likely to be palliative intent compared with trials where enrollment was limited to high-income countries.[9] Furthermore, only 8% of global trials in oncology were led from lower and upper middle-income countries and none of the middle-income and lower middle-income countries got market access drugs to the investigated drugs within 1 year after Food and Drug Administration (FDA) approval as compared to 13% of high-income countries.[10] Thus, equity of access to novel drugs regardless of geography requires dedicated efforts by all stakeholders such as academic investigators, pharmaceutical companies, and regulatory authorities to ensure that less privileged countries are supported in development the necessary infrastructure to participate in clinical trials. As a first step, we, as academic investigators, can promote this by recommending inclusion of our experienced colleagues of less privileged countries, in and outside Europe, to pharmaceutical companies in the early stages of a clinical studies such as in steering committees and to recruitment of patients.

ADVOCATING FOR FAIR TRAVEL BUDGETS FOR PATIENTS

To prevent that long travel distances create inequity in access to novel therapies in trials, we, as investigators, need to be more aware of implementing trial support systems for patients with long travel distances, for example, when negotiation budgets and conditions in the start up phase. That is, to be more conscious of the fact that there are patients outside the immediate vicinity of the trial site for whom the trial could be relevant and will need coverage of trial expenses for patient and in some circumstances also for family members. This is particularly relevant for patients from rural areas with long travel distances to trial sites and for low-income families. For example, only 41% of patients from low-income families were willing to participate in cancer clinical trials that required more visits or travel compared to the site where regular care was provided (61% for higher-income families).[11]

WORKING TOWARD DECENTRALIZED TRIAL DESIGNS

Decentralized clinical trial designs represent opportunities for getting trials to patients at home rather than requiring the patients to travel to the trial site. This can be facilitated by collaboration between researchers at a trial site and a local medical team, supported by digital technologies. Hematology trials frequently involve drugs with significant risk of serious adverse events. Thus, a decentralized trial design will require substantial training efforts of local staff and close oversight by the investigator, who retains final responsibility for noncompliance in relation to tasks delegated to third parties at a decentralized trial site.[12] Results from recent pilot studies suggested that outpatient induction chemotherapy in acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) is feasible without compromising patient safety, provided that appropriate support systems are in place.[13,14] Pragmatic solutions like this could also be applied in clinical trials to deliver as much experimental therapy as possible near to home.

THOUGHTFUL DESIGN OF PATIENT INFORMATION AND ENCOURAGEMENT OF HEALTH LITERACY

Even when trials are available at sites, not all patients are eligible for experimental therapies. A recent US study based on data obtained from 1200 institutions found a cancer treatment trial enrollment rate of 6.3%, higher than the historically estimated <5%, but too low for those whose only hope lies in access to new therapies.[15] To our knowledge, no comparable European data are available, but there is no reasons to assume major differences. In a US study, lower-income patients had 32% lower odds of trial participation, a finding that was consistent across many patient subgroups, although proximity to trial site reduced the impact of income status.[16] Poor health literacy could also lower likelihood of trial enrollment. Informed consent forms can easily cover more than 20 pages and, despite requirements for use of layman's language, which may limit interest in trial participation for patients with low health literacy. Recommendations for simplifying informed consent documents have been provided, including substantial shortening of text parts, use of visual explanations, and removal of some legal aspects to appendices.[17] In a survey conducted in eight European countries, at least 1 in 10 respondents had insufficient health literacy and close to 50% had limited health literacy, with social gradient toward higher numbers for financially deprived, low education level, and social status.[18] Consistently, a recent systematic review found that patients' understanding of fundamental informed consent components was low for important areas such as safety issues, risks, and side effects.[19]

If patients in clinical trials do not represent the whole community, there is the risk that differences in drug metabolism, side effect profiles, and outcomes will be missed. Ethnic subgroups are most often underrepresented in clinical trials. In a US study of 3103 patients enrolled in cancer trials, Black and Hispanic patients had lower phase 1 enrollment, with odds ratios of 0.46 and 0.25, whereas Asian patients had higher enrollment with an odds ratio of 1.38. These results withstood adjustments for important confounders such as age, sex, insurance status, marital status, income, cancer type, and travel distance.[20] Informed consent forms are often only available in the dominant language of a country and ethnic minorities with limited language

proficiency will not be able to participate in trials. A focus on patient friendly recruitment material for trials may facilitate enrollment of participants with broader ethnic, educational, and socioeconomic backgrounds. In addition to patient information in more languages, better interpretation support during trial participation is a key aspects for promoting equity and removing barriers related to ethnicity.

ENCOURAGEMENT FOR FEWER EXCLUSION CRITERIA

The application of numerous inclusion/exclusion criteria in clinical trials also leads to selection of a "healthier," perhaps unrepresentative, group of patients. Fulfillment of organ function criteria, good performance status, and the absence of severe comorbidities are typical requirements, which exclude a significant proportion of cancer patients, many of whom are elderly, with comorbidities and have often undergone multiple prior therapies. In diffuse large B-cell lymphoma, patients ineligible for trial participation due to organ impairment constitute a subgroup with higher lymphoma-related mortality, suggesting that the patients left behind are in fact the ones with the highest unmet need.[21] While inclusion/exclusion criteria are applied in part to safeguard against toxicity, each individual criterion should be considered in the context of the known characteristics of experimental therapy. This, rather than the default use of long standard check lists, will limit exclusion rates and ensure better generalizability of study results to the real-world patient population where the therapies will eventually be used with less restrictions. For example, patients with human immunodeficiency virus (HIV) are often excluded from lymphoma trials, although treatment and outcomes of HIV-associated lymphomas in the era of antiretroviral therapy typically parallel those of patients without HIV in the real-world setting.[22] In a similar fashion, reduced kidney function is a reasonable exclusion criterion if renal excretion is the main route for elimination of a drug. However, when appropriate information on pharmacokinetics is available, the alternative for patients with poor organ function could be adjusted dosing, rather than patient exclusion.

PROMOTING APPROPRIATE USE OF PATIENT AND PUBLIC ENGAGEMENT

Patient engagement in the planning and execution is a key aspect of inclusiveness and oblige investigators to explain and justify the trial design and enrollment plans to patient representatives. The patient involvement roadmap provided by the European Patients' Academy (EUPATI) defines how patients can be engaged at multiple time points during the drug development process, as trained experts or as advisors.[23] Patient engagement should ideally also reflect the patient diversity—that is, patient advisory boards should have a reasonable balance in gender, educational background, socioeconomics, and ethnicity to be able to fully promote the interests of a diverse patient population.

In conclusion, there are several barriers to diverse participation in clinical trials and equity in early access to novel therapies in clinical trials. Some barriers are at the country/site level, with the largest trial sites clustered in urban areas within major academic institutions and in countries with well-developed healthcare systems. Embracing opportunities for novel trial designs with decentralized components may remove geographical barriers to some extent. Also needed are better national support systems for patients (and their families) traveling either across borders or within countries to get optimal treatment. At the study level, critical assessment of inclusion/exclusion criteria when study proposals are reviewed by authorities could facilitate inclusion of patient groups that resemble real-world patients without significant compromise on safety. Appropriate development of robust real-world data exploitation, in the era of digital medicine, is a path to exploring the current access to trial participation in Europe and identify limiting factors. Real-world data can also contribute to understanding the uptake of novel therapies across treatment sites and assess how this correlate with trial activity. However, this will require optimal quality and recording of both clinical data in interoperable formats between European countries. The development of European Health Technology Assessment and the European Health Data Space will contribute to this. However, first and foremost, research that uncovers the full extent of European inequities in access to clinical trials as well as their multiple causes and how they are addressed—including and especially those tied to residence, socioeconomics, and minority status—is warranted to fully understand the status of DEI in European research and to pave the way for removal of the key limiting factors.

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