MULTI-REGIONAL CLINICAL TRIALS
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The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Ethics of Rare Disease Research

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Introduction:

In the United States and Europe, discussions of therapies for rare diseases are often approached through the regulatory frameworks developed for orphan drugs, frameworks that hold important economic and ethical implications. The US Orphan Drug Act of 1983 defined a rare disease as one affecting fewer than 200,000 individuals, or if more prevalent, a condition for which a company is unlikely to recover the costs of newly developed therapies. The EU Orphan Regulation of 2000 defined rare diseases as life-threatening or chronically debilitating conditions affecting fewer than 5 in 10,000 individuals, or for which there is no reasonable expectation that the costs of a developed theory will be recovered, and that present an unmet medical need. Both frameworks aim to provide economic incentives to develop drugs for rare conditions by offering tax credits, fee waivers, and market exclusivity, among other incentives.

Underlying the economics of rare disease research is an ethical challenge. It consists of providing a compelling justification for why limited resources should be devoted to helping the relatively few people suffering from a rare disease, on the one hand, as opposed to addressing the health needs of the many who suffer from more common conditions, or doing more good generally, on the other. This question, which belongs to perennial debates over the ethics of health research priority setting, can be viewed through two broad, competing frameworks: utilitarianism and rights-based approaches. Utilitarianism instructs us to always bring about the greatest good for the greatest number of people, where everyone's well-being or interests count the same. Utilitarianism acknowledges that the intensity of suffering associated with a condition, and not just the number of people it afflicts, matters. However, if it turns out that more suffering can be prevented by investing in more common rather than rare diseases, that is what utilitarianism says we should do, even if it means rare diseases are not funded at all. By contrast, rights-based approaches argue for respecting individual rights even if doing so results in less overall benefit. In rights-based theories, people suffering rare diseases hold a positive right that their health needs be considered, giving rise to an

obligation to develop therapies aimed at meeting their needs, even if more overall good could be done by spending the resources elsewhere.

A second constellation of ethical questions involves considerations of privacy and confidentiality, stemming from the unique nature of rare disease populations. Small disease cohorts and distinct genetic variations make safeguarding privacy and confidentiality increasingly challenging in rare disease research. Small cohorts further increase the privacy risks, present in all cases, of whole-genome sequencing and genetic analyses, even in deidentified data sets, which may be necessary to advance care for these populations. At the same time, many rare-disease communities intentionally choose to share their genomic information, viewing data openness as aligning with their values and urgent needs to accelerate research and treatment development. Creating a tension between the obligation to safeguard privacy and to respect the patient's willingness to assume certain risks. Similarly, maintaining patient registries and sharing data without compromising patient identity remains a significant challenge, even though registries and data sharing are arguably more important for these rare populations.

Questions of study design present additional ethical complexities, given the limited number of patients with rare and ultra-rare conditions. Limited patient availability and small sample sizes may require alternative study designs to ensure that results yield valuable and generalizable knowledge. Small patient populations necessitate crafting eligibility criteria as widely as possible to improve the chances of successful recruitment and access to trial participation. On the other hand, known variation within a disease population may require more fine-grained eligibility criteria to ensure that the results are relevant. Further, the choice of controls or comparator groups in small cohorts is not always obvious or straightforward.

Presentations and Discussion:

During the introductory presentation, one member challenged the idea that utilitarian assumptions disfavor funding rare disease research, given the increasing availability of cost-effective technologies that potentially can advance rare disease therapies. This line of thought seeks to reconcile the funding of rare diseases within a utilitarian framework by emphasizing the broader scientific and societal benefits of rare disease research, while simultaneously raising questions about whether the funds allocated to rare disease research would achieve as much good if applied to more prevalent conditions. In some cases, advances brought to light by focusing on rare diseases, such as base editing, have enabled the development of therapies far beyond the original indication they were developed to treat. Whether investments of similar scope would provide the same level of overall benefit if

applied to more prevalent diseases is unclear.

Further, advances in genetics and diagnostics have allowed conditions once grouped together under a general category (e.g., lung cancer) to be defined more precisely in terms of their genetic markers or otherwise (e.g., non-small cell lung cancer with a BRAF V600E mutation). If diseases are categorized in terms of these narrower categories, many diseases may be classified as "rare" under existing guidelines. One participant pointed out that currently, approximately 50% of new drug approvals are for rare diseases, including the majority of gene-editing therapies.

Discussion compared the US and EU regulatory frameworks, as well as whether there are substantive differences in how regulatory bodies define rare diseases. One attendee wondered if there are diseases in the US that would benefit from the rare disease designation but aren't considered life-threatening or debilitating, and thus do not currently qualify for orphan designation in the US. This raised attention to the EU's broader definition, which emphasizes unmet need. Others questioned how the term "unmet needs" is operationalized and who decides when needs are or are not met.

The conversation also explored how research priorities are shaped by wealthy families and scientists with personal ties to rare diseases. While this funding has led to breakthroughs, concerns were raised about bias and priorities being shaped by individual interests rather than public health needs. Some argued that family-funded research misallocates public resources, since the career development of scientists and scientific expertise are often enabled by public funding. Others countered that the personal career choices of researchers are not typically subject to public approval and that rare diseases should not be an exception.

The discussion shifted to economic and regulatory challenges. One member emphasized that the cost of development is a crucial factor, and that using platform-driven approaches, where similar platforms are used in the delivery of therapies across rare disease indications, can make therapy development for these conditions cost-effective. It was noted that while platform-driven therapies require significant upfront investment that warrants appropriate reimbursement, once the platform is established and development costs decrease, pricing should be fair and avoid creating downstream barriers to access. In the ultra-rare disease space, the issue is an even greater paucity of commercial investment, despite possible cost-recovery. The issue of market failure may be more based on pragmatic and ethical issues, rather than strictly economic ones. Additionally, economic and regulatory definitions of disease (e.g., rare, ultra-rare) create hard cut-offs (e.g., for application to the Orphan Drug Act), below which company investments are unlikely to occur. As a result, some conditions

are essentially excluded from research and development. Members also raised concerns about potential regulatory disincentives. Specifically, inconsistencies across international jurisdictions make global clinical trials—generally a requirement for rare diseases—more difficult and expensive, further hindering research.

One speaker emphasized the need for rigorous design in both preclinical and clinical trials. The preclinical design should utilize multiple models to yield strong rationales before transitioning to human trials, while clinical trials must demonstrate safety and efficacy. However, challenges exist between scientific rigor, on the one hand, and feasibility and access, on the other. The challenges include restrictive inclusion/exclusion criteria that maximize safety at the cost of restricting access (and potentially generalizability); ethical concerns about the appropriateness of placebos and shams in rare pediatric diseases, despite their scientific rigor; and selecting meaningful and measurable endpoints. In light of the potential tensions between scientific rigor, safety, and access, the speaker encouraged us to reconsider traditional standards for preclinical evidence, acceptable risks, and informed consent, emphasizing that the distinction between the objectives of research and clinical care remains crucial for both patients and participants to understand.

One member stated that because the field is still evolving, there is no single right approach. Arguably, there will always be opportunities for generalizable learning in rare and even ultra-rare research; the challenge is deciding on assessment measures and how best to balance individualized care and the prospect of individual benefit against the obligation to learn from these studies.[1] The point was again made that technologies developed for rare diseases often inform treatments for other conditions. For example, Tay-Sachs research has offered insights into other chronic conditions associated with liver disease; however, the applicability of those lessons learned is not always understood, communicated, or applied, raising ethical questions about equity, funding, and infrastructure.

The speaker also addressed post-trial access through a Canadian case example in which a child's expensive therapy coverage was discontinued despite evidence of benefits. Due to public pressure, coverage was reinstated, highlighting ongoing access challenges and tensions between clinical benefit, health policy, and cost. Since trial criteria shape coverage decisions, questions arise about continued access and the obligations of developers and the scientific community to explore benefits beyond initial trials. It was noted that current financial models focus on the costs of intervention, development, anticipated population size, and market value, rather than on obligations for continued studies of new indications in rare

[1] The fact that there can be significant learning even in N of 1 trials should be recognized here.

diseases.

Other ethical considerations were raised regarding costs, priority setting, and resource allocation. With some therapies costing over $500,000 annually, members questioned whether payers should be a part of the decision-making paradigm alongside patients, families, and clinicians. Another ethical dilemma raised is whether to prioritize continued access for existing patients or new access for others, and what obligations developers have to participants who assumed the risks of a trial but may lack insurance coverage, limiting their continued access to a therapy after the study is complete. Relatedly, members expressed concerns about long-term affordability and sustainability challenges. Approvals of therapeutics for rare or ultra-rare diseases in high-income countries often create global inequities, as lower-income countries cannot afford access due to limited national health budgets (e.g., Myozyme in Costa Rica). Similarly, in the EU and elsewhere, some products are excluded from formularies due to high costs, despite demonstrating safety and efficacy.

One member emphasized that post-trial access requires collaboration between sponsors, investigators, and healthcare systems, and raised the unsolved problem of transitioning the sponsor's responsibility for continued access to a therapy to other parties (e.g., insurance companies, national payers, government assistance programs). While reputational pressure plays a significant role in companies' decision-making, continued access is largely governed by informal norms rather than by an ethical framework, and there is no clear regulatory guidance or widely accepted norms regarding the scope (e.g., whether, how, and for how long) of sponsor responsibilities to provide continued access to patients with rare diseases.

Another speaker shared their personal experience of surviving multiple cancers and recognizing that not everyone has equal access to life-saving medical treatments. The speaker emphasized the need to build trust through privacy protections and educating participants on the significance of sharing personal and medical information, while not sacrificing market and economic viability for scientists and businesses.

A third speaker focused on the increase in rare disease drug approvals in recent years, with about half being novel approvals for orphan conditions, attributing this success to the Orphan Drug Act of 1983. Additionally, the Orphan Drug Act has enabled factors for growth, such as advances in the way we think about rare diseases (for example, influencing the FDA to reconsider the nature and timing of confirmatory evidence as a factor for approval), as well as the development of new scientific tools (i.e., genomic medicine, patient registries, and big data).

It was highlighted that there is continued interest and momentum in rare disease research, demonstrated by the FDA's announcement on a new approval process for a subset of rare disease drugs. However, challenges in rare disease research still exist. For one, evidence generation is small in heterogeneous patient populations with variable disease progression. Sample size constraints require multinational clinical trials and coordination across multiple regulatory systems. Further, ethical issues persist in human subject protection, such as in trials involving children, where regulations restrict risk levels unless justified by the prospect of direct benefit.

The discussion that followed addressed the amount of preclinical data required before proceeding to human trials in rare diseases. Some argued that overly conservative regulatory standards may delay life-saving interventions for patients. One member suggested that the risk-benefit assessment is difficult, using the example of Vioxx, where patients made it clear that they wanted it to remain available, as it was the only medication that relieved their pain, despite the high risk of heart attack or stroke. The groups considered whether, in these cases, drugs should remain on the market with stronger warnings, leaving the decision to patients and their doctors. Others suggested conditional approval pathways or more flexible regulatory thresholds tailored to rare conditions.

The discussion shifted to the topics of participant autonomy and informed consent. Members questioned the consent information requirements, emphasizing that the information shared with participants typically focuses on what is known rather than what remains unknown. There was strong emphasis and agreement that participants' ability to understand and make value-concordant decisions should never be underestimated.

The closing discussion emphasized the importance of early and continuous engagement and communication with all stakeholders (i.e., sponsors, HCPs, patients) in the protocol design process. This highlights the need for an open and honest environment where everyone is informed about what is known versus what is unknown, which can lead to more robust discussions between researchers and potential participants, ultimately resulting in more informed decisions. Finally, there was agreement that bioethics should play a more prominent role in discussions surrounding pricing and innovation.

References:

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