MULTI-REGIONAL CLINICAL TRIALS
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How Much Risk Is Too Much? Revisiting the Ethics of Control Arms

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Introduction:

Clinical trials involving investigational therapies often require a comparison group that receives a currently available treatment and/or a placebo from which participants are unlikely to benefit. Additionally, these trials sometimes necessitate invasive and burdensome procedures, such as lumbar punctures (LPs) to obtain cerebrospinal fluid (CSF), injections, imaging, and/or biopsies for scientific reasons. In addition to the experimental arm, participants in the control arm are often subject to these procedures, as they may be needed to maintain the blind for scientific or other reasons. The risks and burdens to participants in these studies may be significant, raising difficult ethical questions about the limits to, and the justification for, research risks to people who do not stand to directly benefit from the research intervention. These issues are particularly salient in pediatric research and other studies in which individuals unable to provide informed consent for themselves are enrolled by a guardian or legally authorized representative.

U.S. institutional review boards (IRBs) are required by federal regulations to ensure that risks to research participants are minimized and justified by the benefits of research, benefits either to the participants themselves and/or from the knowledge expected to result from the research. Risks are minimized to the extent possible, after which, for the IRB to approve the research, the remaining risks must be assessed as reasonable relative to the potential benefits. In research with adults able to consent for themselves, it is generally recognized that there is no a priori limit, imposed by either the regulations or bioethical consensus, on the level of risk that may be justified in light of the benefits.[1] By contrast, in pediatric research that does not hold the prospect of direct benefit for some participants, such as, arguably, in many placebo-controlled trials, the risks to those participants may not exceed a "minor increase

[1] Miller, F. G., & Joffe, S. (2009). Limits to research risks. Journal of Medical Ethics, 35(7), 445–449. https://doi.org/10.1136/jme.2008.026062

over minimal risk."[2] Further, this "minor increase over minimal risk" standard is often used to guide the IRB assessment of whether to approve the enrollment of adults who are unable to consent for themselves in research.

In some placebo-controlled studies with invasive procedures, even minimizing risks may not reduce risks below the relevant threshold (i.e., to no more than a minor increase over minimal risk). While regulatory guidance and other advisory documents offer some guidance on interpreting this threshold, there remains disagreement over how to understand "minimal risk," a necessary first step in the relevant analyses, and then how to define a "minor increase." Notably, some prominent sources (e.g., FDA[2], CIOMS[3], SACHRP[4]) interpret "minimal risk" as being tied to the everyday risks of healthy children. An alternative would be to tie "minimal risk" to the everyday risks experienced by those in the study population, who may generally experience greater everyday risks than healthy people. The guidance from regulators that does exist is limited, but arguably appears to support the conclusion that many of these studies exceed a minor increase over minimal risk, such as, by way of example, the presence of multiple LPs accompanied by multiple episodes of procedural sedation for research-only purposes.[2]

The regulatory language puts IRBs in a difficult position, especially if they believe that the research aims to address an important or unmet need. An IRB that concludes that the risks of a pediatric study (or one that includes adults unable to consent for themselves) with no prospect of direct benefit to the control population exceed a minor increase over minimal risk, even after risks have been optimally minimized, could recommend changes to the study design, but IRBs are not generally in a position to redesign studies. Evidence that patient advocacy groups, as well as patients/caregivers themselves, support the proposed design despite its risk level further complicates the IRB assessment. If guardians and LARs, and patients themselves, support approval, deeper questions about the nature of ethics review

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[2] U.S. Food and Drug Administration. (2022). Ethical Considerations for Clinical Investigations of Medical Products Involving Children Guidance for Industry, Sponsors, and IRBs DRAFT GUIDANCE. https://www.fda.gov/media/161740/download

[3] CIOMS. (2016). International Ethical Guidelines for Health-related Research Involving Humans, Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Guideline 4. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[4] Office for Human Research Protections (OHRP). (2005). Appendix B: Recommendations regarding risk in research involving children. U.S. Department of Health and Human Services. https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2005-july-28-letter-appendix-b/index.html

and paternalism must be addressed. Under what conditions are IRBs justified in restricting research on the grounds of protecting participant populations, when those individuals themselves would be willing to accept the relevant risks and burdens after a clear-eyed, free, and informed consent process? Does the calculus change if participants are unable to consent for themselves but rely on parents, guardians, or LARs? While IRBs always have the authority to decline to permit studies to proceed, exercising that authority can undermine working relationships between IRBs and researchers and, indeed, the patient population that the IRB seeks to protect.

To illustrate these issues, the session began with speakers presenting the following case examples for reflection and discussion:

> Case 1: Antisense Oligonucleotide (ASO) Therapy for Rare Developmental Disease - A randomized, double-blind, placebo-controlled trial evaluates a new intrathecal ASO therapy in children aged 2-18 with a severe neurodevelopmental disease. The study involves multiple LPs to administer either the investigational ASO or placebo, including CSF collection in both the active and placebo arms. It does not contain an open-label extension period.
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> Case 2: Disease-Modifying Gene Therapy (GT) - A randomized, double-blind, sham-controlled trial of a one-time GT in children aged 3-18 with severe neurodevelopmental conditions. Participants receive either an intracerebroventricular (ICV) injection of the drug through a burr hole in the skull or a sham procedure. The sham procedure involves creating a small, circular hole in the skull that does not pierce the dural membrane. While no catheter is inserted, younger children require procedural sedation, which carries attendant risks.
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> Case 3: ASO Therapy for Alzheimer's Disease - A first-in-human study to assess the safety and tolerability of an investigational ASO in adults aged 50-75 with early-stage Alzheimer's disease. The trial includes a placebo control with participants in both the active and placebo arms requiring multiple LPs and CSF collections.

Presentations and Discussion:

After the introductory presentation and case-specific questions, members discussed how firsthand experience with a disease and its impact can influence patients' risk perceptions, noting that risk-benefit assessment and tolerance are highly individualized. Who, other than the patient, is empowered to decide what constitutes an acceptable risk when the disease has significant morbidity, is progressive, or is fatal? For fatal or rapidly progressive diseases, patients and families may be willing to accept greater risks for a chance to benefit from an

investigational therapy.

The group acknowledged that, historically, research ethics guidance documents have interpreted "minimal risk" to mean the level of risk experienced by healthy people in their everyday lives, rather than the relevant affected study population. However, attendees also stressed that not everyone agrees with this interpretation of "minimal risk" when applied to seriously ill populations. Patients (and caregivers of those who are seriously ill), willing to undertake additional research risks, often emphasize the importance of basing comparisons on the patient population—and their own lived experience—rather than on healthy populations. Some patients already undergoing invasive and burdensome procedures, such as LPs, as a component of clinical care, may be willing to participate in additional research or a natural history study to provide baseline data for future studies. Whether these natural history studies that involve biospecimen donation but do not involve any benefit for participants should be assessed any differently than placebo arms in randomized controlled trials is not clear.

While control arms are not generally regarded as providing the prospect of direct benefit for participants, there was a brief discussion of whether the practice of including an open-label extension (OLE) to which all participants, including those on the placebo arm, would be eligible once the double-blind period is complete, attenuated the ethical objection by ensuring that everyone had the opportunity to receive an active investigational agent. However, for some conditions (e.g., progressive disease), time to OLE may significantly alter the likelihood of benefit, as patients may deteriorate during the placebo-controlled period, become ineligible, or even die before OLE enrollment is an option. Optimally, researchers would have natural history data available before a trial begins, which would facilitate baseline comparisons and, in some cases, even eliminate the need for a placebo control. However, this is not always feasible or realistic.

The discussion shifted to methodological and design challenges. Some felt that ethical differences exist between performing LPs to collect biomarker data (or, in the placebo group, to obtain a baseline from which to measure biomarker activity) and performing LPs solely to maintain the blind. In some cases, sham procedures might be used to preserve the blind, replacing invasive procedures.

The second speaker focused on FDA guidance for pediatric studies, emphasizing that the scientific value and necessity of proposed research interventions need to be established before assessing the risks and benefits. This evaluation includes estimating how the investigational product is expected to perform and whether the study design will yield interpretable results. The speaker also stressed the need for creativity in identifying

interventions that may offer direct benefit or eliminate or reduce research risks and burdens.

The speaker referenced the 1977 National Commission report, which states that, to determine the overall acceptability of research, IRBs must evaluate the risks and benefits of protocol activities individually and collectively. While distinguishing between clinically indicated and research interventions can be challenging, the speaker emphasized that for an intervention to offer the prospect of direct benefit, the benefit must arise from the research intervention and directly benefit the participant. The research intervention must not exceed a 'minor increase over minimal risk; additional criteria for non-therapeutic interventions include that they be reasonably commensurate with the risks inherent to the child's actual or expected medical condition, and that the use of invasive research procedures be tied to aims and assessments that are likely to yield generalizable information about the disorder.

Lastly, the speaker addressed FDA's ethical framework for pediatric clinical investigational products, stating that minimal risk is assessed against the standard of a healthy child's daily life and that a minor increase over minimal risk represents a slight increase beyond that threshold; this distinction requires careful judgment. Examples of procedures often (but not always) considered no more than a minor increase over minimal risk include a muscle biopsy, a single MRI without contrast, and a single dose of investigational medical product (IMP) if there is adequate safety information to characterize the risk as not exceeding the minor increase over minimal risk threshold. The speaker also noted that in 2015, the FDA's Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) considered whether non-therapeutic procedural sedation could be deemed no more than a minor increase over minimal risk, but the committee failed to reach consensus. However, the PES did develop recommendations on when sedation may be justified, how to mitigate sedation risks, and the importance of communication and informed consent, including the necessity to disclose that sedation is not therapeutic and carries risks.

Attendees then discussed who in the research ecosystem defines benefit and risk, and how participants and their families can be empowered to make well-informed risk-benefit assessments for themselves. There was additional emphasis on the idea that historical assumptions about how to interpret or assess "minimal risk" and risk generally, including those embedded in guidance and IRB review processes, may not reflect the lived experiences of patients. One discussant, for example, noted that community feedback indicates that some families prefer LPs to finger pricks for blood draws. Related concerns were raised about the ambiguity in existing guidance, particularly regarding whether procedural non-therapeutic sedation might exceed a minor increase over minimal risk, given that sedation is so commonly used in pediatric procedures. Relatedly, the guidance's

characterization of a single LP as a minor increase over minimal risk was noted as challenging for pediatric studies, which often require at least two LPs, one at baseline and one post-dosing, posing challenges for IRB review of studies with several LPs planned for placebo arms. The discussion then shifted to IRB and FDA decision-making dynamics. Members noted that when an IRB views a study as valuable but not approvable under 21 CFR Part 50 Subpart D §50.51, §50.52, or §50.53, the IRB may refer the protocol under §50.54 for review by FDA's PAC. This process involves gathering any necessary information from the sponsor for evaluation by the PES of the PAC, which makes a recommendation to the Commissioner, an opportunity for public commentary, and a decision by the Commissioner. While this option is enshrined in the regulations and widely acknowledged, this process is rarely used.

The third speaker described a shift in patient and parent perceptions on participation in clinical research for rare, life-threatening diseases, particularly in the context of gene therapy research. Patients and families often view experimental gene therapies as potential cures rather than as studies designed to produce generalizable knowledge. This can, in turn, lead to potentially misplaced confidence that active investigational therapies will be preferable to placebo or standard of care. In the Duchenne Muscular Dystrophy (DMD) community, for example, early skepticism about genetic therapies has given way to advocacy for current access to research opportunities, even in the wake of trial-related deaths.

The speaker noted that studies requiring highly invasive procedures, such as direct intracranial administration or procedures (e.g., endoscopies) that require procedural sedation, carry risks. Recruitment to these studies is often challenging. Given that regulatory agencies prioritize clinically meaningful endpoints, they questioned the value of developing surrogate endpoints, particularly when invasive procedures are needed, and whether timelines could be shortened to minimize participant burden and risk. Lastly, the speaker emphasized that risk tolerance varies by context and between groups and individuals; participants with life-threatening diseases, for example, are often willing to accept greater risk and burden than those with less serious conditions.

The final speaker emphasized the importance of meaningful community engagement in clinical trials, noting that this requires valuing community feedback and a genuine bidirectional engagement process. Not all community engagement is equivalent; it must involve thoughtful dialogue and a willingness to incorporate community perspectives into study design. Historical examples from HIV clinical trials in the 1990s were cited as evidence that sustained engagement can significantly influence research practices. Additionally, the speaker expressed the belief that IRBs should actively listen to and incorporate patient perspectives on risk and burden whenever available.

The speaker noted that risk and benefit assessments are context-sensitive and can vary according to the study and who is assessing them. IRBs play a crucial role in assessing benefits, determining whether the study addresses the scientific question, and whether the proposed procedures and interventions are necessary. The speaker stressed that perceptions of the riskiness of different procedures vary across IRBs and institutions and are shaped by different experiences, training, and context. For example, physicians who routinely perform LPs and administer anesthesia in their usual clinical practice are likely to assess the risk of these procedures differently than clinicians who do not routinely perform them. The difference of perspective might also be true of IRBs, depending on their membership and experience.

It was acknowledged that ethical scrutiny is imperative in pediatric research, given that children are unable to provide informed consent. While parents provide permission, limits are necessary to ensure decisions align with the child's best interests. The IRB's role in these cases was described as that of a "scrupulous parent," exercising careful and meaningful judgment on behalf of the child.

The group discussion raised concerns that existing regulations do not always provide clear guidance on weighing risks and benefits, leaving IRBs to exercise judgment and resulting in variability in decisions. A 2017 example of a DMD study was raised, in which a parent's inquiry prompted a §50.54 review—illustrating how ethical concerns can arise from families rather than institutions. Some participants expressed interest in allowing FDA, in addition to the IRB, to initiate a §50.54 review earlier (e.g., during the IND pre-review process) to avoid subsequent barriers or delays.

§50.54 was discussed as a mechanism to support transparent, national-level ethical review and learning. It should not be assumed that protocols escalated to a §50.54 review are ethically questionable. Participants emphasized that IRB reviews are not transparent, whereas the §50.54 process is. However, the §50.54 process is still widely perceived as a barrier, due to perceived time delays (and potential reputational exposure), rather than a viable pathway. IRB representatives at the meeting reported that sponsors often choose to withdraw protocols rather than pursue a §50.54 review.

The role of IRBs was discussed, recognizing that they are designed not only to protect participants but also to support thoughtful ethical decision-making and promote research. However, IRBs were also seen as constrained, both by concerns about how regulators might regard their decisions and by the timing of IRB review, which often occurs too late in the clinical trial lifecycle to influence basic study design. It was agreed that ethical considerations affecting study design need to be addressed earlier, through conversations with FDA,

investigators, and communities, rather than at the point of IRB review, when redesign is rarely possible.

The discussion concluded with a focus on data, biomarkers, and information flow. Members emphasized that first-in-human and GT studies that collect high-quality pharmacodynamic biomarkers can hold great value for participants and participant communities, even if they involve invasive procedures, and that this value should not be underestimated in risk-benefit assessments. Pooled placebo data and shared biospecimen samples were identified as ways to improve interpretability and participant understanding. Across all topics, participants emphasized that the effective exercise of participant autonomy depends on access to accurate and relevant information. While no single framework was proposed, there was support for developing clear guidance to help stakeholders make better decisions in these challenging contexts.