Background

N-of-1 trials share a common feature: they are single-subject study designs with the goal of determining how an individual patient responds to treatment intervention(s). These trials can take several forms, spanning different purposes and study populations, with their own distinctive advantages and challenges.

The April 2023 Bioethics Collaborative focused on various ethical questions that arise in N-of-1 research: How do traditional research ethics principles and analyses, such as the concept of clinical equipoise and ‘social value,’ apply to N-of-1 research? How can the N-of-1 approach be generalized if each “trial” is unique to the individual? Is there a way to gain generalizable knowledge across several individual trials? How should costly N-of-1 research be prioritized against other research priorities? How do we decide, fairly and equitably, who has access to N-of-1 trials, particularly for rare or unique genetic conditions? How should we think about informed consent and make efforts to support it, given the potentially transformative nature of personalized interventions in particular?

Discussion

The meeting began with a brief presentation distinguishing several N-of-1 trial designs. In multicrossover designs, patients act as their own control, with treatment periods being varied with periods of no (or standard of care) exposure, mediated by washout periods as appropriate. Different variations on this basic model are possible (for example, participants may undergo a single treatment-washout-control cycle or several, and different elements of the study can be randomized), and endpoints are typically validated biomarkers. In addition, while this design is limited to interventions that are reversible, data from multiple participants can be aggregated to permit statistical inferences and generalizations.

The second type of N-of-1 study straddles the line between research and innovative care. The line between research and non-validated clinical practice is contested and often blurred; there
is no simple way to distinguish N-of-1 research from innovative care. This may be especially true when the interventions at issue are not FDA-regulated. These issues frequently arise in surgery and, indeed, have recently gained attention in connection with the use of 3-D printed organs to permit the standardization of certain elements of surgical practices.

The final type of N-of-1 trial involves personalized therapies for extremely rare disorders. Participants here are clinically heterogeneous and often have a mutation that is either “private” (i.e., unique to them) or shared by fewer than 30 people worldwide. Interventions are individualized (e.g., CAR-T therapies in oncology) and evaluated by comparing the individual before and after administration. On its face, these studies are not blinded, randomized, or controlled, and typically not possible to generalize or apply the results to others in straightforward ways.

The conversation began with a discussion of the distinction between the ‘population’ and the ‘individual,’ which is highly relevant for conceptualizing N-of-1 research and how it differs from more conventional designs. For example, historically, genetic diseases are categorized by reference to the gene and the symptomatic manifestation of the condition, but it is increasingly relevant to categorize genetic disorders by the specific mutation and by which they can be most powerfully treated. That is, the ability to address nucleotide base changes and edit DNA at the level of the mutation permits conditions to be grouped together at the level of the mutation. Conceptually, this fragments the population of genetic disorders into a series of N-of-1 trials and/or allows them to be grouped in different ways, to some extent upending a fixed distinction between the population and the individual, and segregating N-of-1 trials in contrast to more traditional research designs.

The discussion then gravitated to personalized therapies. The first guest speaker shared their experience with personalized N-of-1 research involving antisense oligonucleotides (ASO) and the development of Milasen, a drug created specifically to treat a unique genetic mutation in a single patient. The speaker recounted the development of Milasen, from identifying a patient with a unique genetic mutation to modeling and manufacturing an ASO targeted to the patient-specific mutation to the regulatory exchange with the FDA and ethical review by the IRB. The conversation brought to light the institutional engagement and the financial and regulatory support needed to make the intervention a success, as well as the importance of engagement, flexibility, and responsiveness by regulators. The needed levels of support here extend beyond a willingness to work through ethical and regulatory issues and into the complex logistics of drug development and manufacturing, as well as study administration and monitoring.

One prominent theme in the discussion was the question of whether the development and administration of highly personalized interventions should be conceptualized as research or innovative care. It was noted that FDA chose to regulate Milasen under the compassionate use
pathway. Further, the ethical assessment of N-of-1 trials involving personalized therapies may differ from more standard therapeutic research since, in the case of the latter, but not the former, the possibility of wider social benefit can contribute to balancing the risks with potential, but uncertain, benefits.

At the same time, participants also raised the possibility of aggregating data from numerous N-of-1 trials, if and when the treatments bear similarities to one another, which could render considerations of social value applicable. To accomplish this, disease- and domain-specific outcome measures, with emphasis on patient-reported quality of life (QOL) measures, would need to be harmonized and adopted, and in general requiring extensive collaboration. Attendees emphasized that organizations such as N=1 Collaborative and the National Institute of Neurological Disorders and Stroke URGenT Network provide a collaborative platform to pursue the formulation of best practices and facilitate data sharing. These initiatives enable researchers to pool their knowledge for conducting N-of-1 trials and to establish a standardized procedure for disease assessments, data collection, and analysis.

Throughout, participants raised questions about justice and access. The research-care distinction may bear on these issues: When thinking about who should receive personalized therapies, there may be reasons to prioritize cases from which we can learn the most. It was acknowledged that some institutions do not permit self-funded or family-funded N-of-1 initiatives. Nonetheless, ethical grey areas around access and justice persist, such as in cases where foundations connected to the family wish to fund N-of-1 studies.

In addition to the matter of which patients are selected for N-of-1 studies, questions of fairness arise about compensation for research injury. One of the unique challenges with N-of-1 trials is that the time course is often unknown, particularly with respect to the length of treatment on ASO and the time of impact of gene therapy. This uncertainty makes it difficult to determine the appropriate compensation framework for adverse events and research injuries. Typically, the investigators and the institutions are held responsible for shouldering the costs associated with adverse events that may arise during the trial, but it is unclear whether and how long such responsibility should be extended.

The second guest speaker focused on the issues raised by N-of-1 studies from the perspective of a private drug development company but stressed many of the same ethical issues and complexities. One issue raised was whether the issues encountered in personalized gene and cell therapies are genuinely novel or have wider applications in other research domains. To the extent that N-of-1 studies require longer-term follow-up than customary clinical trials, they may challenge views of industry sponsor relationships with, and obligations toward, participants.
Several topics were then discussed, from data integrity and bias in N-of-1 studies to the importance of including asymptomatic genetic carriers of mutations in research and the distinction between research and innovative care. Participants agreed that there was work to be done in this domain. Suggestions included pursuing data-sharing models and collaboration across different types of stakeholders, working toward the adoption of best practices for mitigating bias and optimizing our ability to learn from these studies, and formulating ethical and regulatory guidelines for this type of research.