About the Bioethics Collaborative
The (BC) of the Multi-Regional Clinical Trials Center of Brigham and Women’s and Harvard (MRCT Center) is a multi-stakeholder forum convened to discuss ethical challenges in multinational clinical trials. The MRCT Center prepares the topic case statement, relevant examples, and readings prior to the meetings. The BC meetings, conducted under ‘Chatham House Rule’ to encourage frank discussion, includes informal comments from topic experts as well as open discussion. Often, the topic warrants further discussion or development after the meeting.

While the MRCT Center BC meetings are usually open only to invited guests and individuals from the organizations that sponsor the forum, this session was presented in conjunction with the 2023 MRCT Center Annual Meeting and was open to the public.

Background
The MRCT Center is initiating a project on cell and gene therapies (CGTs), led by Carolyn Riley Chapman, PhD MS, Lead Investigator in the Division of Global Health Equity at Brigham and Women’s Hospital and Member of the Faculty at Harvard Medical School. In collaboration with diverse stakeholders, the project will identify and characterize the unique ethical, regulatory, and logistical challenges related to CGT research and development; we will then develop potential solutions or approaches to help address those issues.* This meeting served, in part, as a launching point for the project.

Gene therapy (GT) is a rapidly expanding field that has garnered significant attention in both the scientific and public spheres. Simply put, “gene therapy is a technique that modifies a person’s genes to treat or cure disease” by replacing a gene, inactivating a gene, or introducing a new gene.¹ Genetic material is transferred to patients in a variety of ways using different ‘vectors,’ and may include gene addition or editing, RNA therapy, or the use of genetically-

* We encourage anyone interested in the larger MRCT Center project on CGT to email MRCT@bwh.harvard.edu or crchapman@bwh.harvard.edu.
modified cells. Understandably, there is excitement about the potential for cellular products and gene therapies to transform the therapeutic landscape for many medical conditions. However, there are a number of ethical concerns in GT, some of which are common to a variety of therapies, but some of which are unique.²³

Some unique concerns about GTs relate to their potentially transformative impact on research participants.⁴ Unlike most drugs and devices, a single GT intervention cannot be “discontinued” or undone, although the effects of certain types of GT may diminish over time. In some cases, the effects of treatment may halt disease progression or even be curative, allowing the treated individual to pursue life paths that may not have otherwise been possible. The long-lasting nature of GTs also presents the need for additional safety monitoring far beyond what is typical in clinical research. Additionally, the preparation and treatment itself can be long and difficult, placing significant physical and psychosocial burdens on patients, families, and caregivers. In the research setting, these burdens are compounded by uncertainties in safety and efficacy. Further, individuals who participate in a GT clinical trial are often precluded from future clinical trials using GT and may need to forego other possible treatments for the same condition. This remains true even if the field advances over time and new therapies are offered.

Other ethical issues arising in the context of GT – for example, special considerations for vulnerable populations and informed consent⁴ – are also found in other therapeutic areas but may be heightened in the GT setting due to the complexity of the treatment and the nature of the conditions being treated. GTs often target serious and/or fatal diseases with short therapeutic windows. Many of these diseases have significant morbidity (e.g., sickle cell disease [see below]) or are rare genetic diseases (e.g., inborn errors of metabolism, neurodegenerative disorders) that largely affect children and may not have beneficial alternative therapies. The following is a summary of the core topics and questions that were discussed by the invited speakers and meeting participants during the BC.

Presentations and Discussion

**Informed consent and communication**

Supporting the ethical principle of autonomy, the goal of the informed consent process is to ensure that each research participant or their surrogate makes a voluntary decision after understanding the potential risks and benefits of participation, the nature of the trial, and their rights and responsibilities. This process is complex in the context of GT for several reasons,

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some of which are related to its transformative potential. It is critical for participants to fully understand that once the treatment is given, it cannot be discontinued or “unadministered.” Participants need to be prepared for the possibility of long-term adverse effects, as well as the reality that participation in the trial will often preclude them from receiving other GTs and treatments that may become available for their condition in the future. Some factors that complicate the informed consent process in GT trials relate to the nature of the diseases being targeted. Conditions that are relatively stable allow for a lengthy informed consent process and the option to hold off enrollment until more data are collected if desired. In progressive, irreversible conditions, however, there is an urgency to administer the therapy before the therapeutic window closes.

The experience of conducting a GT trial for sickle cell disease (SCD) was used as a compelling example of challenges with informed consent. SCD is an inherited, autosomal recessive, genetic disorder in which the hemoglobin gene, encoding the oxygen-carrying component of red blood cells, is mutated. Affected patients, generally of sub-Saharan African descent, vary in the severity of their symptoms, which include anemia, periodic and painful “sickle crises” often requiring hospitalization, an increased risk of stroke and acute chest syndrome, and a shortened life span. Medical treatment is largely supportive (e.g., pain and other medications, blood transfusions), and while a bone marrow transplant can be curative, few patients have a suitable bone marrow donor. Thus, SCD is an appropriate focus of GT and two gene therapies for SCD received FDA approval shortly before the meeting.

The presenter, an investigator and physician, described the evolution of their consent process over time, as new information became available, and their own ability to communicate the anticipated trial experience improved. For example, rather than explaining that an adverse event of the therapy is “mouth sores,” the investigator incorporated the vivid description of prior participants: mouth sores felt “like swallowing glass.” Such descriptions facilitate better understanding of events that may occur. It was suggested that industry sponsors and others develop mechanisms for collecting and sharing such first-hand accounts and information. It was also suggested that involving patients’ clinical care teams during the informed consent process might improve the experience for participants. The influence of the media on patients and families was also considered: many potential participants anticipate the benefits but not the risks, making it even more important to take the time to ensure they understand the experimental nature of the trial.

Meeting attendees also discussed communication among trial participants and between participants and patients—potential participants—who are considering enrolling in a study. On
the one hand, direct communication could help individuals during the informed consent process and provide an important source of insight during the trial. On the other hand, some expressed concern about this type of communication compromising trial integrity. The possibility of creating an online service using a third party to facilitate this communication was raised. There was recognition, however, that these interactions cannot be prevented from happening organically.

Value of patient, participant, and community engagement
Collaboration with patients, families, and disease communities is critical in clinical research. Patients and researchers have shared interests but different perspectives; each must learn from the other. A specific point of tension that was raised by one of the invited speakers is that researchers’ definitions of quality of life and what constitutes a meaningful improvement in quality of life may differ substantially from those of patients and families. Meeting attendees discussed the potential utility of conducting social science research on the GT clinical trial experience. For example, participants could be offered the chance to engage in a reflective process to discuss their experiences, results of which could help in gauging the impact of GT trials on the individual and the disease community.

One of the speakers also stressed that bidirectional communication can help to align goals and endpoints, increasing satisfaction on both sides and fostering a trusting working relationship. Additionally, patient and family perspectives can inform the clinical development and trial process. For example, there may be changes that would significantly improve the ease and comfort of participation. Bidirectional communication can also facilitate new discoveries. For example, several participants in one GT trial experienced liver complications unknown at the time to be associated with the underlying disease. As the association, illuminated by the GT trial, was disseminated through the patient community, it became clear that other patients not participating in the trial had liver-related clinical issues; liver involvement became a new focus of consideration.

Autonomy, risk tolerance, and complex decision-making
The intricacy of decisions that can occur in the context of GT research was also discussed in the context of neurodegenerative diseases. These diseases are characterized by the progressive, irreversible loss of function and ultimate death of neurons. Different diseases progress at different rates. Some, like Huntington’s Disease, are caused by a known genetic mutation. While certain symptoms may be treatable, many of these diseases cannot currently be slowed
or cured. Designing a GT clinical trial for one of these diseases – particularly if it is rapidly-progressive and causes declines in memory and cognition – is challenging. As noted above, different stakeholders will have different perspectives on its ethical analysis.

A central issue that arises in this context is risk tolerance. The best way to cure or ameliorate one of these diseases would be to intervene before irreversible changes begin; doing so, however, would require administering investigational treatment (e.g., GT) to an asymptomatic person. Individuals with known disease-causing mutations may be willing to assume significant risks for a chance at preventing the predicted clinical consequences of the disease. This raises many questions: When should human trials begin? Does the therapy need to be optimized or can an early prototype be tested if patients are willing and able to undergo the risk? How much risk is too much? Who should make the decision and what evidence is needed to make it? How can benefit be measured in a person who was asymptomatic at the time of treatment but, without treatment, would develop symptoms at some unknown future time? Symptomatic patients with late-stage disease may also be interested in participating in research. They may feel that doing so would give meaning to their death even if they would not benefit from the treatment. Should they be excluded from trials? If patients are experiencing rapid mental decline, the short window for informed consent becomes even shorter. Might there be alternative mechanisms for allowing these individuals to enroll in a trial, and are the regulations sufficiently flexible to permit some alternatives? These situations must be approached with great care, as missteps are likely to be highly visible and public trust is at stake.

One meeting participant questioned whether ethical issues with GT research are specific to the modality of treatment (GT) or to the disease (e.g., rare and serious disease). The consensus was that both of these aspects contribute to the unique ethical challenges.

**Access to GT clinical trials**

Access to clinical trials – and even to knowledge about rare diseases, the availability of trials, and potential therapies – remains a challenge. When patients are diagnosed with a rare genetic condition, patient advocacy and support communities can provide both support and information. Patients and families also consult with and rely upon one another to learn about the condition, available therapies, and ongoing trials, often through online communications. There are also geographical limitations to trial access. Some patients may be able to travel long distances to access a trial, but many do not have the financial resources to do so, raising questions about justice. While sponsors can and often do relocate participants for a trial, relocation is not without challenges and uncertainties (e.g., ancillary support for caregivers,
long-term support of the patient). Additionally, there may be a need for regulatory changes to allow not only access to experimental treatments in unique circumstances (see above) but also trial participation or other mechanisms for access to experimental treatments in unique circumstances such as the neurodegenerative diseases discussed above. Engagement of the patient and affected community, ethics review board members, regulators, clinicians, and the public are necessary to advance these considerations.

Stakeholders from all spheres of society want gene therapies to be widely available to anyone who would benefit. The reality, however, is that GT is expensive and requires significant technological capability. The Institute for Clinical and Economic Review (ICER) published a report in August 2023 concluding that GTs for SCD “would achieve common thresholds for cost-effectiveness if priced between $1.35M to $2.05M.”5 A question was asked about how the expense is funded in other countries where SCD is more prevalent, particularly those in Sub-Saharan Africa, and whether companies were considering placing trials in those locations. The speaker responded that cell-based GT is “a transplant in disguise,” and unfortunately, there are insufficient transplant-capable medical centers in many countries, so bringing GTs to those countries is not planned at present.

Safety and participant long-term follow-up
Long-term follow-up (LTFU) of participants in GT studies (and patients who have received approved GT therapies) will yield important data. The FDA requires that recipients of investigational GT products be monitored for adverse events for 5 to 15 years after administration. In their 2020 Guidance for Industry, the FDA stated that “continuing LTFU observations is often essential even after a product’s licensure.”6 Panelists highlighted the many benefits of long-term observation. While the goal of LTFU is to monitor safety, it can also offer insight into differences in efficacy across different GTs for the same disease, data on the stage of disease that GT is best administered, and understanding of the diseases being treated. While important and necessary, LTFU increases the burden on trial participants.

Conclusion and Next Steps
The December 14, 2023, meeting of the MRCT Center Bioethics Collaborative enabled discussion of many ethical issues associated with clinical trials of GTs. It served as an important grounding for the broader MRCT Center initiative on ethical, regulatory, and logistical challenges arising in the context of the clinical development of cell and gene therapies.
Meeting attendees appreciated the number of unresolved and difficult issues in GT research. All members of the GT research community—including patients, patient advocates, and families—will need to work together to define and support best practices. Observation, reflection, and communication, as experienced at the December BC, will remain critical components of making that happen.

References


