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HEALTH AND MEDICINE DIVISION

BOARD ON HEALTH SCIENCES POLICY

Exploring Novel Clinical Trial Designs for Gene-Based Therapies: A Workshop

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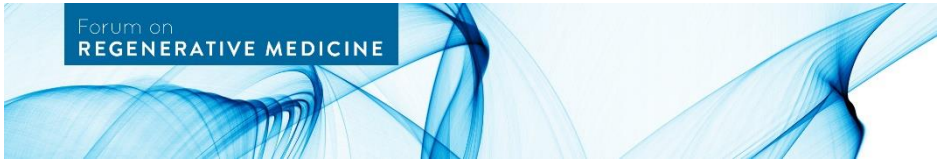
#RegenMedForum



Keynote and Session I: First in Human Gene Therapy Clinical Trials

- Natural history data can be very valuable as controls and can inform development of endpoints as well as interpretation of safety and efficacy data
- Natural history datasets can be made more robust with frequent visits, standardized measures, and an effort to collect high quality patient-level data
- When selecting a starting dose, consideration should be given to selecting a potentially *effective* dose
- When selecting the study population, it's important to identify the genetic diagnosis (if applicable) and be aware of any effects on safety or efficacy with particular genotypes
- Pediatric populations are all different (infants, children, adolescents) and exhibit differences in drug metabolism, excretion, presentation, and off-target effects
- Strong partnerships between patients, families, researchers, and clinicians is critical
- Trial design will need to take into account the unique aspects of each disease/condition including what therapies are available (if any)
- Although some early trials in small or a single patient may be performed with the aim of treatment, transparency and rigorous data collection are critically important in these cases as well

Session II: Patient Selection, Enrollment, and the Consent Process

- Patients and families should be team members or partners in the R&D process
- The informed consent process for gene therapy trials needs to be improved (e.g., abstract, processes for reconsent)
- Trust between patients, families, and those overseeing the clinical trials must be developed over a longer period of time and depends on open communication
- Earlier treatment with gene therapies often results in better patient outcomes and newborn screening can help identify infants with rare, serious conditions
- Population-level newborn screening promotes fair access to treatment, including cutting edge trials
- Certain eligibility criteria (e.g., geography, age, etc.) and the lack of a sibling protocol can be restrictive or extremely challenging for patients and families
- Clinical trial participants and their families incur very high direct and indirect costs
- Patients with SCD often make take into account the potential burdens on their families of other treatment options in decisions about undergoing gene therapy trials
- Many patients find value in having a support system available to them consisting of research nurses, physicians, and others who have gone through the trials

Session III: Developing Endpoints for Gene Therapy Clinical Trials

- Clinically meaningful, reliable, and rigorous endpoints are especially important for gene therapy trials, where trials may be smaller and treatments are irreversible
- Pompe disease and SCD are two examples of conditions that need improved clinical endpoints and predictors of disease severity
- MLMT test provides a quantifiable and reproducible measure of clinically meaningful vision performance, but it was an expensive and lengthy investment
- Defining clinical trial "stopping points" is critical when a gene therapy is not working
- Vector copy number and transduction levels can provide a predictive measurement of gene therapy
- A collaborative, national SCD registry will be an important tool to help with development of reliable clinical endpoints
- Educational materials for patients are critical to help convey that not all gene therapies are created equal
- Investigators and sponsors working on rare disorders often find themselves defining novel endpoints midway through the development process
- Investigators or researchers who want a discussion with FDA about acceptability of their endpoint in a disease can consider participating in the Drug Development Tools program, which includes CBER

Session IV: Long-Term Patient Management and Follow-Up

- Long-term follow up (LTFU) is critical to identify and mitigate delayed risks to patients who receive investigational gene therapies
- Retrospective follow up presents several challenges including loss of contact with patients and refusal to sign medical release documents; prospective approaches are preferable
- Mobile health applications may be useful tools to help with the collection of patient-reported outcomes over several years
- Need further clarity on monitoring for off target effects of genome editing and insertional mutagenesis
- Need to harmonize how LTFU data is collected in order to better understand potential risks
- Patient registries with a strong infrastructure are a valuable tool to help with post-marketing follow up studies
- Significant guidance on LTFU is available from regulatory agencies around the world, including FDA
- Additional surveillance resources can be allocated towards individuals at the highest risk

Next Steps for the Forum

- Forum on Regenerative Medicine will meet tomorrow and identify action items and opportunities to help the field move forward