Title: Gene Therapy Clinical Trials in Rare Diseases: Considerations for Observing Delayed Adverse Events Transnationally

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- **The Methodological Question Being Addressed**

How can patient recruitment and long-term follow-up safety surveillance be improved in gene therapy trials for rare disease patient populations?

- **Introduction (Aims)**

There are roughly 7,000 rare diseases, the overwhelming majority of which have no FDA-approved treatment. As 80% of rare diseases are genetic in origin, these are attractive targets for gene replacement or gene editing therapeutics. Ongoing advances in our understanding of disease mechanisms coupled with advances in the technologies of vectored gene therapy treatments have driven steep growth in the initiation of gene therapy trials in rare disease patient populations. The low prevalence and wide geographic distribution of rare disease patients poses a unique challenge to trial enrollment, as it is not always possible to open a clinical research site in every country that might be needed to achieve statistical power. Cross-Border Enrollment, wherein a patient enrolls in a clinical trial located at a site outside their country of residence, is an effective solution to this dilemma. This solution, however, is at odds with the regulatory requirement for the long-term follow up of patients participating in gene therapy trials. It is neither realistic nor feasible to support several years of international travel required for patient safety surveillance in these studies and remote data collection across geographical location would drastically reduce burden on participants and sites.

- **Methods**

Just as wearable devices are changing the way we collect data from study participants remotely, technology can also be employed to support virtual visits and communication amongst remote teams to ensure proper medical oversight and regulatory-compliant data collection in the transnational context. To accomplish this long-term and log-distance follow up, we are using a device-agnostic mobile phone platform developed to support remote data collection and enable virtual clinic visits.

- **Results**

We are remotely collecting long-term follow up data from international pediatric patients and caregivers who are participating in a rare disease gene therapy 15-year registry (n=50) collecting safety and efficacy data, including adverse events (AEs)/serious adverse events (SAEs), biometrics, and quality of life electronic Patient Reported Outcome (ePRO).

- **Conclusions**

Data collection is ongoing, using a unified global and mobile platform fully translated to the native languages of all home countries represented in this collection of trials. In the rare disease space, clinical drug development is moving away from traditional approaches that rely on patients to travel long distances to clinical sites and toward a more patient-focused paradigm. This new paradigm is especially suited to studies in patients with rare diseases; these studies target small populations of geographically dispersed patients who are rarely located near academic medical centers or key treatment centers. By bringing trials to patients, instead of requiring patients to travel to sites, we can alleviate a primary burden of clinical trial participation and democratize clinical trial access.

- **Disclosures:**

The authors report no conflicts of interest for this work.