Alliance for Regenerative Medicine

11 January 2021

Dear Dr. Millett:

Thank you for inviting us to contribute once again to the important work of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory and reimbursement initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market have demonstrated profound, durable and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing regenerative medicines and advanced therapies. In its 11-year history, ARM has become the global voice of the sector, representing the interests of 370+ members worldwide, including small and large companies, academic research institutions, major medical centers and patient groups.

Following on our previous submission, ARM wishes to reiterate some of our key points and to respond to the WHO's request for further information on select scenarios. We also wish to emphasize that ARM and 13 therapeutic developer members who are part of ARM's Gene Editing Task Force have signed a gene editing statement of principles. ARM and its Gene Editing Task Force endorse the investigation of therapeutic applications of somatic cell gene editing, and call for the evolution of national and regional regulatory frameworks to govern the development of somatic cell gene editing techniques. However, we also believe that germline gene editing is currently inappropriate in human clinical settings due to unresolved ethical, legal, and safety considerations. We therefore welcome the discussion around WHO's scenarios for somatic cell gene editing. Regarding the heritable gene editing scenarios, we simply respond that we do not currently support the use of this approach in human clinical settings.

A few other points we wish to highlight:

In some countries and regions, (e.g., the US and EU), effective governance methods (i.e., regulations) are already in place. The perceived benefit of additional regulations must be weighed against the risk of hampering innovation and slowing down availability of life saving therapies.

We agree with the concerns expressed about rogue clinics offering direct-to-consumer treatments. We believe in the importance of strong regulatory oversight and we support enforcement actions taken against unregulated clinics, as highlighted on our website.

One critical concept that seems to be missing from the "values" described in the WHO governance document is a discussion of informed consent. This would most appropriately fit under the principle of "Respect for individual dignity." In general, the document would benefit from clearer and more forceful language on the importance of informed consent. This "value" would apply to most or all of the identified scenarios.

Response to scenarios 1-3

1. Clinical Trials Involving Somatic Human Genome Editing for Sickle Cell Disease

   The important issues in this scenario are related to patient access, social justice, and the existence (or non-existence) of an appropriate regulatory framework in West Africa. This is a particularly relevant example since somatic cell genome editing does have the potential to provide durable relief to patients with sickle cell disease. As the voice of the global cell and gene therapy sector, ARM requires all members to subscribe to a code of conduct. This code states that patient populations who take part in a given clinical trial should also receive access to that therapy post-approval. Additionally, resources must be made available to treat patients in the control arm with the appropriate standard of care.

   With respect to governance measures, an effective regulatory framework, such as those present in the US and EU, would in all likelihood not allow clinical data from this scenario (as described here) to be used in a regulatory submission for product approval.

2. Clinical Trials Involving Somatic Human Genome Editing Research for Huntington's Disease

   This is another highly relevant example. Many of the benefits of somatic cell gene therapies can and should be measured over the patient's entire lifetime because a defining advantage of such therapies is that they are potentially curative, or at least durable with few doses. However, in the interest of providing timely access to patients with few treatment options, regulatory bodies should consider appropriate surrogate endpoints when evaluating the durability and performance of a gene editing therapy in the necessarily compressed timeframe of clinical trials. The US FDA, for example, recognizes the need for properly validated surrogate endpoints and has included references to such endpoints in regulatory guidance documents. When surrogate endpoint measurements indicate a case for approval, it is important that

measures are put in place to facilitate long-term follow up and confirmation of durability.

Governance measures (e.g., regulations), should require a plan for long-term follow up as a condition of approval, and provide a mechanism for withdrawing approval if the plan is not followed.

3. Somatic Human Genome Editing and Unscrupulous Entrepreneurs and Clinics

Based on the current prevalence of clinics promoting unproven cellular therapies without approval from appropriate regulatory bodies, we can predict that this scenario is likely to become more widespread. The bad actors in this scenario represent not only a threat to vulnerable patients, but also to a well-regulated ecosystem of researchers and developers whose ethical pursuit of pathbreaking treatments would be jeopardized.

With respect to governance measures, we support voluntary actions taken by platforms to prohibit the advertising of unproven therapies, such as the policy that Google put in place in September of 2019. All ARM members sign a code of conduct agreeing never to promote unproven therapies. We support efforts by professional organizations such as the International Society of Cell & Gene Therapy (ISCT) and International Society for Stem Cell Research (ISSCR) to identify and expose unscrupulous clinics. Additionally, we support the mechanisms used by leading regulatory bodies such as the US FDA to investigate and penalize unscrupulous actors.

Sunshine is the best disinfectant for bad actors. Collaboration and communication among stakeholders are critical to ensuring that the public is well informed about these practices. In many cases, local and regional enforcement mechanisms are already in place, but sufficient resources must be provided to facilitate enforcement. A whistleblowing mechanism may be appropriate, but should be put in place with great care, allowing for an appropriate appeal process to prevent misuse.