Alliance for Regenerative Medicine

February 2, 2024

VIA Electronic Submission to: regulations.gov

Tiana Korley
Office of Inspector General
Department of Health and Human Services
Attention: OIG-1123-N, Room 5628, Cohen Building
330 Independence Avenue SW
Washington, DC 20201

RE: Solicitation of Proposals for New and Modified Safe Harbors and Special Fraud Alerts [OIG–1123–N]

Dear Ms. Korley:

The Alliance for Regenerative Medicine ("ARM") appreciates the opportunity to provide comments in response to the solicitation by the Office of Inspector General ("OIG") for proposals and recommendations for developing new, or modifying existing, safe harbor provisions under the Federal Anti-Kickback Statute, Section 1128B(b) of the Social Security Act (the "AKS").

ARM is the leading international advocacy organization championing the benefits of engineered cell and gene therapies ("CGTs") for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis. We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

As outlined below, we recommend that OIG adopt two new safe harbors to permit certain arrangements that seek to overcome significant barriers to access for patients seeking cell and gene therapies: (1) the significant expense of travel and similar expenses to specialized facilities where CGTs can be administered, and (2) the loss of fertility associated with the administration of certain CGTs.

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Background

CGTs hold enormous promise for patients with some of the most serious and historically difficult-to-treat diseases, many of whom are members of under-served and vulnerable populations. As of January 2024, there are nearly 1,000 CGT clinical trials ongoing in the US and nearly 1,900 globally to test the next generation of therapies targeting dozens of indications, including rare monogenetic diseases, oncology, cardiovascular, central nervous system, musculoskeletal, metabolic disorders, ophthalmological disorders, and more.[1]

To date, the Food and Drug Administration (FDA) has approved ten gene therapies for rare genetic diseases and six CAR-T cell therapies for various blood cancer indications. As the promise of CGTs continues to come into focus, the pipeline for both rare and widely prevalent diseases is accelerating. In the past year, therapies for Duchenne muscular dystrophy and hemophilia A, as well as a cell therapy for type 1 diabetes have recently received regulatory approval, as have two gene therapies for sickle cell disease (SCD)—a debilitating disease that overwhelmingly affects people of African descent.[2]

These advances have significant implications not only for patients but also for the Federal health care programs that serve them – as just one example, Medicaid covered nearly 40% of emergency department visits and 50% of hospitalizations for its SCD beneficiaries in 2017,[3] representing a significant cost to both the state and Federal governments. By contrast, because CGTs can offer potentially curative and durable therapies, they have the potential to eliminate or replace the direct cost of chronic care and avert costs associated with downstream complications of diseases progression.[4]

While CGTs offer great promise, and are often administered only once, they are complex to manufacture and administer, involving a number of steps that can take several months. First, as individualized treatments, patients must satisfy certain eligibility criteria, which may involve genetic testing. Then, the patient's cells must be harvested, processed, purified, and then used to create the cell or gene therapy, which is subject to certain quality-control procedures. The patient then receives pre-conditioning treatments to prepare their immune system for administration, and the therapy is then infused at a specialized treatment center where ongoing monitoring occurs. Various consultations are also required in preparation for the administration of a CGT as clinicians ensure throughout the process that a patient remains the

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[1] See Sector Snapshot, Alliance for Regenerative Medicine, Dec. 2023, available at*:* alliancerm.org/wp-content/uploads/2024/01/20231220_Sector-Snapshot-Outline-Fall-2023_V2.pdf.

[2] *See* Data & Statistics on Sickle Cell Disease, Centers for Disease Control and Prevention, July 2023, *available at*: https://www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=SCD%20affects%20approximately%20100%2C000%20A.

[3] *See* Centers for Medicare and Medicaid Services. Sickle Cell Disease Report. March 2023. *Available at:* https://www.medicaid.gov/sites/default/files/2023-03/scd-rpt-mar-2023.pdf

[4] *See, e.g.,* Curative Regenerative Medicines: Preparing Health Care Systems for the Coming Wave, Alliance for Regenerative Medicine, November 2016, *available at*: https://alliancerm.org/wpcontent/uploads/2018/04/IN_VIVO_ARM_WhitePaper_CurativeRegenMed.pdf; Regenerative Medicine is Here: New Payment Models Key to Patient Access, Alliance for Regenerative Medicine, August 2018, *available at*: https://alliancerm.org/wp-content/uploads/2018/07/ARM_WhitePaper3_IV1807_LRS.pdf.

most appropriate candidate. This may commence the initial requirement to travel to a treatment center, followed by traveling for the pre-conditioning treatments then again for administration.

Given the complexity of this process, the potential for CGTs to successfully improve care for patients and reduce the cost of chronic care for Federal health care programs ultimately depends upon reducing barriers to access. These barriers must themselves be understood within the context of the diagnostic odyssey that patients with rare diseases face. Some patients receive incomplete or inconclusive screening results which affects their rare disease diagnosis and may never reach the first step of the multi-step process explained above. Of those who are diagnosed – often only after multiple primary care and specialist visits – still many are not made aware of potential CGT treatments that have a durable, potentially curative effect on their condition. Therefore, when discussing access barriers for patients, it is critical to recognize that those patients who are in a position to seek CGT treatment are a subset of the overall population of individuals living with rare diseases. Additional concerns related to access – such as issues with cross-state credentialing for Medicaid providers and inadequate payment models – have policy solutions outside the purview of OIG and the AKS. However, clear regulatory guidance from OIG can provide the certainty needed for CGT biotechnology companies, providers, and others to address common barriers to access. Further, we encourage OIG to coordinate with the Centers for Medicare and Medicaid Services and other Federal agencies as appropriate to address these additional barriers.

As the OIG has repeatedly emphasized, the AKS may be violated where one purpose of remuneration provided to patients is to induce referrals for items or services reimbursable by a Federal health care program. However, OIG has likewise explained that certain remuneration to patients may serve the critical function of promoting access to care. Indeed, such arrangements may be permissible where the remuneration provided supports critical access, does not interfere with clinical decision-making, does not lead to over-utilization or inappropriate utilization, and does not raise safety or quality concerns.[5] Using this approach, we believe the two proposed safe harbors set forth below facilitate common-sense, much-needed assistance to help patients to access CGTs in a manner consistent with the Anti-Kickback Statute's guardrails. We discuss each of the proposed safe harbors, in turn.

Proposed Safe Harbor for Travel, Lodging, and Associated Expenses Incurred While Receiving Treatment at Specialized Treatment Facilities

ARM first recommends that the OIG establish a safe harbor for payments to certain patients for travel, lodging, and associated expenses incurred in receiving CGT treatment at specialized treatment facilities.[6] Specifically, OIG should establish a new safe harbor to permit a CGT

[5] *See, e.g.,* Advisory Opinion No. 20-09, OIG, December 28, 2020, *available at*: https://oig.hhs.gov/documents/advisory-opinions/772/AO-20-09.pdf

[6] For purposes of this request, we are defining a "specialized treatment facility" as a facility that requests and agrees to become a treatment center for the administration of the drug, meets certain objective criteria established by the CGT biotechnology company in accordance with the company's regulatory submissions to the FDA, and completes the company's training on the drug and its administration.

biotechnology company or other entity to provide payments for travel, lodging, and associated expenses in the following circumstances:

- The patient seeks initial visits to prepare for and the actual administration of a CGT treatment in a context in which the FDA or other appropriate considerations (as further discussed below) limit the available network of facilities at which the treatment can be administered, such as to a network of facilities certified to administer a specific CGT treatment.
- The patient or his or her caregiver demonstrate financial need in association with lodging, travel, and similar costs to access the most appropriate specialized treatment facility.
- Payment is limited to suitable lodging, travel, and associated costs that permit the patient or his or her caregiver to stay comfortably within a reasonable distance of the facility administering the CGT treatment.
- With respect to lodging in specific, the patient or caregiver cannot otherwise be lodged at the facility at which the patient is receiving the treatment.
- The patient or caregiver does not have insurance or similar assistance that can be applied to travel, lodging, and associated costs for CGT treatment.

The proposed safe harbor is justified by the on-the-ground realities of administering CGT treatments. It is common for the FDA in approving CGTs to require risk evaluation and mitigation strategies ("REMS") as well as elements to assure safe use ("ETASU") in the form of requirements that hospitals and clinics that provide CGTs be specially certified.[7] Understandably, these requirements are intended to ensure safe administration of CGTs to patients but have the practical effect of restricting the network of providers at which CGTs are available. This results in patients being required to travel significant distances to reach a certified facility. In addition, as further discussed in the Advisory Opinions detailed below, CGT administration frequently requires that a patient either make multiple visits to a facility, or remain at a facility for multiple days at a time (sometimes to receive the treatment and sometimes also to undergo post-treatment monitoring), or both.

[7] *See, e.g.,* FDA Approves First Cell-Based Gene Therapy for Adult Patients with Relapsed or Refractory MCL, FDA, July 24, 2020, *available at*: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-relapsed-or-refractory-mcl#:~:text=Because%20of%20the%20risk%20of,CAR%2DT%20therapy%2C%20Yescarta; FDA Approval Brings First Gene Therapy to the United States, FDA, August 30, 2017, *available at*: https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states; FDA Approves New Treatment for Adults with Relapsed or Refractory Large-B-Cell Lymphoma, FDA, February 5, 2021, *available at*: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-relapsed-or-refractory-large-b-cell-lymphoma.

The proposed safe harbor is highly consistent with guidance the OIG has already issued in this context in the form of AO 20-02[8] and AO 20-09,[9] both of which involved payments for travel, lodging, and associated expenses for patients to undergo leukapheresis, drug administration, and monitoring at facilities that were required to be specially certified under the FDA's REMS/ETASU framework. As is common in the case of CGTs, the patients at issue in AO 20-02 and AO 20-09 had to make one trip to a specialized treatment facility to undergo leukapheresis, and then later make a second trip for administration and monitoring.

The OIG concluded that it would not impose administrative sanctions for these arrangements, relying on several reasons:

- The arrangements were particularly aimed at "help[ing] indigent and rural patients travel and stay in proximity" to a facility certified to administer the treatment they required, who would otherwise be "disproportionately impacted by significant health risks or even death if they cannot travel."[10]
- The arrangements were intended to permit patients to receive treatment in a manner that "enable[d] physicians to meet the FDA requirements in the Drug's prescribing information and to mitigate patient harm from potentially lethal Drug side effects."[11]
- "Under the REMS with ETASU imposed by the FDA, only Centers that meet all REMS with ETASU requirements […] may administer the Drug; therefore, the number of Centers that can administer the Drug is limited."[12]
- The treatments were "a one-time, potentially curative treatment" that did not pose a risk of inducing the repeated ordering of the treatment and payment by a Federal health care program.[13]
- The payments were limited to patients living a significant distance from a certified facility who could not be lodged at that facility (or who had other assistance available to pay for the lodging).[14]

Our recommended safe harbor is thus consistent with the OIG's existing guidance. Creating a safe harbor that addresses the facts common to CGT treatments can provide greater certainty to biotechnology companies and other entities seeking to reduce barriers, as well as obviate the need for the OIG to issue advisory opinions on factual scenarios driven by the common core of practical realities of CGT treatments. Moreover, the safeguards discussed above will appropriately limit the safe harbor to arrangements aimed at ensuring that out-of-pocket incidental costs associated with the highly specific CGT treatment infrastructure do not create a

[8] *See* Notice of Modification of Advisory Opinion 20-02, OIG, May 26, 2022, *available at*: https://oig.hhs.gov/documents/advisory-opinions/1035/Modification-AO-20-02.pdf.
[9] *See* Advisory Opinion No. 20-09, OIG, December 28, 2020, *available at*: https://oig.hhs.gov/documents/advisory-opinions/772/AO-20-09.pdf.
[10] AO 20-09, p. 9.
[11] AO 20-09, p. 9-10.
[12] AO 20-09, p. 10.
[13] AO 20-09, p. 10-11.
[14] *See* AO 20-09, p. 11.

barrier to access. As the OIG has already observed in this context, patients generally undergo CGTs for serious conditions for which curative, durable treatments are not otherwise available, and receive treatment within a very limited network. These facts mitigate the risk that payment assistance for travel, lodging, and associated costs would act either cause over-utilization or steering to particular providers or therapies.

Proposed Safe Harbor for Fertility Preservation for CGT Patients

Prior to the infusion of CGTs, conditioning agents are used to remove diseased stem cells this then allows the treatment to stimulate the formation of healthy stem cells. While both the underlying conditions CGTs treat and current standard of care are known to impact fertility, conditioning agents utilized in CGT approaches do have the potential to result in permanent sterility. As such, ARM next recommends that the OIG establish a safe harbor for payments to certain patients for fertility preservation. Specifically, the safe harbor should permit a CGT biotechnology company or other entity to make payments for fertility preservation under the following circumstances:

- The patient receives a CGT treatment, the administration of which is known to have a significant impact on fertility, such as in the case of recently approved CGTs for SCD.
- The patient receives a fertility preservation treatment that is specifically intended to preserve fertility for the future – such as embryo or sperm cryopreservation – as opposed to treat other current fertility problems or utilize existing cryo-preserved embryos or sperm.
- Payments would be limited to patients (1) demonstrating financial need; and (2) who otherwise lack insurance or other assistance for fertility preservation.

Addressing fertility risks is critical to ensuring access to CGTs for vulnerable populations because many treatment processes that carry infertility risks are also those addressed to conditions from which vulnerable populations suffer disproportionately. Today, a patchwork of coverage for fertility preservation across states and insurers leads to uncertainty and inequities in access and care. As of September 2023, only 15 states require coverage for fertility preservation for medically-induced infertility and only two states – New York and Illinois -- currently require that these costs are covered by Medicaid, exacerbating an already gaping health inequity for patients who do not have the financial means to pursue these benefits on their own.[15]

The NIH has noted that infertility "is a high-risk and long-term side effect associated with […] gene therapy approaches to sickle cell disease," and that infertility "is a common reason people of reproductive age give for not pursuing these therapies,"[16] just as other researchers have noted that "inequitable access to fertility preservation for girls and women with [sickle cell

[15] *See* Resolve: The National Infertility Association. Insurance Coverage by State, 2024 *available at:* https://resolve.org/learn/financial-resources-for-family-building/insurance-coverage/insurance-coverage-by-state/

[16] *See, e.g.,* NIH researchers work to preserve fertility for people undergoing gene therapy, NIH, Oct. 2023, *available at*: https://www.nih.gov/news-events/news-releases/nih-researchers-work-preserve-fertility-people-undergoing-gene-therapy.

disease] […] is a meaningful barrier to optimizing [sickle cell disease] care."[17] In one survey of adult SCD patients considering an experimental treatment, about two-thirds of respondents were willing to accept a risk of mortality from the procedure, while only half were willing to run the risk of long-term infertility.[18] Fertility preservation is also important to the long-term well-being of CGT patients, as studies have shown that even individuals receiving life-saving treatment commonly experience regret and depression as a result of treatment processes that permanently impair fertility.[19]

Although fertility preservation, unlike travel and lodging payments for CGTs, is not currently the subject of OIG guidance in the form of advisory opinions, many of the principles enunciated in the OIG's advisory opinions on CGTs are likewise applicable here:

- As with travel and lodging, costs associated with fertility preservation are a serious barrier to patient access that can be overcome with targeted financial assistance.[20]
- CGTs impacting fertility can offer "one-time, potentially curative treatment" that does not induce further "purchasing [of] the drug when it would be payable by a Federal health care program."[21]
- Assistance would be limited to patients with financial need and who did not otherwise have coverage for fertility preservation through other insurance or assistance.[22]

Moreover, fertility preservation can help to serve the AKS' ultimate goal of safeguarding the public fisc and, particularly, the financial soundness of Federal health care programs. CGTs target some of the most expensive-to-treat chronic conditions, including SCD. As noted above, Medicaid is believed to cover the majority of emergency department visits and hospitalizations associated with SCD, over a patient's non-elderly lifetime, are estimated to average around $1.7 million per patient.[23] Now that CGT therapies exist in this therapeutic area, these chronic costs

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[17] *See* Pecker L et al., Knowledge gaps in reproductive and sexual health in girls and women with sickle cell disease, Br J. Haematol., Sep. 2021; 194(6), *available at*: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8448913/.

[18] *See* Chakrabarti S et al., A survey on patient perception of reduced-intensity transplantation in adults with sickle cell disease, Bone Marrow Transplantation, 2007; 39, *available at*: https://www.nature.com/articles/1705622.epdf?sharing_token=kW4SHXiXrHTGzXNlyn66htRgN0jAjWel9jnR3ZoTv0N_rUlkDixUVXtrzI1dQiQSFK22Kgxzx-xfJJ4kYcpTlyfF7pF_hiizwKUDy7bztHh0t3WNvtAjaNG_9J37MUi8vHNCbk5OJ12ZuCxwBVVKEx3_4dzcEi4QSBMLs4CetCRUNJPAP1EcRXTVGNqzZoKLDlDu9Iv98TCZ994TYR3ELA%3D%3D&tracking_referrer=www.statnews.com.

[19] *See, e.g.*, Loren, A et al., Fertility preservation in patients with hematologic malignancies and recipients of hematopoietic cell transplants, Blood, 2019; 134(9), *available at*: https://www.sciencedirect.com/science/article/pii/S0006497120723256?ref=pdf_download&fr=RR-2&rr=8377b10abed84cf5.

[20] AO 20-09, p. 9.

[21] AO 20-09, p. 10-11.

[22] A0 20-09, p. 11.

[23] *See* Johnson K et al., Lifetime medical costs attributable to sickle cell disease among nonelderly individuals with commercial insurance, Blood Adv, Feb. 2023; 7(3), *available at*: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9898623/. Although this study was based on commercial insurance data, the study notes that the previously-accepted estimate of around $1.2 million was based on a nearly-twenty year old study of a single state's Medicaid program; thus, although the data is somewhat incomplete,

can be avoided. Removing barriers to Medicaid patient's receipt of durable CGT therapies for the treatment of SCD therefore has the potential to generate savings for the Medicaid program.

Conclusion

ARM proposes that the above-described safe harbors can provide regulatory clarity as to arrangements addressed to common barriers to accessing CGTs. CGTs differ in kind from other types of medical treatment and those differences justify clear regulatory guidance that will enable patients, especially patients in underserved populations, to benefit from innovations in regenerative medicine. CGTs also represent the future of medicine, necessitating a congruent regulatory structure to both encourage uptake and propel innovation.

We thank you for your consideration of these comments, and we look forward to continuing engagement with the OIG and other stakeholders to achieve better outcomes for patients with complex health conditions, for some of whom CGTs may be the only treatment option and have the potential to yield savings for Federal health care programs.

Sincerely,

Erica Cischke, MPH
Vice President, Government Affairs

it is plain that, whichever estimate is used, the chronic care costs of treating sickle cell disease represent an enormous financial burden to Federal health care programs.