



September 2, 2025

The Honorable Bill Cassidy
Chair
Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, DC 20510

Dear Chair Cassidy:

The TRANSPLANT Act of 2021 requires the Secretary of the Department of Health and Human Services (HHS), in consultation with the Director of the National Institutes of Health (NIH), the Commissioner of the Food and Drug Administration (FDA), the Administrator of the Health Resources and Services Administration (HRSA), the Advisory Council, and other stakeholders, where appropriate given relevant expertise, to conduct a review on the appropriateness of adult stem cells and birthing tissues as new types of therapies for the C.W. Bill Young Cell Transplantation Program (CWBYCTP). The agencies are required to submit a report with recommendations based on the review to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives.

Based on the review of the state of science, HHS makes the following recommendations:

1. The proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that: The CWBYCTP should include only those adult stem cell and birthing tissue products, including those with new uses outside of hematologic or immunologic reconstitution, that:
 - a) are utilized as treatments for serious or life-threatening conditions,
 - b) require donor matching if appropriate, and
 - c) have been approved by FDA as safe, pure and potent or safe and effective, or if FDA approval is not required, through adoption as a standard of care.
2. Based on the criteria above, the inclusion in the CWBYCTP of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time.
3. Based on the criteria above, a modified umbilical cord blood product, omidubicel-only (Omisirge, Gamida Cell Ltd.), approved by the FDA in April 2023, for use in hematologic and immunologic reconstitution, meets the proposed criteria for inclusion in the CWBYCTP because it has been approved by the FDA, it is indicated for treatment for serious or life-threatening conditions, and it requires donor matching for the treatment of an individual patient.
4. As the science advances and new classes of cell-based products are developed that meet regulatory approval standards for safety and efficacy, it may be appropriate to include such

products in the CWBYCTP. The recently approved mesenchymal stromal cell product remestemcel-L-rknd, however, does not meet the criteria for inclusion into the CWBYCTP because it does not require donor matching. Reevaluation by HRSA, NIH, and FDA (in conjunction with appropriate expert consultation) of the status of adult stem cells and birthing tissues for potential inclusion in the CWBYCTP continues to be recommended on a periodic basis (every two to three years or as needed).

Sincerely,

A handwritten signature in black ink, appearing to read "Gary Andres". The signature is fluid and cursive, with the first name "Gary" being more prominent than the last name "Andres".

Gary Andres
Assistant Secretary for Legislation

Enclosure



September 2, 2025

The Honorable Brett Guthrie
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chair Guthrie:

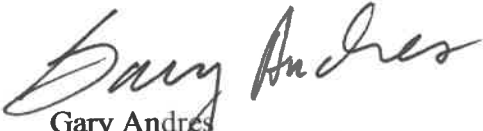
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Sincerely,



Gary Andres
Assistant Secretary for Legislation

Enclosure



September 2, 2025

The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Representative Pallone:

The TRANSPLANT Act of 2021 requires the Secretary of the Department of Health and Human Services (HHS), in consultation with the Director of the National Institutes of Health (NIH), the Commissioner of the Food and Drug Administration (FDA), the Administrator of the Health Resources and Services Administration (HRSA), the Advisory Council, and other stakeholders, where appropriate given relevant expertise, to conduct a review on the appropriateness of adult stem cells and birthing tissues as new types of therapies for the C.W. Bill Young Cell Transplantation Program (CWBYCTP). The agencies are required to submit a report with recommendations based on the review to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives.

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Sincerely,


Gary Andres
Assistant Secretary for Legislation

Enclosure



September 2, 2025

The Honorable Bernie Sanders
Ranking Member
Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, DC 20510

Dear Senator Sanders:

The TRANSPLANT Act of 2021 requires the Secretary of the Department of Health and Human Services (HHS), in consultation with the Director of the National Institutes of Health (NIH), the Commissioner of the Food and Drug Administration (FDA), the Administrator of the Health Resources and Services Administration (HRSA), the Advisory Council, and other stakeholders, where appropriate given relevant expertise, to conduct a review on the appropriateness of adult stem cells and birthing tissues as new types of therapies for the C.W. Bill Young Cell Transplantation Program (CWBYCTP). The agencies are required to submit a report with recommendations based on the review to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives.

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Sincerely,

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Gary Andres
Assistant Secretary for Legislation

Enclosure

REPORT TO CONGRESS

The Appropriateness of the Inclusion of Adult Stem Cells and Birthing Tissues as New Types of Therapies in the C.W. Bill Young Cell Transplantation Program

Required by Section 2(c) of the Timely ReAuthorization of Necessary Stem-cell Programs Lends Access to
Needed Therapies Act of 2021
(Public Law 117-15)

Department of Health and Human Services

June 2025



Executive Summary

The Timely ReAuthorization of Necessary Stem-cell Programs Lends Access to Needed Therapies Act of 2021 (Public Law 117-15, Section 2(c)) requires this report to the Senate Committee on Health, Education, Labor, and Pensions and the House of Representatives Committee on Energy and Commerce. The report is a statement of the Secretary of Health and Human Services (HHS), working with others, regarding the appropriateness of adult stem cells and birthing tissues as new types of therapies that should be included in the C.W. Bill Young Cell Transplantation Program (CWBYCTP). For the purposes of this report, adult stem cells and birthing tissues are defined as cells or tissues derived from blood, bone marrow, umbilical cord, placenta, adipose tissue, or other adult tissues that are used for purposes other than for hematologic or immunologic reconstitution.

The CWBYCTP is administered by the Health Resources and Services Administration (HRSA), whose mission is to improve health outcomes and address health disparities through access to quality services, a skilled health workforce, and innovative, high-value programs. The purpose of the CWBYCTP is to help individuals who need a stem cell transplant from an unrelated marrow donor, peripheral blood stem cell donor, or cord blood unit. It does so by making information about bone marrow, peripheral blood, and cord blood transplants available to patients, families, health care professionals and the public; by providing a single point of access to identify suitably matched marrow donors and cord blood units; by increasing the number of unrelated marrow donors and cord blood units available for transplant; and by collecting data and expanding research to improve patient outcomes. The CWBYCTP currently facilitates transplants for over 70 diseases for which hematologic or immunologic reconstitution using bone marrow, peripheral blood, and cord blood. These uses of stem cells have been incorporated into professional guidelines for the management of many different diseases, and there are several cord blood products, including a modified umbilical cord blood product omidubicel-only (Omisirge, Gamida Cell Ltd.), approved¹ by the Food and Drug Administration (FDA) for use in hematologic and immunologic reconstitution.

Stem cells derived from allogeneic (cells from one individual to another) and autologous (cells from one's own body) bone marrow and peripheral blood, cord blood, as well as stem cells derived from adipose and other sources, have been and continue to be investigated for the treatment of a wide variety of different conditions ranging from arthritis to neurologic disorders to cardiac diseases. Aside from a single product, remestemcel-L-rknd (Ryoncil, Mesoblast, Inc.), an allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy indicated for treatment of steroid-refractory acute graft versus host disease in pediatric patients 2 months of age and older, clinical trials have yet to demonstrate sufficient evidence to support the efficacy of other adult stem cells or stem cells derived from birthing tissues for the treatment of a variety of diverse non-hematologic conditions. In addition to lacking demonstrated efficacy, significant safety concerns have been reported regarding a variety of other uses of adult stem cell and cord blood products for purposes other than hematologic and immunologic reconstitution. Adult stem cells and birthing tissues therefore remain unapproved for these other indications.

The CWBYCTP currently facilitates access to potentially life-saving therapies that are generally accepted by the medical community as safe and effective, namely stem cells derived from blood, bone marrow, or cord blood used for hematologic or immunologic reconstitution. At this time, with the exception of one approved product (Ryoncil, Mesoblast, Inc.), adult stem cells and birthing tissues as defined above fall into a different category of products: those that are unapproved for their intended uses. The inclusion in the CWBYCTP of unapproved products such as adult stem cells and birthing tissues that require, but have not

¹ FDA approval to market a biologic is granted by issuance of a biologics license under section 351 of the Public Health Service Act. For the purposes of this report, we will use the terms "approval" and "licensure", with respect to biological products, interchangeably.

yet received, approval by FDA could give patients and providers the erroneous impression that these products are as safe and effective for their intended uses as are stem cell products used in hematopoietic stem cell transplants for hematologic and immunologic reconstitution. This could be detrimental to product development because it will remove incentives for the conduct of clinical trials. Furthermore, it could undermine the statutory and regulatory systems in place for evaluation and approval of drugs, biological products and devices by the FDA, including the regenerative medicine-related provisions of the 21st Century Cures Act, which provide opportunities to facilitate development and expedite FDA review of certain regenerative medicine therapies. Ensuring that the CWBYCTP lists only products that have been approved by FDA or are otherwise compliant with applicable law will allow the greatest access for patients to safe, effective, and innovative cellular and tissue-based products.

In terms of access, the availability of investigational therapies to patients and providers is facilitated by information available on ClinicalTrials.gov, which is administered through the National Institutes of Health (NIH) in coordination with FDA. There are statutory and regulatory requirements that certain clinical trials be listed in this publicly accessible database; other trials may be listed electively at the sponsor's or investigator's discretion. In addition to information relevant for patient participation, ClinicalTrials.gov also contains clinical trial summary results information.²

Based on the considerations discussed above, and the evolution of the field of stem cell-based therapies, the Department of HHS makes the following recommendations:

1. The proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that:

The CWBYCTP should include only those adult stem cell and birthing tissue products, including those with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
 - b) require donor matching if appropriate, and
 - c) have been approved by FDA as safe, pure and potent or safe and effective, or if FDA approval is not required, through adoption as a standard of care.
2. Based on the criteria above, the inclusion in the CWBYCTP of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time.
 3. Based on the criteria above, a modified umbilical cord blood product, omidubicel-only (Omisirge, Gamida Cell Ltd.), approved³ by the FDA on April 17, 2023, for use in hematologic and immunologic reconstitution, meets the proposed criteria for inclusion in the CWBYCTP because it has been approved by FDA, it is indicated for treatment for serious or life-threatening conditions, and it requires donor matching for the treatment of an individual patient.
 4. As the science advances and new classes of cell-based products are developed that meet regulatory approval standards for safety and efficacy, it may be appropriate to include such products in the CWBYCTP. The recently approved mesenchymal stromal cell product remestemcel-L-rknd, however, does not meet the criteria for inclusion into the CWBYCTP because it does not require donor matching. Reevaluation by HRSA, NIH, and FDA (in conjunction with appropriate expert consultation) of the status of adult stem cells and birthing tissues for potential inclusion in the CWBYCTP continues

² See section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)), as amended by section 801 of the Food and Drug Administration Modernization Act of 2007 (Public Law 110-85); 42 C.F.R. Part 11.

³ [OMISIRGE | FDA](#)

to be recommended on a periodic basis (every two to three years or as needed).

Table of Contents

Executive Summary	1
Statutory Mandate	4
Purpose of the C.W. Bill Young Cell Transplantation Program	4
Outcomes Data Collection and Reporting Currently Facilitated Through Funding from the CWBYCTP	5
Consultations Performed Relevant to this Report	6
Background on Stem Cell Therapies	6
Hematopoietic Stem Cells and Birthing Tissues for Hematologic or Immunologic Reconstitution	7
Adult Stem Cells and Birthing Tissues for Other Uses	7
Regulatory Framework for Stem Cell Therapies	9
Efforts to Expedite Progress Developing Adult Stem Cell and Birthing Tissue-based Treatments ...	11
Proposed Criteria for Inclusion of New Cellular Therapies in the CWBYCTP	12
Key Findings Regarding Inclusion of Adult Stem Cells and Birthing Tissue Products in the CWBYCTP	12
Recommendations	14
References	16
Appendices	18
NIAMS Roundtable Agenda: Cartilage Preservation and Restoration in Knee Osteoarthritis, September 22, 2022	19
NIH-FNIH Workshop Agenda: Future of Regenerative Medicine and Cell-based Therapies, November 6-7, 2023	20
Supporting References for Research Vignettes	22

Statutory Mandate

The Timely ReAuthorization of Necessary Stem-cell Programs Lends Access to Needed Therapies Act of 2021 (Public Law 117-15, Section 2(c)) amended section 379 of the Public Health Service Act to provide that “Not less frequently than every 2 years, the Secretary, in consultation with the Director of the National Institutes of Health, the Commissioner of Food and Drugs, the Administrator of the Health Resources and Services Administration, the Advisory Council, and other stakeholders, where appropriate given relevant expertise, shall conduct a review of the state of using adult stem cells and birthing tissues to develop new types of therapies for patients, for the purpose of considering the potential inclusion of such new types of therapies in the Program. Not later than June 30, 2025, the Secretary shall (A) complete the second review required by paragraph (1); and (B) informed by such a review, submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives recommendations on the appropriateness of the inclusion of new types of therapies in the Program.”

Under the direction of the Secretary of HHS, the preparation of this report represents a collaborative effort by HRSA, NIH, and FDA in consultation with the HHS Advisory Council on Blood Stem Cell Transplantation (ACBSCT) and other appropriate stakeholders, in fulfillment of this statutory mandate. The findings and recommendations herein represent the perspectives of HHS.

For the purposes of this report, adult stem cells and birthing tissues are defined as cells or tissues derived from blood, bone marrow, umbilical cord, placenta, adipose tissue, or other adult tissues that are used for purposes other than for hematologic or immunologic reconstitution.

Purpose of the C.W. Bill Young Cell Transplantation Program

HRSA, whose mission is to improve health outcomes and address health disparities through access to quality services, a skilled health workforce, and innovative, high-value programs, is the federal agency that administers the CWBYCTP.

The Stem Cell Therapeutic and Research Act of 2005, P.L. 109-129 authorizes:

- CWBYCTP – to increase the number of bone marrow and cord blood transplants for recipients suitably matched to biologically unrelated donors.
- National Cord Blood Inventory (NCBI) – to contract with qualified cord blood banks (CBBs) to meet the statutory goal of building a public inventory of at least 150,000 new, high quality, and genetically diverse cord blood units.
- HHS ACBSCT – to advise, assist, consult with, and make recommendations to the HHS Secretary, through the HRSA Administrator, on matters related to the activities of the CWBYCTP and the NCBI Program.

The CWBYCTP provides a structure to facilitate blood stem cell transplantation with blood forming cells from unrelated donors for people in the United States who have leukemia, lymphoma, sickle cell anemia, or other inherited metabolic or immune system disorders

(https://bloodcell.transplant.hrsa.gov/transplant/understanding_tx/index.html#Diseases).

The CWBYCTP, through its Stem Cell Therapeutic Outcomes Database (SCTOD) function, enables the collection of data on the clinical outcomes of those transplant recipients as well as data on blood stem cell products. The CWBYCTP implements five functions (i.e., bone marrow coordinating center, cord blood coordinating center, patient advocacy, single point of access, and outcomes database) through three

major contracts awarded through a competitive process during September 2022. The following is a description of the major contracts:

- The SCTOD collects, maintains, analyzes, and reports patients' outcomes data for all allogeneic (cells from one individual given to another) hematopoietic stem cell transplants and other therapeutic uses of blood stem cells, in a standardized electronic format.
- The Office of Patient Advocacy (OPA) establishes and maintains a system for patient advocacy, which serves patients searching for a bone marrow donor or cord blood unit through the CWBYCTP, from diagnosis through survivorship. The OPA engages in public and professional educational activities related to treatment options.
- The Single Point of Access- Coordinating Center establishes a system for health care professionals and physicians searching on behalf of patients to search electronically for cells derived from adult marrow donors and cord blood units through a single point of access and supports coordination activities for bone marrow and cord blood transplants.

Outcomes Data Collection and Reporting Currently Facilitated Through Funding from the CWBYCTP

The SCTOD is administered through an HRSA contract that is in place with the Medical College of Wisconsin. The SCTOD supports the collection, analysis, and reporting of outcomes data for all allogeneic hematopoietic stem cell transplants (HSCTs) performed in the United States. Further, the SCTOD provides information about such transplants to patients, families, health care professionals, and the public, in fulfillment of the statutory mandate of the CWBYCTP. Also, a contractor of the SCTOD voluntarily, and outside of the scope of its HRSA contract, collects information on other types of transplants, such as autologous hematopoietic stem cell transplants using stem cells derived from bone marrow or peripheral blood and cord blood; it also collects information on some cellular therapy products.

To date, the SCTOD has primarily included therapies that have been FDA-approved (e.g., cord blood products) or that are regulated under section 361 of the Public Health Service Act and 21 CFR part 1271 (e.g., peripheral blood stem cell products⁴) or otherwise available under applicable law (minimally manipulated bone marrow) for the treatment of hematologic and immune system disorders. It includes data on both allogeneic and autologous bone marrow-derived and peripheral blood-derived stem cell transplants as well as cord blood transplants, which have been clearly demonstrated to be safe and effective for hematologic reconstitution in settings such as the treatment of hematologic malignancies.

Data are included in the SCTOD on allogeneic HSCTs occurring in the United States using a product procured through the federally authorized CWBYCTP. The patient data included in the SCTOD are collected using the Office of Management and Budget-approved forms. Per the SCTOD contract requirement, patient data are collected immediately pre-infusion and immediately post-infusion as well as post-transplant at 100-days, 6-months, 1-year, and annually through 6 years after HSCT and every other year thereafter. Data collection for the SCTOD started in December of 2007; data for approximately 8,000 new allogeneic HSCT recipients are added each year. In addition to these data, the SCTOD contractor collects pre-transplant research samples from recipients and their related donors to constitute a Related Donor

⁴ Per 21 CFR 1271.10(a), certain peripheral blood stem cell products that are, among other things, only minimally manipulated, intended for homologous use, and for autologous use or allogeneic use in a first or second degree blood relative, do not require FDA approval and are regulated solely under section 361 of the Public Health Service Act and 21 CFR part 1271.

Research Repository. Data derived from assays of these biospecimens are linked to the clinical outcomes data (e.g., SCTOD data) for research studies that evaluate genetic and immune-biologic factors as well as clinical phenotype data. However, the SCTOD contract does not provide federal funds for biospecimen assays.

Consultations Performed Relevant to this Report

Consultations noted below include discussions relevant to HHS efforts to move the field of cell-based therapies forward; consultations on the state of the science of adult stem cells and birthing tissues included:

1) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Roundtable on Cartilage Preservation and Restoration in Knee Osteoarthritis: Challenges, Gaps, and Opportunities held in September 2022

The roundtable focused on challenges, gaps, and opportunities regarding regenerative medicine approaches for cartilage preservation and restoration in knee osteoarthritis in order to move the field forward (3). The event brought together investigators with expertise in regenerative medicine, experts in clinical treatment of knee osteoarthritis, and FDA and patient representatives.

The agenda is provided as Appendix 1, and the video recording is available at <https://videocast.nih.gov/watch=45004>.

2) NIH-FNIH Workshop on the Future of Regenerative Medicine and Cell-based Therapies, held in November 2023

The focus of this workshop was to understand the experiences of investigators with regenerative medicine research projects, identify activities to help accelerate collaborative research and regulation, and refine topics for inclusion in a potential public-private partnership effort focused on cellular therapies within the Accelerating Medicines Partnership through the Foundation for the NIH.

The agenda is provided as Appendix 2, and the video recording is available at <https://www.niams.nih.gov/about/meetings-events/roundtables/nih-fnih-host-workshop-future-regenerative-medicine-and-cell>.

3) HHS Consultation with the HHS ACBSCT held in September 2023

This meeting was convened with a quorum of the ACBSCT. The purpose was to update the ACBSCT on the state of the science using adult stem cells and birthing tissues to develop new types of therapies for patients. The scientific landscape was reviewed to consider the potential inclusion of therapies from adult stem cells and birthing tissues in the CWBYCTP for new uses outside of hematologic or immunologic reconstitution. Despite scientific and technological progress, no FDA approved products in the category of adult stem cells or birthing tissues for use outside of hematologic or immunologic reconstitution were identified for potential inclusion in the CWBYCTP.

Background on Stem Cell Therapies

Regenerative medicine, including classes of products such as adult stem cells and birthing tissues, is a rapidly emerging and expanding field that offers great potential benefit by the possibility of providing innovative treatments that may restore health and address unmet medical needs (4). Although many researchers are working to understand the underlying basic biology, manufacturing processes, and critical quality attributes that will ultimately support the development of safe and effective adult stem cell and birthing tissue products, much remains to be learned. Representative vignettes of this research are provided in text boxes 1-4. Reflecting the current state of the science, today there is only one FDA-approved adult stem cell product or stem cell product derived from birthing tissue or birthing tissue products for use outside of hematologic or immunologic reconstitution. In 2024, the FDA approved remestemcel-L-rknd (Ryoncil, Mesoblast, Inc.), an allogeneic bone marrow-derived MSC therapy indicated for treatment of steroid-refractory acute graft versus host disease in pediatric patients 2 months of age and older.

Hematopoietic Stem Cells and Birthing Tissues for Hematologic or Immunologic Reconstitution

Certain hematopoietic stem cell therapies offer the potential to treat diseases or conditions for which few treatments exist. For example, bone marrow-derived stem cells, peripheral blood-derived stem cells, and cord blood-derived stem cells have clearly demonstrated safety and efficacy for hematologic reconstitution or immunologic reconstitution in specific settings such as the treatment of bone marrow failure syndromes and inherited hematologic disorders, the treatment of hematologic and certain other malignancies, and for the treatment of certain immunologic disorders (5).

The safety and efficacy of such stem cell transplantation are documented in hundreds of publications in the literature. For example, severe aplastic anemia was previously associated with high mortality. It is now curable in most cases, eligible for hematopoietic stem cell transplantation, particularly in children and younger adults (6). Transplantation of cord blood (derived from birthing tissues), when appropriate, has become integrated into standard clinical practice for the treatment of patients with acute leukemia, and its use has been associated with favorable long-term outcomes in relapsed or refractory hematologic malignancies (7). There are several FDA-approved cord blood products.

Adult Stem Cells and Birthing Tissues for Other Uses

Stem cells derived from bone marrow, peripheral blood, and cord blood, as well as stem cells derived from other sources, such as adipose tissue, have been investigated for the treatment of a wide variety of

DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 1

Stem Cell Therapy for Amputees

More than 1.7 million people in the United States suffer from limb loss. Those with prosthetics often experience skin breakdown at the stump site due to friction or pressure as they use these devices—resulting in pain, ulceration, and infection. The thick and tough skin on palms and soles, called volar skin, is resilient under high-pressure conditions, such as walking, and could be beneficial at these contact sites. Strategies for converting non-volar skin to volar skin using injections of volar fibroblasts derived from a patient's own tissue are currently being investigated by researchers. Initial studies of volar and non-volar fibroblasts—grown in 2-dimensional cell culture systems and in 3-dimensional hydrogels—were used to identify features indicative of successful conversion of non-volar fibroblasts to volar cells. A subsequent phase 1 clinical trial involving injection of volar fibroblasts from the sole of the foot into the thighs of healthy volunteers demonstrated a modest reprogramming of non-volar skin—including increased expression of proteins associated with volar fibroblasts and a thickening of the outer layer of the skin, called the epidermis, up to five months after injection. Some challenges to advancing this therapeutic approach remain, such as improving the efficacy of volar fibroblast survival and reprogramming. Nonetheless, these results have been used to support a phase 2 trial to test the ability of volar fibroblast injections to thicken the skin of the stump site in people with below-the-knee amputations.

[See Appendix 3 for supporting references]

disorders.⁵ These include musculoskeletal diseases like osteoarthritis and rheumatoid arthritis; neurologic diseases such as stroke, Parkinson's disease, and amyotrophic lateral sclerosis; and cardiac conditions such as congestive heart failure (8, 9, 10). The scientific rationale for the use of adult stem cells or birthing tissues for the treatment of these disorders is that they can potentially replace missing or diseased cell types by differentiating into the needed cell type based on local environmental factors. Alternatively, adult stem cells or birthing tissues may have an immunomodulatory effect that is beneficial to diseases that have an autoimmune basis (11). These two mechanisms are also not mutually exclusive. However, in most cases, data from definitive clinical trials evaluating the efficacy of adult stem cells or birthing tissues have yet to substantiate either of these alternatives as the mechanisms of action, and in fact, randomized clinical trials have yet to demonstrate clinical efficacy in a compelling manner (12, 13, 14). The exception is the recently approved mesenchymal stromal cell product remestemcel-L-rknd. This product, however, does not meet the criteria for inclusion into the CWBYCTP because it does not require donor matching.

In addition to lacking demonstrated efficacy in many of the proposed applications, such as the treatment of orthopaedic or neurologic conditions, adult stem cell products and cord blood used for purposes other than hematologic and immunologic reconstitution sometimes have been found to have significant safety concerns. For instance, attendees at a 2016 FDA public workshop discussed several cases of severe adverse events, and some of these cases have now been reported in the literature (15). Three individuals became blind, and a fourth had diminished vision due to stem cells injections into the eye (16). An individual received stem cell injections that caused the growth of a tumor compressing the spinal cord, and another received an injection of stem cells into the kidney that resulted in the need for surgical removal of the kidney (17, 18). Additionally, since that public workshop, other complications have been reported in the literature, including potentially life-threatening blood infections (19). Other potential safety concerns for unproven treatments include the ability of cells to move from placement sites or change into inappropriate cell types due to the microenvironments into which the cells are placed. It should be noted

DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 2

Stem Cell Therapy for Temporomandibular Joint Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease caused by the breakdown of protective connective tissue called cartilage. This can result in joint pain and dysfunction. Current treatments for OA are limited to surgery or symptom management, which do not stop disease progression or reverse cartilage damage. Less invasive alternatives--such as OA drugs that maintain healthy cartilage structures--represent a much-needed therapeutic strategy. Using animal and cell models of the temporomandibular (jaw) joint (TMJ), researchers identified an adult stem cell population that provides critical signals to the cells responsible for healthy cartilage formation. Importantly, these adult stem cells are lost naturally due to aging and when OA occurs following a trauma. To compensate for the loss of these cells and to repair OA-damaged cartilage, investigators developed a long-lasting, injectable hydrogel that can replace some lost cell functions by delivering missing cell products directly in the damaged joint. The minimally invasive and localized delivery of the protein sclerostin was shown to restore healthy cartilage formation and improve joint function in animal models of TMJ OA. This approach shows real translational potential for helping to restore healthy cartilage formation and to treat OA in the TMJ and in other joints throughout the body.

[See Appendix 3 for supporting references]

⁵ The Stem Cell Therapeutic and Research Act of 2005, P.L. 109-129, and as amended allows cord blood units that are collected, but that are not appropriate for clinical use, to be made available for peer-reviewed research. The data resulting from such research uses are captured by entities other than the CWBYCTP. Cord blood units that are collected may also be made available for use in clinical trials that are conducted under Investigational New Drug (IND) applications on file with FDA. Relevant findings of such investigational studies are reported to FDA under the IND application.

that such safety concerns are likely underreported because the products are often administered outside of clinical trials under appropriate regulatory oversight.

Early phase clinical investigations of a wide variety of different applications of adult stem cell and birthing tissues are currently ongoing under appropriate regulatory oversight. However, despite the potential safety concerns and lack of documented efficacy noted above, many adult stem cell and birthing tissue products are currently being administered to patients as part of patient-funded clinical trials without appropriate FDA oversight or as part of commercial marketing operations in violation of FDA regulatory authorities.

It is worth noting that in its 2016 Guidelines for Stem Cell Research and Clinical Translation, the International Society for Stem Cell Research notes that “for the vast majority of medical conditions for which putative ‘stem cell therapies’ are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events subsequent to such procedures have been reported and the long-term safety of most stem cell-based interventions remains undetermined.” (20) The 2021 update to the Guidelines noted “The number of clinical trials and other interventions involving stem cells has increased significantly over the last 5 years, as have the number of inappropriate uses and exaggerated or false claims.” (21) Thus, concerns regarding the inappropriate clinical use of adult stem cells and birthing tissues outside of the setting of appropriately authorized and conducted clinical trials remain.

Regulatory Framework for Stem Cell Therapies

Minimally manipulated bone marrow for homologous use, not combined with another article (except for water, crystalloids, or certain sterilizing, preserving, or storage agents) is excluded from the definition of human cells, tissues, or cellular or tissue-based products in FDA’s regulations.⁶ With that exception, oversight of stem cells, including more than minimally manipulated bone marrow and bone marrow-derived stem cells used for other purposes, peripheral blood-derived stem cells, cord blood, as well as stem cells derived from other sources, such as adipose tissue, are regulated by the FDA. The FDA has licensed multiple blood banks to manufacture cord blood stem cells for hematopoietic and immunologic reconstitution. FDA has also licensed a modified umbilical cord blood product called omidubicel-only for hematologic and immune reconstitution, which is recommended for inclusion in the CWBYTP, as it requires donor matching for an individual patient.

DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 3

Insulin-Producing Gastric Stem- Cell Based Organoids as a Treatment for Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disease in which the immune system launches a misguided attack that destroys insulin-producing β (beta) cells in the pancreas. Thus, people with T1D require lifelong insulin administration to regulate their blood glucose levels. Researchers are investigating the replacement of these lost β -cells as a strategy to cure T1D. Currently, the only FDA-approved cell therapy for T1D uses cells from deceased donors, requires immunosuppression, and is only suitable for a limited number of people. These limitations prevent the wider application of this therapy. To make T1D cell therapies more widely available, scientists are studying ways to generate new sources of insulin-producing cells for transplantation, such as by reprogramming other cell types into β -cells. A person’s own gastric (stomach) stem (GS) cells are a promising cell source for β -cell reprogramming due to their accessibility by biopsy and ability to rapidly form large quantities of organoids (cells grown in a 3-dimensional environment that mimic organ function). Human GS cells isolated from stomach biopsies were reprogrammed in as little as 10 days, with high efficiency (70 percent), to produce large quantities of insulin-producing β -like cells. When transplanted into diabetic mice these cells were able to stabilize blood glucose levels for over 100 days. This work represents an important platform for generating insulin-producing organoids and may provide new opportunities for creating T1D therapies.

[See Appendix 3 for supporting references]

⁶ 21 CFR 1271.3(d)(4).

FDA and HRSA have ongoing collaborations to share information and discuss applicable regulatory requirements and updates on relevant research or scientific issues related to hematopoietic stem cells for transplantations or other relevant products. FDA and HRSA representatives participate in the HHS ACBSCT.

Adult stem cell products and birthing tissues are regulated under the FDA's regulatory framework for human cells, tissues, and cellular and tissue-based products (HCT/Ps). Under this risk-based framework, the criteria in the Code of Federal Regulations (CFR), particularly, 21 CFR 1271.10(a), are used to determine whether HCT/Ps are regulated as drugs, devices, and/or biological products requiring FDA premarket review and approval, or whether they are appropriately regulated solely under section 361 of the Public Health Service Act and 21 CFR part 1271.

As described in FDA's final 2020 guidance for industry "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use," and in accordance with the regulations in 21 CFR 1271.10(a), some birthing tissue products can be appropriately regulated under section 361 of the Public Health Service (PHS) Act and 21 CFR part 1271 if they meet the criteria set forth in FDA's regulations, including that they are minimally manipulated and intended for a homologous use.⁷ One example is the amniotic membrane that is minimally manipulated and intended for a homologous use, such as serving as a covering and protection from the surrounding environment for skin wounds, such as ulcers, and meets the other criteria in 21 CFR 1271.10(a). In contrast, other birthing tissue products are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act. Examples of such birthing tissue-derived products regulated as drugs, devices, and/or biological products include amniotic membrane that is more than minimally manipulated or used for some purpose other than covering, and autologous cord blood when used for

DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 4

Patient Derived Stem Cells as a Treatment for Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative condition that affects up to 10 million people globally with symptoms including tremors and difficulty controlling movement and balance. PD is characterized by the degeneration of midbrain dopamine (mDA) neurons. At the time of diagnosis, approximately 60 percent of these neurons are typically lost. Current PD drug therapies are effective in the short-term but can lead to additional complications after prolonged use. Reprogramming patient-derived induced pluripotent stem cells (iPSC) into mDA neurons could eliminate these problems. Using patient derived cells also avoids issues associated with other cell therapy approaches, such as suppressing the immune system and a limited ability to scale up production for larger patient populations. Initial data from animal models has shown that iPSC derived mDA neurons can support functional recovery for at least two years. These results have been used as evidence to advance this iPSC strategy, which has seen significant progress in both quality control of manufacturing and safety testing. These early successes have led to a recently initiated phase 1 clinical trial—a first in-human test of iPSC-derived mDA transplantation in PD. This trial is assessing the safety of these injected cells and their ability to alleviate PD symptoms. The outcome of these trials will be monitored closely and will have important implications for the health and well-being of patients with PD.

[See Appendix 3 for supporting references]

⁷FDA's regulations 21 C.F.R. 1271.3 provide definitions of minimal manipulation and homologous use. As defined in 21 C.F.R. 1271.3(f), minimal manipulation means:

- 1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and
- 2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

As defined in FDA's regulations at 21 C.F.R. 1271.3(c), homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

treatment of cerebral palsy or autism.

Efforts to Expedite Progress Developing Adult Stem Cell and Birthing Tissue-based Treatments

Regenerative medicine is a rapidly expanding field that offers great potential. However, much remains to be understood regarding the science underlying these advanced therapeutic products as well as how to manufacture them consistently. Because of this, the 21st Century Cures Act (Public Law 114-255) tasked NIH with establishing the Regenerative Medicine Innovation Project (RMIP) in coordination with FDA. The purpose of the RMIP is to accelerate the field of regenerative medicine by supporting clinical research, including clinical trials, on adult stem cells, including autologous cells, while promoting the highest standards for carrying out such research and protecting patient safety. The 21st Century Cures Act authorized \$30 million in federal awards over four years (FY 2017-2020) for the RMIP and required award recipients to match the federal funds provided in at least an equal amount with non-federal contributions. Details of the FY 2017-2023 solicitations and a list of awardees are available online at <https://www.nih.gov/rmi>.

As part of the RMIP program, grant recipients are providing representative samples of source stem cells and clinical-grade stem cell products to an NIH designated core facility that is conducting independent in-depth characterization of the materials. The results of the cell characterization are shared broadly along with the clinical trial data (if applicable), thereby potentially enabling correlation of stem cell attributes with clinical outcomes.

The 21st Century Cures Act also included important regenerative medicine provisions that amended FDA's statutory authority, including provisions establishing the Regenerative Medicine Advanced Therapy (RMAT) designation program. This program is intended to help facilitate and expedite the development and review of regenerative medicine therapies, including certain cellular therapies. It does so through, for example, opportunities for early and frequent interactions between sponsors and FDA, with the goal ultimately of providing patient access to safe, effective and innovative regenerative medicine therapies. As of December 31, 2024, FDA has received 317 designation requests for RMAT designation and has granted 152 of these.

The RMAT sections of the 21st Century Cures Act provide that RMAT designation is available only for a regenerative medicine therapy that meets certain requirements. Regenerative medicine therapy is defined as including "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations." The statute also provides for the request for designation as a regenerative advanced therapy to be submitted concurrently with or at any time after submission of an application for clinical investigation of the products under Investigational New Drug (IND) applications. These regenerative medicine-related provisions of the 21st Century Cures Act thus limit the benefits of the RMAT designation to products that are subject to pre-market review and approval by FDA.

In November 2017, building on FDA's risk-based regulatory framework and the provisions in the 21st Century Cures Act and with the goal of helping to support and facilitate the development and review of safe and effective regenerative medicine products so that they can be available expeditiously to patients, FDA issued its comprehensive regenerative medicine framework. This consists of four guidance documents, including some focused on the RMAT sections of the 21st Century Cures Act and some that are built upon FDA's existing risk-based regulatory approach (22). Under this framework, FDA detailed its science-based process for helping to ensure the safety and effectiveness of these therapies, while

facilitating development in this area.

To facilitate product development that will ultimately benefit patients, FDA is exercising considerable flexibility and encouraging developers of cell and tissue-based therapies to discuss with the Agency novel development plans that can help expedite development of these products. In fact, with an understanding of the challenges that developers of cellular products may face, the 2019 guidance “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions,” issued by FDA as part of the regenerative medicine framework, outlined the accelerated approval pathways available for regenerative therapies that have been granted RMAT designation, and described considerations in the clinical development of regenerative medicine therapies and opportunities for sponsors of such products to interact with CBER review staff.

Developers of novel adult stem cell and birthing tissue products are also being encouraged to have early non-binding conversations with FDA regarding necessary regulatory aspects of product development through participation in the INTERACT program (Initial Targeted Engagement for Regulatory Advice on CBER Products) initially launched in 2018 by the Center for Biologics Evaluation and Research. These informal meetings can 1) assist sponsors conducting early product characterization and preclinical proof-of-concept studies, 2) initiate discussion for new delivery devices, 3) inform sponsors about overall early-phase clinical trial design elements, and 4) identify critical issues or deficiencies for sponsors to address in the development of innovative products.

Finally, at the time that FDA issued the regenerative medicine framework noted above, it also made clear its policy on enforcement and compliance in this area. FDA’s enforcement discretion policy ended May 31, 2021, and stem cell products requiring an IND application and Biologics License Application must be in compliance with the FDA’s regulations. FDA is currently taking regulatory action regarding such products that pose significant safety or public health concerns. Such a policy is necessary because numerous stem cell clinics around the United States have been reported to be offering for sale unapproved adult stem cell products and those derived from birthing tissues to treat a wide variety of conditions (23). These products are being purported by their providers to be safe and efficacious for many different conditions; patients are paying out of pocket for them, sometimes tens of thousands of dollars, even though they are not approved by FDA, nor are they even being studied under an IND.

Proposed Criteria for Inclusion of New Cellular Therapies in the CWBYCTP

The purpose of the CWBYCTP is to help patients who need a potentially life-saving transplant from an unrelated bone marrow or stem cell donor or from a cord blood unit by facilitating the matching of donors and recipients and by making information about transplants and their outcomes available to patients, families, health care professionals, and the public. In keeping with this programmatic purpose and the mission of HRSA to improve health through access to quality services, the proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that the Program should include only those adult stem cell and birthing tissue products with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
- b) require donor matching if appropriate, and
- c) have been demonstrated to be safe and effective as evidenced by FDA approval, or if FDA approval is not required, through adoption as a standard of care.

Key Findings Regarding Inclusion of Adult Stem Cells and Birthing Tissue Products in the CWBYCTP

HRSA, NIH, and FDA have a shared goal of providing access to safe and effective products. As an

embodiment of the HRSA mission to improve human health through access to quality services and care, a central goal of the CWBYCTP is to promote patient access to suitably matched bone marrow and cord blood transplants in potentially life-saving settings. These procedures are widely accepted by clinicians as representing a standard of care in certain settings, such as in the case of relapsed acute leukemia.

As noted above, through the SCTOD, the CWBYCTP collects outcomes data in a standardized electronic format on the use of suitably matched bone marrow and cord blood transplants for hematologic and immunologic indications. The hematologic and immunologic stem cells provided by suitably matched bone marrow and cord blood are relatively similar to one another; the outcome measures are similar or the same for the various applications that the different products are used for (e.g., non-relapse mortality); and, as a result, the data can meaningfully be analyzed across the products.

Adult stem cells and birthing tissues for other unapproved applications (i.e., other than hematologic and immunologic reconstitution or for the indication of the one FDA-approved adult stem cell product) represent an array of products that are used for experimental interventions for different diseases with widely different outcome measures. Their use currently does not inherently represent a standard of care for disease management. While such applications hold promise, at present they are without proven safety or efficacy, and in some instances, have resulted in significantly adverse patient outcomes. Information regarding the clinical trials investigating these products and the results of these trials is useful to patients interested in enrolling in such studies and is also of potential interest to the public. However, for many products in early-stage clinical development (e.g., phase 1 clinical trials), and for all products in advanced stages of clinical development (e.g., phase 2 or phase 3), this information is already available in a congressionally mandated and federally funded database, ClinicalTrials.gov, which is dedicated to this purpose.

The inclusion in the CWBYCTP of adult stem cells and birthing tissues that require premarket review and approval by FDA, but for which FDA approval has not been granted would have the CWBYCTP overseeing the maintenance and dissemination of information about some products that are purely experimental and whose use may not be consistent with the applicable law, which may pose risks to patient safety when patients seek out products they have seen in the CWBYCTP database without understanding that they may not have been fully tested or proven to be both safe and effective. It is likely that many, if not most, of these investigational products will never be proven safe and effective. However, patients are likely to be confused and possibly even be misled regarding which CWBYCTP products are investigational or experimental. Furthermore, the conclusion from an updated review of the available science and research is that such a mingling of proven effective and unproven products in the CWBYCTP could be detrimental to public confidence in potentially life-saving bone marrow-derived, peripheral blood-derived, and cord blood-derived stem cell transplants and could undermine the goal of the CWBYCTP in its mission to ensure access to and improve patient outcomes from these treatments.

The appropriate registry for investigational products currently being tested in clinical trials and pending regulatory approval is ClinicalTrials.gov, the congressionally mandated and federally funded database administered by NIH in coordination with FDA. The database includes information regarding certain clinical trials studying FDA-regulated products (regardless of whether the product being studied is approved, licensed, or cleared by FDA), including phase 2 and later clinical trials subject to the statutory and regulatory requirements for registration, and, since January 18, 2017, all NIH-funded clinical trials (including phase 1 studies). Sponsors and investigators may voluntarily submit information to ClinicalTrials.gov for those clinical trials that are not NIH-funded and do not study an FDA-regulated product in a phase 2 or later clinical trial. ClinicalTrials.gov facilitates patient access to and participation in clinical trials and facilitates public access to summary results information from clinical trials. It is an

important and unique public information resource for those interested in learning more about products under development whose safety and efficacy have yet to be established for their intended uses.

Finally, inclusion of investigational cell-based products derived from adult stem cells and birthing tissues in a government-sponsored health services program like the CWBYCTP could be detrimental to adult stem cell and birthing tissue product development overall. Products listed in a registry sponsored by the CWBYCTP could be mistaken as being the equivalent of safe and effective. If such inclusion results in the continued marketing of unapproved products, it could greatly reduce or eliminate the incentive for legitimate product development and private sector investment in accordance with all applicable regulations such as the incentives that led to the development, study, and recent FDA approval of the first adult stromal cell product. Furthermore, it could undermine the statutory and regulatory systems in place for evaluation and approval of drugs, biological products and devices by the FDA, including the regenerative medicine-related provisions of the 21st Century Cures Act, which provide opportunities to facilitate development and expedite FDA review of certain regenerative medicine therapies.⁸ Ensuring that the CWBYCTP lists only products that have been approved by FDA or are otherwise compliant with applicable law will allow the greatest access for patients to safe, effective, and innovative cellular and tissue-based products.

Recommendations

Based on the considerations discussed above, and the evolution of the field of stem cell-based therapies, HHS makes the following recommendations:

1. The proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that:

The CWBYCTP should include only those adult stem cell and birthing tissue products, including those with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
- b) require donor matching if appropriate, and
- c) have been approved by FDA as safe, pure and potent or safe and effective, or if FDA approval is not required, through adoption as a standard of care.

The purpose of the CWBYCTP underpins this recommendation. The CWBYCTP exists to help patients who need potentially life-saving transplants from unrelated bone marrow or stem cell donors or from cord blood units by facilitating the matching of donors and recipients and by making information about transplants and their outcomes available to patients, families, health care professionals and the public. Key concepts in this purpose are reflected in the proposed criteria: treatments for serious or life-threatening conditions that are based, if appropriate, on material from an unrelated donor and that require suitable matching.

The CWBYCTP currently facilitates access to potentially life-saving therapies that are generally accepted by the medical community as safe and effective: stem cells derived from blood, bone marrow, or cord blood used for hematologic or immunologic reconstitution. At this time, adult stem cells and birthing tissues as defined in this report fall into a different category of products: one approved adult stromal cell product for the treatment of acute graft versus host disease, and many others that are investigational for their intended uses. Furthermore, the large majority of such uses do not address serious or life-threatening conditions, in distinct contrast to the use of stem cells derived from blood, bone marrow, or cord blood used in HSCT for hematologic and immunologic reconstitution.

⁸ Sections 1001(b)(4)(D), 3033, 3034, and 3036 of the 21st Century Cures Act, Public Law 114-255.

2. Based on the criteria above, the inclusion in the CWBYCTP of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time.

The use of adult stem cells and birthing tissues for other uses holds significant promise for the treatment of life-threatening conditions. However, with one exception, such applications are presently experimental, have not been proven safe and effective, and therefore do not meet the criteria described above for inclusion as new cellular therapies in the CWBYCTP.

The inclusion in the CWBYCTP of investigational adult stem cells and birthing tissue products that require but have not yet received approval by FDA could give patients and providers the erroneous impression that these products are comparably safe and effective for their intended uses as other FDA-approved products or stem cell products used in HSCT for hematologic and immunologic reconstitution and could be detrimental to product development. This is a disservice to patients and the public and to the field of cell-based therapies.

3. Based on the criteria above, a modified umbilical cord blood product, omidubicel-only (Omisirge, Gamida Cell Ltd.), approved⁹ by the FDA on April 17, 2023, for use in hematologic and immunologic reconstitution, meets the proposed criteria for inclusion in the CWBYCTP because it has been approved by FDA, it is indicated for treatment for serious or life-threatening conditions, and it requires donor matching for the treatment of an individual patient.
4. As the science advances and new classes of cell-based products are developed that meet regulatory standards for FDA approval (e.g., safety and efficacy), it may be appropriate to include such products in the CWBYCTP. Therefore, reevaluation by HRSA, NIH, and FDA (in conjunction with appropriate expert consultation) of the status of adult stem cells and birthing tissues for potential inclusion in the CWBYCTP continues to be recommended on a periodic basis (every two to three years or as needed).

⁹ <https://www.fda.gov/vaccines-blood-biologics/omisirge>

References

1. (Definition of life-threatening) 21 CFR 312.81(a).
2. (Definition of serious disease or condition) 21 CFR 312.300.
3. Chu CR, Hochberg M, White D, et al. Transformative approaches for effective clinical trials to reduce the disease burden of osteoarthritis. *Semin Arthritis Rheum*. 2025 Apr; 71:152652.
4. Cossu G, Birchall M, Brown T, et al. Lancet Commission: Stem cells and regenerative medicine. *Lancet* 2018; 391:883-910.
5. Singh AK, McGuirk JP. Allogeneic Stem Cell Transplantation: A Historical and Scientific Overview. *Cancer Res* 2016; 76:6445-6451.
6. Young NS. Aplastic Anemia. *N Engl J Med* 2018; 379:1643-1656.
7. Munoz J, Shah N, Rezvani K. Concise review: umbilical cord blood transplantation: past, present, and future. *Stem Cells Transl Med* 2014; 3:1435-43.
8. Law L, Hunt CL, van Wijnen AJ, et al. Office-Based Mesenchymal Stem Cell Therapy for the Treatment of Musculoskeletal Disease: A Systematic Review of Recent Human Studies. *Pain Med*. 2018 Dec 29. doi: 10.1093/pm/pny256. [Epub ahead of print].
9. Zheng H, Zhang B, Chhatbar PY, et al. Mesenchymal Stem Cell Therapy in Stroke: A Systematic Review of Literature in Pre-Clinical and Clinical Research. *Cell Transplant* 2018; 27:1723-1730.
10. Lalu MM, Mazzarello S, Zlepzig J, et al. Safety and Efficacy of Adult Stem Cell Therapy for Acute Myocardial Infarction and Ischemic Heart Failure (SafeCell Heart): A Systematic Review and Meta-Analysis. *Stem Cells Transl Med* 2018; 7:857-866.
11. Bernardo ME, Fibbe WE. Safety and efficacy of mesenchymal stromal cell therapy in autoimmune disorders. *Ann N Y Acad Sci*. 2012; 1266:107-17.
12. Luk F, de Witte SF, Bramer WM, Baan CC, Hoogduijn MJ. Efficacy of immunotherapy with mesenchymal stem cells in man: a systematic review. *Expert Rev Clin Immunol*. 2015; 11:617-636.
13. Sipp D, Robey G, Turner L. Commentary: Clear up this stem-cell mess. *Nature* 2018; 561: 455-457.
14. Galipeau J, Weiss D, Dominici M. Response to *Nature* commentary "Clear up this stem-cell mess." *Cytotherapy* 2019; 21:1-2.
15. FDA Workshop, September 8, 2016: Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval. [https://www.federalregister.gov/documents/2016/04/22/2016-09373/scientific-evidence-in-development-of-human-cells-tissues-and-cellular-and-tissue-based-products#:~:text=The%20Food%20and%20Drug%20Administration%20\(FDA\)%2C%20Center%20for%20Biologics,inclusing%20stem%20cell%2Dbased%20products.](https://www.federalregister.gov/documents/2016/04/22/2016-09373/scientific-evidence-in-development-of-human-cells-tissues-and-cellular-and-tissue-based-products#:~:text=The%20Food%20and%20Drug%20Administration%20(FDA)%2C%20Center%20for%20Biologics,inclusing%20stem%20cell%2Dbased%20products.)
16. Kuriyan AE, Albin TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for AMD. *N Engl J Med* 2017; 376:1047-1053.
17. Berkowitz AL, Miller MB, Mir SA, et al. Glioproliferative lesion of the spinal cord as a complication of "stem-cell tourism." *N Engl J Med* 2016; 375:196-8.

18. Thirabanasak D, Tantiwongse K, Thorner PS. Angiomyeloproliferative lesions following autologous stem cell therapy. *J Am Soc Nephrol* 2010; 21:1218-22.
19. Perkins KM, Spoto S, Rankin DA, et al. Notes from the field: infections after receipt of bacterially contaminated umbilical cord blood–derived stem cell products for other than hematopoietic or immunologic reconstitution — United States, 2018. *MMWR Morb Mortal Wkly Rep* 2018; 67:1397–1399.
20. Daley GQ, Hyun I, Apperley JF, et al. Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines. *Stem Cell Reports*. 2016 Jun 14;6(6):787-797. doi: 10.1016/j.stemcr.2016.05.001. Epub 2016 May 12. PMID: 27185282
21. Lovell-Badge R, Anthony E, Barker RA, et al. ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update. *Stem Cell Reports*. 2021 Jun 8;16(6):1398-1408.
22. FDA Framework for the Regulation of Regenerative Medicine Products
<https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm585218.htm>
23. Knoepfler PS, Turner LG. The FDA and the US direct-to-consumer marketplace for stem cell interventions: a temporal analysis. *Regen Med* 2018; 13:19-27.

Appendices

Appendix 1. NIAMS Roundtable Agenda: Cartilage Preservation and Restoration in Knee Osteoarthritis, September 22, 2022.

Appendix 2. NIH-FNIH Workshop Agenda: Future of Regenerative Medicine and Cell-based Therapies, November 6-7, 2023.

Appendix 3. Supporting References for Research Vignettes.

Appendix 1

NIAMS Roundtable Agenda: Cartilage Preservation and Restoration in Knee Osteoarthritis, September 22, 2022

Challenges, Gaps, and Opportunities

Co-Chairs: Drs. Constance Chu and Scott Rodeo

11:00-11:25 (Eastern time)	Welcome and introductions (<i>Dr. Lindsey Criswell, Dr. Robert Carter</i>)
11:25-11:35	Patients' perspectives in OA management (<i>Ms. Amye Leong</i>)
11:35-12:00	Blood derived orthobiologic therapies for OA (<i>Dr. Constance Chu</i>)
12:00-12:25	Stem-cell based cell therapies for OA (<i>Dr. Scott Rodeo</i>)
12:25-12:50	Cartilage regeneration by chondrogenic small molecule drugs (<i>Dr. Marc Hochberg</i>)
12:50-1:20	Group Photo and Lunch Break
1:20-1:45	Matrix-based therapies and tissue-engineered cartilage (<i>Dr. Daniel Grande</i>)
1:45-2:10	Therapeutic potentials of exosomes in OA (<i>Dr. Daniël Saris</i>)
2:10-2:35	Gene therapy and gene-editing approaches for OA (<i>Dr. Farshid Guilak</i>)
2:35-3:00	Limitations and challenges in clinical use of biologics in orthopaedic treatment for OA (<i>Dr. Frank Barry</i>)
3:00-3:15	Break
3:15-3:40	Regulatory considerations for products intended to treat knee osteoarthritis (<i>Dr. Larissa Lapteva</i>)
3:40-5:20	Discussion
5:20-5:30	Closing thoughts (<i>Dr. Lindsey Criswell, Dr. Robert Carter</i>)

Appendix 2

NIH-FNIH Workshop Agenda: Future of Regenerative Medicine and Cell-based Therapies, November 6-7, 2023

Monday, November 6, 2023 (Day 1)	
8:30 a.m.–9:00 a.m.	Welcome, Introductions, and Scene Setting <i>Dr. Robert Carter and Dr. Santa Tumminia</i>
9:00 a.m.–10:30 a.m.	Session 1: What are the benefits of a coordinated, NIH- or agency-wide approach to funding RM research, focusing on challenges and opportunities that are shared across tissues and conditions? <i>Moderators: Dr. Robert Carter and Dr. Fei Wang</i> RMIP Investigators will present on the challenges they've encountered and the solutions for overcoming those challenges that would have been difficult through R01 outside of RMIP.
10:30 a.m.–10:45 a.m.	BREAK
10:45 a.m.–12:00 p.m.	Session 2: What strategies and approaches need to be implemented to overcome the shared challenges to bring novel RM modalities to patients? <i>Moderators: Dr. Santa Tumminia and Dr. Martha Lundberg</i> Non-RMIP investigators will present on the challenges and opportunities, which they have experienced, that apply across tissues and diseases.
12:00 p.m.–1:00 p.m.	Session 3: What do others who have a collective overview of RM see as the needs for an integrated NIH/federal approach? <i>Moderators: Dr. Candace Kerr and Dr. Aron Marquitz</i>
1:00 p.m.–1:15 p.m.	LUNCH
1:15 p.m.–1:45 p.m.	Session 4 (Working Lunch): FDA presentation on regulatory issues and shared interests.
1:45 p.m.–2:00 p.m.	Session 5: FNIH Cell-based Therapy Consortium (CBTC) concept
2:00 p.m.–3:30 p.m.	Session 6: Potential topic for FNIH CBTC: tissue-specific stem cells. <i>Moderators: Dr. Krishnendu Roy and Dr. Johnny Huard</i> Presenters will address non-clinical, translational, and scale-up/production issues related to tissue-specific stem cells so that we can identify a few areas of focus that would be appropriate as topics to include a Cell-Based Therapies Consortium.

Monday, November 6, 2023 (Day 1)	
3:30 p.m.–3:45 p.m.	BREAK
3:45 p.m.–4:30 p.m.	Session 7: Discussion to identify cross-cutting research needs for acceleration of stem cells into clinical application. <i>Panel Discussion</i>

Tuesday, November 7, 2023 (Day 2)	
8:00 a.m.–9:30 a.m.	Session 8: Potential topic for FNIH CBTC: iPSC <i>Moderators: Dr. Pamela Robey and Dr. Valeria Canto-Soler</i> Presenters will address non-clinical, translational, and scale-up/production issues related to iPSCs so that we can identify a few areas of focus that would be appropriate as topics to include a Cell-Based Therapies Consortium.
9:30 a.m.–9:45 a.m.	BREAK
9:45 a.m.–10:30 a.m.	Session 9: Discussion to identify cross-cutting research needs for acceleration of iPSC into clinical application. <i>Panel Discussion</i>
10:30 a.m.–11:15 a.m.	Session 10: Integration across agencies and stakeholders: Define opportunities for future collaborative approaches ... and funding. <i>Panel Discussion</i>
11:15 a.m.–11:50 a.m.	Session 11: Group discussion: Finding common ground with FNIH, federal and Industry interests. <i>Panel Discussion</i>
11:50 a.m.–12:00 p.m.	Closing: Synthesis and next steps/action items. <i>Dr. Robert Carter and Dr. Santa Tumminia</i>

Appendix 3
Supporting References for Research Vignettes

Vignette 1: Stem Cell Therapy for Amputees

- i. Lee SS, Sweren E, Dare E, et al. The use of ectopic volar fibroblasts to modify skin identity. Science. 2024 Sep 6;385(6713).
- ii. <https://clinicaltrials.gov/study/NCT03947450>

Vignette 2: Localized Delivery of Stem Cell Factors for Osteoarthritis

- i. Ruscitto A, Chen P, Tosa I, et al. Lgr5-expressing secretory cells form a Wnt inhibitory niche in cartilage critical for chondrocyte identity. Cell Stem Cell. 2023 Sep 7;30(9):1179-1198.

Vignette 3: Insulin-Producing Stomach Stem-Cell Based Organoids

- i. Huang X, Gu W, Zhang J, et al. Stomach-derived human insulin-secreting organoids restore glucose homeostasis. Nat Cell Biol. 2023 May;25(5):778-786.
- ii. <https://www.fda.gov/vaccines-blood-biologics/lantidra>

Vignette 4: Patient Derived Stem Cells as a Treatment for Parkinson's Disease

- i. Osborn TM, Hallett PJ, Schumacher JM, et al. Advantages and Recent Developments of Autologous Cell Therapy for Parkinson's Disease Patients. Front Cell Neurosci. 2020 Apr 3;14:58.
- ii. <https://clinicaltrials.gov/study/NCT06422208>

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