

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

Report Overview

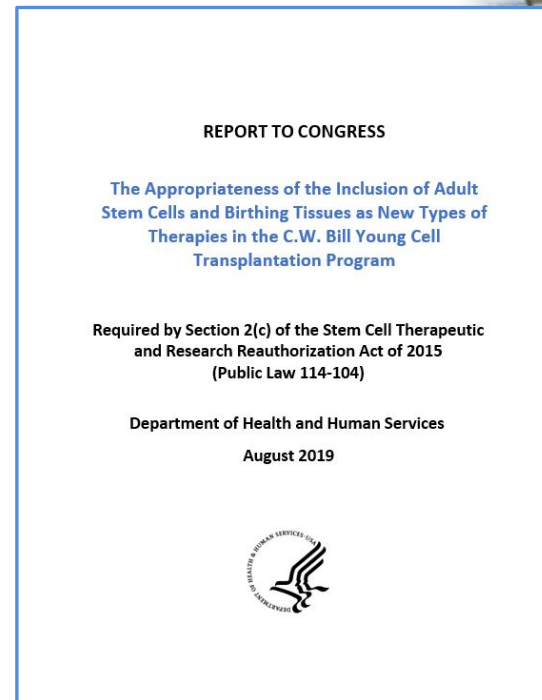
Advisory Council on Blood Stem Cell Transplantation

September 10, 2019 Briefing



Topics

- **Review of relevant provisions of the Stem Cell Therapeutic and Research Reauthorization Act of 2015**
- **Overview of report**
- **Discussion of findings and recommendations**



Stem Cell Therapeutic and Research Reauthorization Act of 2015

- **HHS Secretary to consult the NIH Director, FDA Commissioner, HRSA Administrator, and the Advisory Council on Blood Stem Cell Transplantation regarding:**
 - **A review of the state of the science 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 C.W. Bill Young Cell Transplantation Program (CWBYCTP)**
- **Report to Congress:**
 - **Must include recommendations on the appropriateness of such new types of therapies for inclusion in the CWBYCTP**
 - **Due June 30, 2019**
 - **To be submitted to:**
 - **Senate Committee on Health, Education, Labor, and Pensions**
 - **House Committee on Energy and Commerce**

Report Sections

- **Executive Summary**
- **Statutory Mandate**
- **Purpose of the C.W. Bill Young Cell Transplantation Program**
- **Outcomes Data Collection and Reporting Currently Facilitated Through Funding from the CWBYCTP**
- **Consultations Performed Relevant to this Report**
- **Background on Stem Cell Therapies**
 - **Hematopoietic Stem Cells and Birthing Tissues for Hematologic or Immunologic Reconstitution**
 - **Adult Stem Cells and Birthing Tissues for Other Uses (3 exemplary vignettes)**
 - **Regulatory Framework for Stem Cell Therapies**
 - **Efforts to Expedite Progress Developing Adult Stem Cell and Birthing Tissue Treatments**
- **Proposed Criteria for Inclusion of New Cellular Therapies in the CWBYCTP**
- **Key Findings Regarding Inclusion of Adult Stem Cells and Birthing Tissue Products in the CWBYCTP**
- **Recommendations**
- **References and Appendices**

C.W. Bill Young Cell Transplantation Program

- Purpose is to increase the number of bone marrow and cord blood transplants for recipients suitably matched to biologically unrelated donors
- Provides a structure to facilitate blood stem cell transplantation with blood-forming cells from unrelated donors for individuals with leukemia and other life-threatening blood disorders
- Five key functions/components currently
 - Facilitate bone marrow and cord blood transplantation
 - National Cord Blood Inventory
 - Office of Patient Advocacy
 - Single Point of Access Coordinating Center
 - Stem Cell Therapeutic Outcomes Database



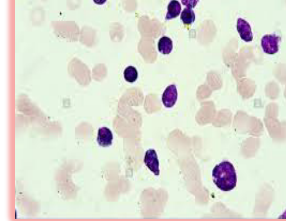
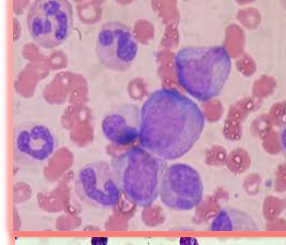
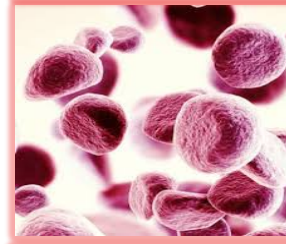
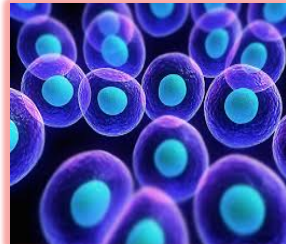
Consultations Relevant to this Report

- **FDA workshop: Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval (Sept. 2016)**
- **NIH-FDA workshop: Regenerative Medicine Innovation Workshop: Focus on Adult Stem Cells (Dec. 2017)**
- **National Academy of Sciences Forum on Regenerative Medicine meetings (Oct. 2016, June 2017, Oct. 2018)**
- **Center for International Blood and Marrow Transplant Research meetings**
 - **Regenerative Medicine Registry Meeting (Aug. 2017)**
 - **Cellular Therapy Registry Forum (Oct. 2018)**



State of the Science: Stem Cell Therapies

- **Hematopoietic stem cells and birthing tissues for hematologic or immunologic reconstitution**
 - Applications include use of bone marrow-derived stem cells, peripheral blood-derived stem cells, and cord blood-derived stem cells for treatment of:
 - Bone marrow failure syndromes, hereditary hematologic disorders, hematologic and certain other malignancies, certain immunologic disorders
 - Safety and efficacy clearly documented in hundreds of publications (examples provided)
 - Currently several FDA-approved cord blood products



State of the Science (cont.)

- **Adult stem cells and birthing tissues for other uses**
 - Have been and are being investigated for the treatment of a wide variety of different disorders, including:
 - Rheumatologic diseases such as osteoarthritis and rheumatoid arthritis; neurologic diseases such as stroke, Parkinson's disease, and amyotrophic lateral sclerosis; and cardiovascular diseases such as congestive heart failure
 - Clinical trials conducted in each of these areas have yet to demonstrate clinical efficacy
 - Significant safety concerns have been documented (examples provided)
 - Currently no FDA-approved adult stem cell products or birthing tissues products for use outside of hematologic or immunologic reconstitution

State of the Science (cont.)

- **Adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution generally require study under **Investigational New Drug applications** (INDs) and approval of Biologic Licensing Applications (BLAs) prior to marketing (section 351 of the Public Health Service Act)**
 - **Suite of guidance documents was issued in November 2017 to clarify **the risk-based regulatory approach** to novel stem cell uses and to facilitate development in the field**
 - **Regenerative Medicine Advanced Therapy Designation (RMAT) was enacted by Congress as part of 21st Century Cures in part to help **facilitate development and approval** of novel stem cell products for serious or life-threatening diseases**

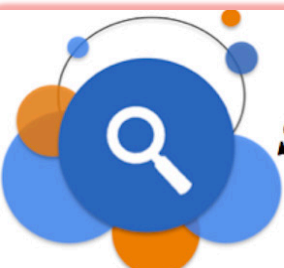


National and International Expert Forums

- Convened to explore state of the science and clinical application
 - While cell therapies offer potential promise, much must be learned about cell function and product manufacturing before safe and effective products can be administered in the clinic

Use of a Registry: Definition and Examples

- **Key characteristics of a registry**
 - Single (or a few) similar well-defined products included
 - Outcome measures are similar for the different products
 - Able to meaningfully analyze data across comparable products
- **Hematopoietic Stem Cell Transplantation Registry has these characteristics**
 - Blood- and bone marrow-derived cells, cord blood
 - GvHD rates, relapse rate, and survival for similar clinical indications (hematologic and immunologic reconstitution)
 - Compare different product categories
- **Products derived from adult stem cells and birthing tissues for clinical purposes other than hematologic and immunologic reconstitution are highly diverse and do not meet the criteria for inclusion in such a registry**



Search the Registry



Proposed Criteria for Inclusion of New Cellular Therapies in the CWBYCTP

- The **purpose of the CWBYCTP underpins the proposed criteria** for inclusion of new cellular therapies in the CWBYCTP
 - To help patients who need a potentially **life-saving** bone marrow transplant or umbilical cord blood transplant from an **unrelated** marrow donor or 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
- The **HRSA mission also underpins the criteria**
 - To improve health through **access to quality services**



Proposed Criteria (cont.)

- In keeping with that purpose and mission, the **proposed criteria for inclusion of new cellular therapies in the CWBYCTP** are that it should include:



Only those adult stem cell and birthing tissue products—including those with new uses outside of hematologic or immunologic reconstitution—that:

- 1) are utilized as treatments for serious or life-threatening conditions;
- 2) require donor matching if appropriate; and
- 3) 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

Inclusion of Adult Stem Cell and Birthing Tissue Products in the CWBYCTP: Key Findings

- **Bone marrow and cord blood transplants are widely accepted** by clinicians as representing a standard of care in certain settings (e.g., relapsed acute leukemia)
- **Adult stem cells and birthing tissues for other investigational applications inherently do not 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**



Key Findings (cont.)

- **Information regarding the clinical trials** investigating these products and the results of these trials are useful to patients interested in potentially enrolling in such studies and are also of potential interest to the general public (**access and transparency**)
 - However, access to this information is **already facilitated by ClinicalTrials.gov**, a congressionally-mandated and federally-funded database administered by NIH in coordination with FDA
 - **Statutory requirement and NIH policy** that certain trials be listed in this public database and others may be listed electively at the investigator's discretion
 - Provides information relevant to **patient participation** and **summary safety and outcomes results for completed trials**
 - Represents an important and unique public information resource for those interested in learning more about products under development **whose safety and efficacy is yet to be established**

Key Findings (cont.)

- Intermingling of proven and unproven/unapproved therapies in the CWBYCTP would:
 - Have the **Program overseeing the maintenance and dissemination of information about some products with proven effectiveness and some products that are purely experimental**
 - **Confuse patients** and possibly even mislead them regarding which CWBYCTP products are effective, and which products are investigational
 - **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
 - Be **detrimental to public confidence** in potentially life-saving bone marrow-derived and peripheral blood-derived stem cell transplants and cord blood transplants
 - **Undermine the goal of the CWBYCTP** to ensure access to and improve patient outcomes from these treatments

Key Findings (cont.)

- Inclusion of investigational adult stem cells and birthing tissue products 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 will greatly reduce or eliminate the incentive for legitimate product development and private sector investment in accordance with all applicable regulations
 - **Undermine the regenerative medicine-related provisions of the 21st Century Cures Act**, which encourage sponsors to obtain the needed clinical evidence for obtaining marketing approval from the FDA
 - Supporting the intent of the 21st Century Cures Act will allow the greatest access for patients to safe, effective, and innovative cellular and tissue-based products

Recommendations



- **HHS Recommendation 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 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**

Recommendations (*cont.*)

- **Rationale:**
 - **Criteria are in keeping with purpose of CWBYCTP to facilitate access to potentially life-saving transplants from an unrelated donor or cord blood unit by facilitating matching**
 - **CWBYCTP currently facilitates access to potentially life-saving therapies that are generally accepted by the medical community as safe and effective**
 - **In distinct contrast to the use of hematopoietic stem cells and birthing tissues for hematologic and immunologic reconstitution, adult stem cells and birthing tissues for other uses are investigational and many such uses do not address serious or life-threatening conditions**

Recommendations (cont.)

- **HHS Recommendation 2:**

- **Based on these criteria, the inclusion of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time**



- **Rationale:**

- **While the use of adult stem cells and birthing tissues for other uses holds significant promise, such applications are presently experimental, have not been proven safe and effective, and therefore do not meet the criteria for inclusion as new cellular therapies in the CWBYCTP**
- **Inclusion of investigational products that require but have not yet received FDA approval could give patients and providers the erroneous impression that these products are comparably safe and effective as are stem cell products used for hematologic and immunologic reconstitution**

Recommendations (cont.)

- **HHS Recommendation 3:**

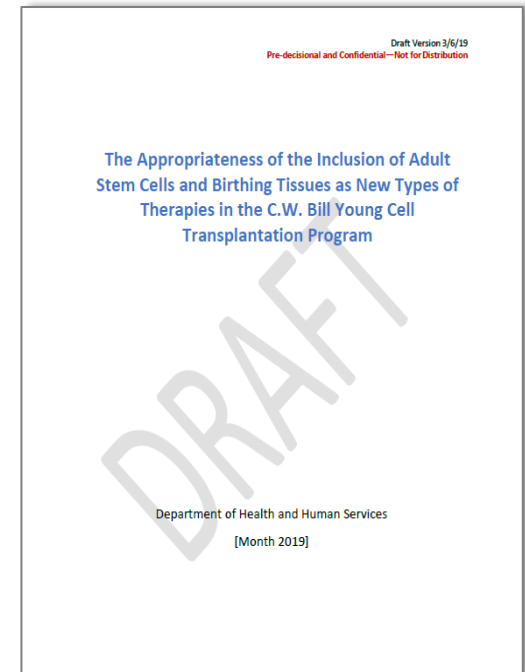
- **As the science advances and new classes of cell-based products are developed that meet regulatory approval standards for safety and effectiveness, it may be appropriate to include such products in the CWBYCTP**

Therefore, re-evaluation 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 is recommended on a periodic basis (every 2-3 years or as needed), with issuance of a report on the outcomes of these evaluations when relevant



Consultation: Advisory Council on Blood Stem Cell Transplantation

- **Quorum of appointed members convened March 2019**
 - **Members included the Workgroup on New Uses for Adult Blood Stem Cells and Birthing Tissue**
 - **Draft report provided in advance for ACBSCT review**
 - **Overview of report presented followed by discussion**
- **Council members also provided written comments**



ACBSCT Feedback

- Report provides a comprehensive review of the state of the science as it relates to considerations regarding the appropriateness of including additional adult stem cells and birthing tissues in the CWBYCTP
- Council members agreed with the premise of and recommendations in the report and acknowledged the potential risks posed by unproven therapies
- Comments and questions focused primarily on the three key elements of the proposed criteria for inclusion of new cellular therapies in the CWBYCTP
 - **Criteria and recommendations modified in response to ACBSCT suggestions**



In Sum

- Report outlines an approach that, if implemented, provides a sound foundation for maintaining public trust in the CWBYT Program:
 - Report amply reflects the **state of the science** of clinical use of adult stem cells and birthing tissues
 - Recommendations uphold the intended purpose of the Program and promote the **reliability and integrity** of the information it provides
 - Report proposes a process for **reassessing the field as science advances** and any implications for future inclusion of additional products in the CWBYCT Program

