OPTN Operations and Safety Committee
Meeting Summary
July 27, 2023
Conference Call

Alden Doyle, MD, MPH, Chair
Kim Koontz, MPH, Vice Chair

Introduction

The OPTN Operations and Safety Committee (henceforth the Committee) met via Citrix GoTo teleconference on 07/27/2023 to discuss the following agenda items:

1. Regulation of Allograft Heart Valves

The following is a summary of the Committee's discussions.

1. Regulation of Allograft Heart Valves

Summary of Presentation:

The Food and Drug Administration (FDA) representative began the presentation with an introduction to the Committee including their relevant work experience with the Organ Procurement Organization (OPO), LifeNet, that maintains a large tissue bank and is a manufacturer of allograft heart valves. The FDA representative also informed the Committee of their experience with heart procurements and preservation of procured heart valves, and provided the overview of their presentation pertaining to answering different questions regarding allographs and how they are to be regulated. The FDA representative noted that they will have to refer to allograft tissues as products and the steps in the recovery, processing, storage, labeling, packaging, and distribution of tissues as manufacturing as it is required by regulatory language.

The presentation then moved on to covering the background of the FDA's investment and commitment to protecting the safety of public health as they relate to tissue allographs noting that the use of tissues as medical products of human origin have expanded in their application and become more commonplace since their first use. The FDA representative provided an overview of this portion of the presentation starting with disease transmission history by tissue allografts, then covering the FDA's subsequent regulatory approach for controlling disease transmission, then briefly covering parts of the Title 21 Code of Federal Regulations (CFR) Part 1271 and finishing with the new allograft heart valve proposal.

A table documenting worldwide disease transmission by tissue allografts from 1954 to 2011 was displayed. The FDA representative pointed out that most of the diseases covered in the table indicate that fresh, refrigerated, and cryo-preserved tissues pose the highest risk of disease transmission with heart valves being no exception. The FDA representative moved on to cover the proposed approach to the regulation of tissues by the FDA which began in 1997 at a time where there was an increased demand for tissues, new manufacturing techniques becoming commonplace, and a disparity in industry standards needed to be addressed. They began with a tiered, risk-based approach with the goals being preventing unwitting use of contaminated tissues; preventing improper handling or processing resulting in contamination and damage to tissues and to ensure the clinical safety and effectiveness is

demonstrated for tissues that are highly processed, used for non-natural purposes, are combines with non-tissue components, or that have systemic effects on the body.

The regulatory authority the FDA acts on is delegated from the Surgeon General and the Secretary of Health and Human Services (HHS) allowing them to create and enforce regulations necessary to prevent the spread of communicable diseases. The FDA representative noted that it is under this authority where the Title 21 CFR Part 1271 regulations were promulgated seeing as human cells, tissues, and other cellular based products (HCT/Ps) carry risk of spreading disease between healthcare personnel, tissue handlers, recipients, and close contacts of recipients. Examples of HCT/Ps include but are not limited to bone, ligament, skin, cornea, reproductive tissue, dura mater, and heart valves. The FDA made note that the following articles are not considered HCT/Ps: vascularized human organs, whole blood or blood components, tissues derived from animals, in vitro diagnostic products, and blood vessels recovered with an organ that is intended for use in organ transplantation.

The FDA representative highlighted the two regulatory tiers. The first is the 361 HCT/P which is regulated under the authority of section 361 of the Public Health Service (PHS) Act and subject to 21 CFR part 1271 but does not require a premarket review. For products to fall under this category, HCT/Ps need to meet the following criteria:

1. be minimally manipulated (MM).
    a. This means, for structural tissue, that processing does not alter the original characteristics of the tissue's utility; and for nonstructural tissues, that processing does not alter the relevant biological characteristics of the cells within the tissue.
        i. The aortic valve and its outflow tract with myocardial skirt as well as a pulmonary heart valve with its outflow tract were used as examples.
2. intended for homologous use (HU).
    a. This is defined as 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—such as heart valves.
        i. Allograft heart values used in a double root replacement was used as an example.
3. not combined with another article.
    a. This means the manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent.
4. and either has no systemic effect and is not dependent upon living cells for its primary function, or has a systemic effect, or is dependent upon the activity of living cells for its primary function and is for autologous, allogeneic, or for reproductive use.

The second tier is 351 HCT/Ps which is regulated under the authority of section 361 and section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act, but does require a premarket review.

The FDA representative proceeded to cover the new allograft heart valve protocol consisting of recipient identification and medical necessity (i.e., Tetralogy of Fallot and Truncus arteriosus), setting donor criteria parameters, donor identification with screening and testing, procurement, tissue packed and shipped, and finally implantation. At this point, one of the meeting attendees from the OPTN Heart Committee pointed out that there is a is a big concern with the new protocol how it relates to maximizing the beneficence of the organs regarding Tetralogy of Fallot and Truncus arteriosus patients as there are surgical alternatives for these populations that do not require the use of a transplanted organ for prolonging life and substantially improving their heart function. The OPTN Heart Committee attendee continued that making use of scarce organs for this subset of patients and diverting much

need organs from people who have been on the waiting list for an already long time is concerning as the patient who has no alternatives should be getting the organ, not a patient who has other options at their disposal. The FDA representative thanked the OPTN Heart Committee attendee for their opinion and clarified the FDA does not necessarily regulate the use of the tissue itself.

The FDA representative moved on to covering donor eligibility, which is based on donor screening and testing for communicable diseases and disease agents, i.e., Human Immunodeficiency Virus types 1 and 2, Hepatitis B, Hepatitis C, Sepsis, West Nile Virus, Zika Virus. It was also noted an HCT/P must not be implanted, transplanted, infused, or transferred until the donor has been deemed eligible by means negative disease screening by the establishment responsible for donor eligibility determination. Once donor eligibility has been determined, the following records are to accompany the HCT/P: a distinct identification code on the HCT/P container that relates the donor to the HCT/P, a statement whether the donor has been determined to be eligible or ineligible, and a summary of the records. At this point, another meeting attendee from the OPTN Multi-Organ Transplantation Committee requested clarification on who is screening the donor for this protocol or if it is happening through a third-party organization. The FDA representative confirmed that this is happening through a third-party organization. Another attendee from the OPTN Organ Procurement Organization Committee also confirmed, but also informed the Committee that since there is no stand process currently, other OPOs are all trying to navigate how this will be fit into their practice.

Moving on to donor screening, the FDA representative went over the screening process which necessitates screening donor cells or tissues by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, and communicable disease risks associated with xenotransplantation. The next step is donor testing. At this point in the presentation, the FDA representative showed a graphic that listed out all adequate and appropriate testing that the FDA recommends reducing the risk of disease transmission and noted that the donor testing establishment must use a FDA licensed, approved, or cleared tests.

The FDA representative moved on to the recovery of tissues, defining recovery as obtaining from human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer. They also stressed that recovery establishments must recover each HCT/P in a way that does not cause contamination or cross-contamination, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P. After recovery, packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination and establish and maintain appropriate shipping conditions during transit.

In the event of a recipient having an adverse reaction--defined as fatal, life-threatening, permanently impairing, or necessitates medical or surgical intervention--an investigation is required, and it must be reported to the FDA on a 3500-A form within 15 calendar days to ensure the limitation of potential disease distribution. A follow-up report may be required if additional information is requested.

Summary of Discussion:

The presentation discussion began with a member from the OPTN Pediatric Transplantation Committee (PTC) asking how the OPTN are currently recognize donors and potential recipients and what the future outlook will be for these valves' relationship to OPOs. Support staff responded that the valves fall under the preview of the FDA so there will be limited efforts that can be taken outside of the FDA for regulation or policy related thereof. The OPTN PTC member noted their weariness about the lack of ability to track these patients' long term, or to affect regulatory work. The FDA representative reminded the OPTN PTC member of the history behind the utilization of heart valves in Ross procedures, so those surgeons and clinicians got together and created a database that is still ongoing today.

A member voiced their concern that this type of therapy would be out of reach for lower socio-economic individuals due to the differences between it and the heart transplant process. A member of the OPTN OPO Committee expressed concern about OPOs that are interested in accessing these valves as they could easily be treated like a tissue that has to then take on the burden of determining recipient eligibility. The FDA representative responded that OPOs are taking the spot of manufacturer in certain steps, but there is no real processing going on, but tasks such as donor eligibility determination would be in their purview. This member continued by noting potential issues observed in regards to how and for how long can these valves be stored if the OPOs do not have any oversight. The FDA representative noted they would be handled in the same manner as any other solid organ.

The member from the OPTN PTC again brought up concern in finding donors and recipients; as of right now, it does not seem to be concrete, which is unfair. The member noted that this poses serious implications for smaller facilities with less resources and access for their pediatric patients as they will not have the space or means to store tissues. The member stressed the need for a better system with consideration to these points.

The OPTN OPO Committee member expressed concern that the level of surgical technical skills needed to implant allograft heart valves would not exist in many hospitals, even if there were patients who could benefit from the procedure and asked for reconciliation. Other meeting attendees informed them that more congenital heart centers and hospitals that do medium to large volume heart surgeries would be able to handle the skills necessary for a procedure like this.

A member of the OPTN Heart Committee voiced their concern about the lack of guardrails concerning regulation. The member noted that most can agree if you find a heart that is going to be non-utilized, but have otherwise found a use for a donated tissue, that improves the beneficence of the organ donation and would indeed be a good use of it. However, the member continued be stating they have read the entire protocol and deems the protocol does not help with dictating that would be the case in every case and it does not dictate weather or not a patient can be placed on the waiting list in order to gain a partial heart transplant. This member stressed the need for the language in the protocol to be reviewed further with consideration to promote better understanding of the allocation of these tissues. Another OPTN Heart Transplant Committee member clarified that there is nothing stopping a center from listing a patient for a heart when they have valvular heart failure and qualify for listing on the basis on valvular heart failure which can be treated with a partial heart transplant. They continued that the way the protocol is outlined, there is nothing stopping a center from taking a whole heart for the need of a partial heart.

The discussion wrapped up with multiple meeting attendees voicing their desire for language refinement in the protocol to more clearly delineate duties in addition to allocation and outcome language.

The meeting was adjourned.

Upcoming Meetings

- August 24, 2023 (teleconference)
- September 28, 2023 (in-person)
- October 26, 2023 (teleconference)

Attendance

- **Committee Members**
  - Anja DiCesaro
  - Jami Gleason
  - Julie Bergin
  - Kaitlyn Fitzgerald
  - Kimberly Koontz
  - Laura Huckestein
  - Sarah Koohmaraie
  - Stephanie Little
- **HRSA Representatives**
  - Jim Bowman
  - Kayla Rochelle
  - Vanessa Arriola
- **SRTR Staff**
  - Katie Audette
- **UNOS Staff**
  - Betsy Gans
  - Joann White
  - Kelley Poff
  - Kerrie Masten
  - Lauren Mauk
  - Liz Robbins Callahan
  - Robert Hunter
  - Susan Tlusty
- **Other Attendees**
  - Emily Perito
  - JonDavid Menteer
  - Kyle Herber
  - Lisa Stocks
  - Lori Markham
  - Neha Bansal
  - Rachel Engen
  - Raymond Lee
  - Rocky Daly
  - Scott Brubaker
  - Scott Lindberg
  - Shelley Hall