Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) Tissue Biovigilance Subcommittee –

Gap Analysis Report and Proposed Recommendations

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Introduction

A Tissue Biovigilance Subcommittee was established at the November 2022 Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) meeting in response to a presentation highlighting a persistent traceability problem between donors and recipients, as documented in the 2022 briefing by the Centers for Disease Control and Prevention (CDC) on tuberculosis and M. hominis transmissions through human tissue products. The presentation additionally highlighted that there is no requirement for consignees or end users to report adverse reactions involving cell and tissue products and that this status quo presents an ongoing risk of patient harm, especially from products that contain viable cells. The proposal to form a Subcommittee passed with unanimous approval. The Subcommittee was managed by the Office of Infectious Disease and HIV/AIDS Policy (OIDP) within the U.S. Department of Health and Human Services (HHS).

Co-chairs of the Subcommittee were selected to include one federal representative and one non-federal transplant surgeon. The co-chairs and OIDP staff worked to ensure balanced and sufficient representation by stakeholders and subject matter experts on four working groups within the greater subcommittee. The working groups included experts on significant steps in a tissue product's lifecycle: Tissue Source, Tissue Processing, End User Consignee Receipt and Use, and Adverse Events. The goal for each group was to identify and document gaps for processes within its step. The gaps identified by each of the working groups have been compiled into this document to present to the ACBTSA for consideration to improve tissue biovigilance in the United States.

Working Group One: Tissue Source

The scope of the Tissue Source Working Group included donation authorization and informed consent, donor screening, the decision to proceed, tissue recovery /acquisition procedures, donor testing, and the chain of custody.

The Working Group met on June 16, 2023, August 24, 2023, March 14, 2024, and July 16, 2024.

Potential Recommendations

1. To close gaps and to promote collection of information that could inform donor eligibility policy when screening donors of cells and tissues, standardized donor medical history interview forms and related tools should be developed and recommended in guidance issued by professional societies and regulatory authorities.

2. To optimize control of contamination, effective practices surrounding cell and tissue recovery/acquisition procedures should be identified and standardized across industry.
3. To inform cell and tissue donor screening policies, information collected from investigations and adjudication processes involving reports of probable transmission of disease to organ or tissue recipients must be disseminated widely by all groups involved in investigations.

Gap Analysis

Donation Authorization and Informed Consent

No gaps were identified.

Methods of obtaining authorization or consent via requirements described in the Uniform Anatomical Gift Act (UAGA) and adopted by U.S. states, including first-person consent and next-of-kin authorization procedures, are sufficient. For deceased donation, consent and authorization processes are typically performed by organ procurement organizations (OPOs). A high rate of compliance is observed through assessments, including Centers for Medicate & Medicaid Services (CMS) site surveys of OPOs that typically occur every 4 years, and during inspections by voluntary professional accreditation bodies (e.g., Association of Organ Procurement Organizations (AOPO), the Eye Bank Association of America (EBAA), and the American Association of Tissue Banks (AATB)) that inspect their constituencies generally every 3 years.

1. See this regulation that CMS uses when it performs site surveys to check compliance: § 486.342 Condition: Requesting consent. (https://www.ecfr.gov/current/title-42/section-486.342)
2. UAGA information can be accessed here:
    a. https://www.uniformlaws.org/committees/community-home?CommunityKey=015e18ad-4806-4dff-b011-8e1ebc0d1d0f
    b. https://www.hrsa.gov/advisory-committees/organ-transplantation/recommendations/19-28

Donor Screening

There are gaps in tissue donor screening that affect the completeness and reliability of the information gathered. For organ, tissue, and eye donors in the Unites States, there is no endorsement of a single, standardized donor history questionnaire (the Uniform Donor Risk Assessment Interview [UDRAI] forms/tools) like that which is used for blood donation (the Donor History Questionnaire [DHQ] forms/tools). In addition, there is a lack of information collection by industry regarding donor screening/testing experience that could inform donor eligibility policy.

1. There is no endorsement to require use of a single, standardized (uniform) donor risk assessment interview (i.e., UDRAI) form and procedures when obtaining tissue donor medical, travel, and behavioral risk information from a living donor or from the person (proxy) providing the history for a deceased donor.
    a. The UDRAI form and associated tools are considered industry best practice and, if used, could reduce variability in donor screening policies and decision-making processes. The design of questions used in the interview should capture all relevant information.
    b. The DHQ and accompanying tools, which are used for blood donation in the United States, were developed more than 20 years ago by the DHQ Task Force, a group of stakeholders from the blood industry that works with FDA input and is managed by the AABB. When indicated, the group continues to update these tools today. A similar government/non-governmental organization partnership should be developed to further work related to the UDRAI forms and tools, which were developed a decade ago by a "UDHQ Task Force" and a "UDRAI Stakeholder Review Group" for organ, tissue, and eye donation.
    c. The only data available regarding how many organizations currently use the UDRAI for organ, tissue, or eye donors is from the EBAA, which reports that only two eye banks do not use it—i.e., that the UDRAI is used by 90to 95% of all eye banks accredited by the EBAA.
2. The donor screening process may be complicated by language barriers, citizenship status of involved individuals, limited knowledge of proxy historians, and potential reticence to divulge personal history due to perceived legal repercussions.
3. Inconsistencies in the pursuit of and access to a donor's existing relevant medical records (e.g., electronic health/medical records, primary care physician records) affect the accuracy and completeness of information used to establish risks.
    a. Obtaining patient health records, including electronic health records, can be difficult and time consuming.
    b. Information gathering is done quickly due to time constraints related to limits of the tissue preservation method (e.g., refrigerated corneas).
4. Collection of information by industry is completed through periodic surveys (e.g., EBAA Annual Statistical Report, the 2012/2015 National Tissue Recovery through Utilization Survey); however, data collection is susceptible to interpretation bias, and the information does not inform policies involving donor eligibility criteria.
5. Recommendations agreed upon during an ACBSA meeting held in November 2009 and sent to the ASH in January 2010 appear to have been seriously considered by the ASH but not acted upon. The recommendations identified that there is currently no standardized approach to collecting the medical and social history of donors that provides information to assess infectious disease risks, and this gap affects organ and tissue safety:

a. For organs: “The Committee recommends the Secretary support development and validation of a uniform donor health history screening questionnaire.”
b. For tissues: “Develop uniform questionnaire for donor screening to optimize patient safety.”

Decision to Proceed

Donor eligibility criteria vary for identifying a tissue donor at risk of sepsis. There is no clear basis for challenging the judgment of medical directors who develop these criteria, and their criteria may be influenced by tissue processing methods. The practice of referring screened tissue donors to multiple tissue processors until one accepts should be made transparent by including the reasons for any prior rejection in a subsequent referral.

1. Donor eligibility criteria are primarily determined by policies established by medical directors of tissue banks, and eligibility decisions they make may be influenced by risk assessments based on tissue processing methods (e.g., including an irradiation step).
    a. Policies regarding donor eligibility criteria vary among tissue processors (e.g., musculoskeletal, cardiovascular), primarily due to differing viewpoints regarding how to identify “sepsis.”
    b. Some medical directors question the validity of a sepsis diagnosis made by attending physicians and claim such diagnoses are documented to facilitate medical reimbursement or are utilized as a differential diagnosis. However, when evaluating an organ donor for risk of infection such as sepsis, OPO donation coordinators speak directly with the donor’s attending physicians.
    c. Donor screening information gathered by OPO, tissue bank, and eye bank personnel is guided by consultation with medical directors or physician consultants.
    d. FDA guidance that provides recommendations to reduce the risk of transmission of disease due to sepsis should be revised based on findings from the Tissue Biovigilance Subcommittee.
2. After collecting donor screening information, a tissue recovery program may call multiple processors until one accepts. Tissue processors should inquire as to whether a donor has been previously rejected by other tissue banks and request the reasoning for a prior rejection. Such information is not readily or automatically shared.
3. In general, inspectors do not challenge donor eligibility decisions made by medical directors.
    a. Inspection frequency varies among voluntary professional accreditation bodies and the Food and Drug Administration uses a risk-based approach to develop an annual inspection plan.

Tissue Recovery / Acquisition Procedures

There is a lack of standardization of tissue recovery/acquisition procedures, which hinders the development and wide use of best practices that could reduce tissue contamination rates.

1. A recovery organization may contract with up to twelve musculoskeletal tissue processing partners, and each processor has different protocols related to recovery procedures, such as supplies and reagents used for prepping the skin of a donor, how to perform culturing of tissue, and wrapping and labeling each tissue recovered.
2. Best practices (e.g., donor skin prep) may be identified by recovery organizations and can be linked to outcomes such as lower contamination rates based on tissue culture reports. However, tissue processing partners are reluctant to make changes.

Donor Testing

No gaps were identified.

Tracking/Coding/Records (Chain of Custody)

The process of labeling tissues at recovery and assigning an identification number to the tissue donor is not uniform throughout the industry, which allows multiple numbers to be assigned to one donor. There appears to be a gap in the collection and dissemination of information to tissue establishments concerning investigations of possible disease transmission to organ recipients and, separately, in sharing investigation results for cases of probable transmission of disease. Information collection and dissemination by a central repository could inform donor screening policies.

1. Although the coding systems used differ, barcodes are used for labeling procured organs and for labeling tissues at recovery.
2. Tissue recipient adverse reaction reports may not be shared by tissue processors with OPOs involved with screening the donor and recovery of the donor's tissue. This lack of sharing may occur to protect patient confidentiality; however, it can impact the OPO's ability to improve their donor screening processes, and it may delay communication with transplant centers who are caring for recipients of organs from the same donor.
3. United Network for Organ Sharing, Organ Procurement and Transplantation Network (OPTN/UNOS) policies closed a gap in communication after a sentinel event in 2011. However, when the UNOS ad hoc Disease Transmission Advisory Committee (DTAC) adjudicates reports of possible transmission of disease to organ recipients, a final report of the investigation's outcome is not always shared, and tissue from a donor involved in the investigation remains in quarantine storage for a lengthy period.
4. When a donor is both an organ donor and an eye or tissue donor, information sharing occurs among all organizations involved when a possible communicable disease transmission has been identified post-transplant of organs or after use of tissue products. However, there is no central repository through which data can be collected, analyzed, and disseminated.
5. The process of labeling tissues and assigning an identification number to a tissue donor is not uniform throughout industry. Regulations require a "distinct identification code" for

human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are traceable to the donor and to consignees – inclusive of all products generated during manufacture. Two professional standards organizations, EBAA and AABB, have promoted the use of ISBT 128 coding. The result is that multiple numbers can be assigned to one donor.

6. Between 2005 and 2009, the Transplantation Transmission Sentinel Network (TTSN) was led by CDC in a cooperative agreement with UNOS to develop a system prototype to track tissue products from donation to tissue implantation and to potential adverse events. A system was piloted with the participation of OPOs, tissue banks, and transplant centers, and specific challenges to implementation were identified. For an overview of challenges, see:
    a. https://pubmed.ncbi.nlm.nih.gov/20652419/
    b. https://pubmed.ncbi.nlm.nih.gov/19016348/

Other Important Information – Not Gaps

During 2023, there was an unusual increase in positive reports for HBsAg results when testing eye and/or tissue donors. Discordant results were found, and the issue may be related to a specific testing company or test kit and/or testing platform. Investigation into the cause continues.

Accreditation by professional societies (e.g., AATB, EBAA, AABB) is voluntary, and therefore not all cell or tissue establishments in the United States are accredited and will follow standardized procedures published by these societies.

Working Group Two: Tissue Processing

The scope of the Tissue Processing Working Group includes the chain of custody of biological materials; bioburden assessment, culture method, and molecular method suitability; preservation and storage of materials; process validation and tissue suitability for release; donor eligibility determination; data collection that can inform standards and policies; and product distribution.

The Working Group met on June 13, 2023, August 22, 2023, March 12, 2024, and July 17, 2024.

Potential Recommendations

1. To optimize cell and tissue product traceability from donor to recipient and back to the donor, the use of electronic systems must be required by health authorities; electronic health records must have functionality to accommodate a variety of long, distinct identification codes assigned to products; and manufacturers' requests for product disposition information from end users should be required.
2. To overcome bioburden assessment and process validation procedures that are inadequate for detecting contamination of tissue products that pose the greatest risk to recipients,

microbiological process validation and surveillance programs must be effective, standardized by experts, and followed by industry.

3. To improve accountability and reduce variability that can affect recipient safety, donor eligibility determinations made by responsible persons should be independently monitored and noncompliance formally addressed.
4. To inform national standards, recommendations, and policies, cell and tissue donor screening experiences, donor testing outcomes, and data regarding use of products must be periodically collected, formally analyzed, and published every 2-3 years.

Gap Analysis

Chain of Custody

Although processors do not use a single "globally" unique coding system to label tissue products, disruptions to the chain of custody occur only after product distribution. Traceability gaps identified include 1) electronic health record software used by end users cannot accommodate a long product code number that a popular coding system provides (i.e., ISBT-128); 2) domestic and international end users often do not respond to manufacturers' requests to voluntarily provide information regarding the final disposition of products; 3) industry follow-up protocols and parameters used to evaluate information are not uniform; and 4) systems to collect information may not facilitate tracing if they are not electronic.

1. Identifying tissue recipients or other final disposition of products is hampered due to the lack of cooperation from, and lack of recordkeeping practices by, end users (e.g., dental offices, busy orthopedic practices or surgical centers). End users do not voluntarily communicate disposition information when requested by manufacturers (e.g., through return of implant cards or other recipient follow-up data collection protocols).
2. If responses to implant cards or similar methods are received by a processor, they may be logged using manual methods and may not be searchable. Systems maintained electronically are preferred.
3. Electronic health records do not accommodate long tissue product identification numbers, including ISBT-128 coding when it is used by a processor.
4. Tissue processing centers may not utilize systems that provide a "globally" unique identification number for tissue products, with the exception of eye banks and HPC apheresis collection centers, which have adopted ISBT-128 coding.
5. Standards of professional accreditation bodies require recipient follow-up data collection protocols, but protocols are not uniform and parameters for evaluating the information collected are not specifically described. In addition, compliance by end users with data collection requests varies and is especially challenging for tissues distributed to areas outside of the United States.

6. Compliance with traceability requirements during tissue product processing is generally assessed, but traceability gaps have been identified after tissue products are distributed.
7. Regarding content of labels used on tissue products, the regulations in 21 CFR part 1271 do not require a description of the extent to which or how the product was processed. This information, when included voluntarily on labels (e.g., in Instructions for Use documents), is useful to clinicians (end users) and assists with communicating risks to recipients.

Bioburden Assessment, Culture Method, and Molecular Method Suitability

Instead of following published professional association guidelines or other recommendations for human tissues which outline microbiological process validation and establishment of a surveillance program, procedures used by processors can be determined through local discretion. In addition, assessment of tissue bioburden limits may reflect variations in donor eligibility criteria and may rely heavily upon the expected capabilities of a processing method to reduce or eliminate pathogens. Although molecular testing (e.g., PCR) and conventional culture methods can be used to detect contamination, validation of the suitability of the method and/or selection of a sampling plan may be inadequate. These inadequacies have resulted in transmission of disease by cell/tissue products, and those products preserved as fresh, refrigerated, frozen, or cryopreserved pose the greatest risk.

1. AATB Guidance Document No. 5 provides guidelines for adequately assessing tissue bioburden, validating the suitability of culture methods and processing steps, and monitoring contamination and cross-contamination; however, following this guidance is not required. The procedures used are subject to local discretion.
2. Tissue processing centers rely on donor screening to identify risk of transmission (e.g., disease-prevalent areas, donor risk factors and conditions) and use this information—in combination with processing capabilities—to determine methods for assessing tissue bioburden and for establishing donor acceptance policies.
3. Gaps in assessing tissue bank compliance were identified in inspectors' knowledge regarding bioburden assessment and culture method suitability, which affect their ability to assess compliance with expected practices.
4. The national laboratory that tested bone product samples for presence of *Mycobacterium tuberculosis* (Mtb) during outbreaks in 2021 and 2023 relied on PCR analysis, which raises concerns about interfering substances and additional confounding elements that may be present within tissue samples and that can affect test results. Such issues should be accounted for when determining the bioburden of tissues using PCR methods, particularly for bacteria and mycobacteria that are difficult to identify by culture methods (e.g., Mtb). Validation of the suitability of the PCR method is also critical. Therefore, testing a post-processing sample may not be as good as testing a pre-processing sample.

5. Non-viable tissues and tissue products are highly unlikely to result in disease transmission. Tissues and cells preserved as fresh, refrigerated, frozen, or cryopreserved pose the greatest risk of disease transmission.

Process Validation and Tissue Suitability (For Release)

Current guidelines surrounding validation of tissue processing steps to control contamination and cross-contamination are insufficient, and knowledge gaps exist regarding how to adequately assess bioburden, perform method suitability testing, and validate processing steps.

1. Working Group members indicated that process validations often rely on voluntary professional standards to maintain private accreditation.
2. The process validation guidance from the U.S. Food and Drug Administration may be insufficient and would benefit from additional information.
3. Gaps in assessing compliance were identified related to inspectors' lack of knowledge regarding process validation, bioburden assessment, and method suitability testing.

Donor Eligibility Determination

Responsible persons, such as medical directors or non-physician designees, who make donor eligibility determinations rely heavily on algorithms that can result in unintended consequences and the under-utilization of review of the donor's full medical records. On the other hand, the criteria for evaluating septicemia in donors allow too much "creativity" in an evaluation that should be "black and white." Another issue is the lack of upper limits on how many donor charts one medical director or designee can be responsible for reviewing over a given period with "good results." Inspectors generally do not challenge donor eligibility decisions, but they should be empowered to do so. In terms of donor selection, relationships between firms may benefit some OPOs more than others and this can cause variability of accepted donor criteria.

1. Medical directors, who can come from a variety of specializations (e.g., pathology, surgery), are determined to be qualified by the tissue banks that employ them.
2. Inspectors should be empowered to challenge donor eligibility decisions made by medical directors.
3. Donor eligibility determinations may be made by "responsible persons" and professional accreditation bodies may refer to 'medical directors' who are involved in providing donor criteria used for these determinations. Non-physician designees may also make donor eligibility determinations. Provisions regarding training and education are established by each OPO, tissue bank, or eye bank.
4. Expectations for medical chart assembly and review during a donor eligibility determination varies among tissue and eye banks.
5. Strictly using algorithmic criteria, such as for evaluating sepsis, to determine the eligibility of a donor may lead to under-utilization of review of the donor's full medical chart.

6. Septicemia (e.g., elevated cytokines) is the most variable donor screening factor; its identification depends on medical judgement calls made by many individuals, and criteria for these judgments may be difficult to enforce. This variability allows too much “creativity” in an evaluation that should be “black and white,” and can result in inaccurate disqualification of potential donors.
7. Tissue processors that have longstanding relationships with tissue recovery programs can experience a better selection of eligibledonors.
8. No one has established an upper limit on the number of donor charts that one medical director can be responsible for reviewing over a given period with “good results.”

Data Collection That Can Inform Standards and Policies

There is no collection and analysis of donor screening experiences, donor testing outcomes, or data (i.e., a useful denominator of tissue products transplanted to determine incidence of adverse events) that could be used to inform national standards, recommendations, and policies.

1. The EBAA collects information annually regarding eye tissue suitability, including reasons for excluding tissues and donors. This information is made available in the Eye Banking Statistical Report; a copy of the 2023 report is available at https://restoresight.org/members/publications/statistical-report/.
2. The National Tissue Recovery through Utilization Survey (NTRUS), sponsored by the U.S. Department of Health and Human Services, measured activity in 2012 and 2015 involving AATB-accredited tissue banks, which provided a snapshot of the reasons why donors were deemed ineligible. The report is available here: https://www.hhs.gov/sites/default/files/ntrus-report-2015.pdf
3. The AATB does not capture statistics regarding donor exclusion at different stages of eligibility determination. Variations in exclusion criteria are influenced by variations in acceptance criteria. Collecting this data would present a large burden and require substantial efforts.
4. Sufficient data are lacking on multiple basic elements of cell/tissue donations. For example, no reliable estimate is available for the number of total allograft tissue products distributed and transplanted; this number could be used as a denominator to determine incidence of adverse events, which could inform national standards and policies. Data surrounding tissue transplantation could be obtained by surveying hospitals that use the National Blood Collection and Utilization Survey (NCBUS) or other mechanisms as a template; however, generating and disseminating the survey represents a significant challenge.

Preservation and Storage

Cell/tissue products that are not sterilized and are preserved and stored fresh, refrigerated, frozen, or cryopreserved pose the highest risk for transmission of infectious agents.

1. Processing to remove contamination/bioburden may involve only the use of antibiotic soaks, and tissue products that are preserved and stored (i.e., fresh, refrigerated, frozen, or cryopreserved) that contain viable cells pose the highest risk for transmission of infectious agents.

Working Group Three: Tissue End-User/Consignee Receipt and Use

The scope of the End User-Consignee Receipt and Use Working Group includes tracking, coding, and records; inspection, storage, preparation for use; electronic health records (EHR) and biovigilance; linkages between inventory and recipients; and final disposition of transferred tissues.

The Working Group met on August 1, September 14, 2023, April 10, 2024, and July 11, 2024.

Potential Recommendations

1. To improve the capabilities and effectiveness of electronic systems that healthcare software companies provide for tracking tissue products, software standards-setting organizations should identify and finalize critical data elements that must be included to support tissue biovigilance, and the software must be capable of electronic exchange with EHRs.
2. To improve quality, equity, and outcomes related to tissue biovigilance, the federal agency with oversight of healthcare coverage should promulgate regulations that require healthcare facilities to use electronic documentation to track tissue products, ensure all critical data elements are documented, and require investigation of adverse events related to tissue recipient infections.

Gap Analysis

SMEs/Participants

Healthcare providers include HCA Healthcare and the Veterans Health Administration (within the Dept of Veterans Affairs).

Healthcare software companies include Epic and Oracle Health, which provide healthcare providers with electronic health records (EHRs).

Standards-setting organizations include the Joint Commission, which accredits more than 22,000 US healthcare organizations and programs.

Federal agencies providing healthcare coverage include CMS, which provides healthcare coverage to more than 160 million individuals through Medicare, Medicaid, the Children's

Health Insurance Program, and the Health Insurance Marketplace. CMS works in partnership with the entire healthcare community to improve quality, equity and outcomes in the healthcare system.

Tracking, Coding, and Records

Healthcare providers

A variety of tissue tracking software systems are available to healthcare providers that may also capture barcode information; however, these systems may not be capable of electronically interfacing with EHRs, leading to manual entry of some product information, which reduces effectiveness overall. Although controls may be in place to source tissue products only from approved providers, oversight by a single responsible party is generally lacking; as a result, ordering, storage, and management of tissue products is departmentalized and protocols are not harmonized— for example, among acute care hospital operating rooms, clinics, and ambulatory surgical centers.

1. Healthcare providers use a variety of tissue tracking software systems, but manual methods continue to also be used, and software systems may or may not be capable of interfacing with EHRs.
2. Tissue tracking software systems can capture barcode information on tissue product labels, and they can also generate barcodes for relabeling tissue products with a unique identifier; however, manual entry of some product information occurs, which can affect tissue tracking.
3. Although controls may be in place to source tissue products only from approved providers, oversight by one responsible party is generally lacking; as a result, ordering, storage, and management of tissue products is departmentalized, and protocols are not harmonized—for example, among acute care hospital operating rooms, clinics, and ambulatory surgical centers.
4. Utilizing a variety of tracking and tracing systems to monitor the chain of custody and utilization of tissue products may reduce the effectiveness of the system overall and increase the difficulty of providing adequate staff training. Adopting a unified enterprise system may improve the overall chain of custody.

Healthcare software companies

Electronic systems that healthcare software companies provide can support barcodes used by all three approved issuing agencies under the Unique Device Identification (UDI) final rule (GS1, ISBT 128, HIBCC), and can track tissue products from purchasing to EHRs of recipients. However, use of multiple barcodes on a single tissue product can cause confusion and affect tracking, and use of any other barcode system is not supported. Limitations of software for tracking tissue products include: software standards-setting organizations have not designed

infrastructure to capture critical data elements; there is currently no requirement to complete electronic documentation; multiple systems may be used by centers; and centers rely on documentation at the point of use.

1. Although systems that healthcare software companies provide can support all three approved issuing agencies under the Unique Device Identification (UDI) final rule (GS1, ISBT 128, HIBCC), and can track tissue products from purchasing to recipient EHRs, complaints are common regarding use of multiple barcodes on a single tissue product because it can affect tracking.
2. Tissue product tracking is more difficult, and may require manual entries, when barcode systems are created by small organizations for internal use only, are from non-contract providers, or are used for novel one-time items that are not maintained in the software's enterprise resource planning (ERP) system.
3. Software systems can identify when a single unit of tissue is used for multiple recipients, which does occur.
4. Software interoperability could be improved through utilization of a top-down design approach in which standards-setting organizations identify critical elements and healthcare software companies design their infrastructure to capture those data.
5. Data input compliance is lacking. EHRs must be able to document unique device identification barcodes, but a requirement to complete this documentation does not currently exist.
6. Tracking of patient implant records and identification of tissue products are limited by documentation at the point of use (e.g., operating rooms, hospital departments, and ambulatory care centers).
7. Outpatient facilities may not use EHRs and often rely on manual documentation, and acute centers may use multiple different EHR systems to maintain patient information.

Standards-setting organization

A single organization provides standards that assist hospitals, ambulatory surgical centers, and laboratories to manage tissue products, including standards for tracing tissues and for tracking and investigating recipient adverse reactions. However, specific guidelines/procedures that describe how to perform these functions are not available and no directly responsible party is clearly designated.

1. A single organization provides standards that assist hospitals, ambulatory surgical centers, and laboratories with managing tissue products, including standards for procedures to trace tissues bidirectionally and for investigating adverse events related to tissue recipient infections. However, more specific guidelines/procedures that describe how to perform these functions are not provided.

2. There are challenges with applying standards for managing tissue products when directly responsible parties are lacking, and when the responsible party is one person, staff turnover can lead to loss of institutional knowledge.

Federal agency that provide health coverage

The federal agency that provides health coverage does not have regulations that require tissue product tracking; therefore, tissue product tracking and other biovigilance efforts remain voluntary and without oversight.

1. The federal agency that provides health coverage does not have regulations that require tissue product tracking.

General comments on tracking/coding/records gaps

Multiple barcode systems can be used for tracking tissue products and, when more than one barcode system is used to label a single product, it can cause confusion for hospital staff and add complexity to the process of maintaining electronic records.

1. Although ISBT-128 coding is voluntarily used in the United States for coding, barcoding, and tracking blood products and ocular tissue products, GS1 is the most popular coding used for non-ocular tissue products.
2. A centralized UNOS tracking system identifies organs using a single, uniform coding system for donors; however, blood vessels that are recovered for use only with a solid organ (i.e., liver) transplant can be used in ways in which they were not intended, such as in emergent cases not associated with organ transplantation.
3. Tissue banks can use more than one barcode system to label a single tissue product, which can cause confusion for hospital staff when scanning a barcode for entry in their software tracking system. In addition, many tissue suppliers use labels and stickers that may be scanned or manually placed on a page of the health record. The combination of barcodes and issuing agencies increases the complexity of inputting and maintaining tissue product information.

Inspection, Storage, Preparation for Use

1. Depending on the healthcare provider's policies and procedures regarding responsible parties that can acquire tissue products, supply chain irregularities can occur that affect tracking. Acting as the first step in the supply chain, a group purchasing organization (GPO) may be involved in ordering tissue products for healthcare providers, but company sales representatives may deliver high priority tissue products directly to the operating room where the surgeon is the responsible party.
2. Procedures for data input should indicate the stages of data acquisition (e.g., obtaining the product, preparing the product, and implanting the product).

Electronic Health Records (EHRs) and Biovigilance

When available for use with tissue products, EHRs are key to biovigilance monitoring and reporting but can be prone to manual entry errors; in addition, when notification of tissue product recalls occur, manual efforts may be required to trace the implicated products.

1. EHRs are key to biovigilance monitoring and reporting but may be affected by manual entry errors involving tissue products.
2. Biovigilance "packages" are available for blood products and may be used for eye tissue, but they are not available for tissue products.
3. Gaps that affect tissue product biovigilance include variabilities in data collection, difficulties in transferring data between healthcare centers, the lack of information gathered from small healthcare centers, and continued reliance upon manual data entry.
4. GPOs may coordinate communication of alerts to all facilities when tissue product recalls are received from manufacturers; however, if a notification of recall occurs outside of the GPO, manual efforts would be required to trace implicated tissue products.
5. EHRs and data collection measures should include the tissue product's intended use and its preservation method. Because healthcare teams are often not aware of how to properly prepare tissue products for use, the method of preparation should also be collected in EHRs.

Linkages Between Inventory and Recipients

1. The time required to identify tissue products associated with specific donors, and the recipients of those products, is highly variable and may be an extended period.

Final Disposition of Transferred Tissues

Tissue product sharing between hospitals makes tracking difficult and limits knowledge regarding use.

1. Tissue product sharing occurs between hospitals and can make tracking difficult.
2. The efficiency rates of tissue product usage are difficult to discern, particularly as products are moved between systems.

Other Important Information - Not Gaps

- It is unknown how often facilities are cited by an accreditation organization for tissue tracking failures; citations appear on a Safety Matrix that includes number of times cited and probability of further citations.
- Issues concerning tissue products tend to arise with communications between departments of healthcare providers.

- Healthcare software companies do not receive requests for donor information. Surgeons have information about products, not particular donors. Information pertaining to other biologics is unavailable.
- Healthcare provider maintains year-round assessment teams to review any materials that may be of interest to state regulatory bodies to ensure compliance among their departments.
- In the past, healthcare provider compared and assessed their tracking systems with those of other healthcare systems using SMART IT; however, this review is not currently performed.
- Tissue products not included within the formulary may be difficult to acquire when required for special uses.

Working Group Four: Tissue Recipient Adverse Events/Reactions

The scope of the Tissue Recipient Adverse Events/Reactions Working Group included professional and public expectations of the tissue donation system; procedures and guidelines; and recognition, investigation, and reporting of adverse events. Considerations include existing federal regulations, state or local laws, voluntary professional standards, and assessments of compliance.

The Working Group met on July 31, 2023, September 7, 2023, April 15, 2024, and July 8, 2024.

Potential Recommendations

1. To improve communication from healthcare professionals to inform a patient who may receive a tissue product that there is a potential for risk of disease transmission, such as descriptions regarding higher risks attributed to tissue products that contain live cells, national guidelines should be developed to improve processes used to describe such risks and professional societies should be encouraged to promote those guidelines.
2. Federal and state regulations should publish guidelines to assist end users (i.e., physicians and hospitals), and physicians who treat tissue recipients, how to properly identify a reaction that may be attributed to a tissue product, and these regulators should require end users to report tissue recipient adverse reactions and to cooperate with investigations.
3. Recipients of human tissues should give informed consent for the products they receive. Labeling information to inform clinicians of risk (e.g., absence of bioreduction) is fundamental for informed consent.

Gap Analysis

Professional and Public Expectations

Healthcare professionals, certain members of Congress, and the public appear to have the perception/expectation that the safety of medical devices and safety of tissue products should be the same.

1. Congressional representatives from Michigan are acting to bring awareness to the issues of tissue transplant associated infections and have drafted a letter to the FDA "to issue guidance or regulations to protect patients and increase accountability for human tissue transplant products." A press release and copy of the letter are available at the following website: "https://moolenaar.house.gov/media-center/press-releases/moolenaar-peters-stabenow-dingell-urge-fda-take-action-bone-graft". Information on the introduction of a legislative bill can be accessed here: "https://moolenaar.house.gov/media-center/press-releases/moolenaar-legislation-prevent-tb-outbreaks-moves-forward".
2. Professionals and the public appear to hold the perception/expectation that safety of medical devices and safety of tissue products should be the same, but risks intrinsic to tissue product types differ and the risk-benefit ratio of using them differs. In addition, estimates of risk attributable to tissue products are not accurate because formal surveys and reports of how many tissue transplants occur are scarce, surveillance of outcomes is lacking, and elective surgeries occur outside of controlled healthcare environments.

Procedures

Communication from healthcare professionals is inadequate for informing a patient who may receive a tissue product that there is a potential risk of disease transmission, the processes used to describe such risks vary, and communication of the risk of disease transmission may not occur at all. If disease transmission risks are included, for example, in an informed consent process for patients, no guidelines supported by professional societies promote descriptions regarding higher risks of tissue products that contain live cells. The following factors cause tracking challenges that hinder investigations of a possible adverse reaction caused by a tissue product:

- whether software systems can utilize barcodes to track tissue products to recipients;
- when tissue products are transferred/re-distributed among healthcare facilities;
- who manages the storage of inventory (i.e., the vendor or the healthcare facility/system);
- when products are distributed internationally; and,
- end user non-compliance with requests from manufacturers to share recipient and recipient outcome information.

1. Procedures used for obtaining informed consent from patients who may receive an allograft differ markedly from the process for obtaining informed consent from patients who may receive blood and blood products. The procedures may be improved by ensuring adequate communication of risks associated with tissue processing and preservation methods. Currently, the information provided in tissue product package insert materials may not be conveyed to patients/recipients or fully understood by the healthcare provider.
2. Patients might be informed of the risks associated with receiving a tissue product as part of the typical informed consent process before a surgical procedure; however, communication surrounding disease transmission associated with use of tissues that contain viable cells may not be addressed at all and likely varies across healthcare professionals and medical centers. Recommendations for communicating such risks may be provided by professional societies, but currently no federal mandate exists.
    a. The AAOS statement could be updated to include risks associated with tissue products containing live cells. Currently the AAOS states that "The AAOS supports informed consent, for both the donor family and the recipient of human tissue, in accordance with local, state and federal regulations and laws." (https://www.aaos.org/globalassets/about/bylaws-library/information-statements/1011-use-of-musculoskeletal-tissue-allografts.pdf).
3. Electronic medical records do not easily accommodate information about tissue biovigilance. Some healthcare services have partnered with third parties to increase accessibility.
4. The chain of custody for allograft products varies depending upon tissue product types and who stores them (i.e., vendor, healthcare system), whether a software system can utilize barcodes for product monitoring and for entry into patient charts, and geographic distribution—international distribution in particular can pose tracking challenges.
5. Based on business policies/agreements, tissue vendors utilize establishment-specific policies for the distribution and return of tissue products, instead of following a uniform policy or professional standards.
6. Gaps in traceability after product distribution— particularly with respect to product transfer/re-distribution among healthcare facilities—also undermine communication about risks.
7. Eye banks accredited by the EBAA are required to obtain patient identifying information and contact implant surgeons post-distribution of corneas or sclera to request recipient information; however, compliance by end users varies. Compliance is especially challenging for ocular tissue distributed to areas outside of the United States and following implants in which the product had been maintained by the healthcare system for an extended period. The EBAA uses distribution only within the United States as the denominator for estimating incidence of adverse events and reactions.

8. There are difficulties with determining the origin of post-operative infections involving tissue products, including the type of infection and implant site sampling methods (i.e., deep within the operative site) that are most useful for determining the likelihood of transmission originating from the tissue product.

Recognition of an Adverse Event

The difficulty of recognizing tissue recipient adverse events/reactions increases with time but may be addressed through increased communications with recipients and between end users and other hospital professionals, including infectious disease specialists and epidemiologists. Infections caused by tissue products are typically recognized when they are caused by atypical bacteria or fungi; however, post-operative infections are usually considered to be related to a reaction only at the surgical site rather than due to the tissue product. Because implanting surgeons learn to identify and report adverse events primarily through experience, it is paramount that guidelines be published to help end users to properly identify a reaction that may be attributed to a tissue product. Such guidelines could increase the likelihood of recognizing and reporting tissue recipient adverse events.

1. Surgeons typically follow up post-surgery with their patients, but follow-up is often voluntary and is affected by patient compliance.
2. Post-operative infections are most commonly considered an adverse consequence of the inevitable introduction of microbes during the surgical procedure rather than introduced by tissue product. Tissue allograft donor-derived infections are typically identified when they are caused by atypical bacteria and fungi, which likely leads to underestimates of the actual rate of product-derived infections.
3. Healthcare professionals report difficulties in determining the origin of post-operative infections. They often rely upon the type of infection to determine origin, and may utilize deep implant site sampling methods to determine the likelihood of transmission from the tissue product.
4. The difficulty of recognizing adverse events resulting from tissue implantation increases with time and may be addressed through increased communications between end users and other hospital professionals, including infectious disease specialists and epidemiologists.
5. Additional guideline documents for end users may increase the likelihood of reporting tissue recipient adverse events.
6. Implanting surgeons learn to identify and report adverse events primarily through experience gained during training and practice.

Investigating Adverse Events

The chain of custody and the ability to trace tissue products are essential for investigating adverse events, which is especially important when multiple patients are at risk who have

received tissue products linked to a common donor or processing center. In all cases, healthcare institutions need to rapidly identify the disposition of these products and quarantine products to avoid placing more patients at risk. An FDA guidance document provides HCT/P establishments with recommendations for investigating and reporting adverse reactions, and the EBAA provides guidance to eye banks after the eye bank has received a report. However, investigations of post-operative infections require communicating with the physician or affiliated staff overseeing the patient, and end users often do not respond to with tissue manufacturer or FDA requests for clinical information and/or cultures, which adversely affects investigations and identification of the source of the infection. Currently no federal regulations require end users to cooperate with investigations of tissue recipient adverse reactions.

1. The chain of custody and traceability of tissue products are essential for investigating adverse events, including identifying at-risk patients and quarantining products during an investigation.
2. Communications regarding post-operative infections often occur through the physician overseeing the patient of interest, however, cooperation to provide clinical information and/or culture reports is often lacking and adversely affects the investigation.
3. When an investigation of adverse reactions identifies multiple patients that have received tissue products originating from a common donor or processing center, rapid identification of the disposition of other donor-derived products is needed.
4. Working group members proposed generating recommendations to state authorities to promote end user reporting of potential adverse events or reactions to the eye bank or tissue bank that supplied the tissue product, and to encourage participation in an investigation of such a report.
5. The EBAA provides guidance to eye banks for investigating adverse events after the eye bank has received a report, and an FDA guidance document provides HCT/P establishments recommendations for investigating and reporting adverse reactions.
6. Currently no federal regulations require end users to cooperate with investigations of tissue recipient adverse reactions.

Reporting Adverse Events

Guidance documents to assist physicians in reporting adverse events are not readily available, even though a national project collected useful information and draft guidance was developed. To facilitate tissue recipient adverse event reporting, end user professional organizations could encourage wide use of guidance documents. Eye bank professionals are periodically informed of rates of infections associated with reports of the use of corneas, and there are efforts to explore the development of systems for reporting adverse reactions. However, statistics indicate that under-reporting persists. Under-reporting may be influenced by concerns that those who report may face repercussions, be scrutinized, or be viewed as perpetuating unsafe practices. Such concerns could be addressed by working to generate a culture of safety among

physicians and healthcare centers to avoid the perception that punitive measures may result from reporting adverse events. Under-reporting may also be influenced by non-compliance among recipients, including patients not reporting events to overseeing physicians or to the FDA. Oversight authority for some healthcare facilities (e.g.., ambulatory surgical centers (ASCs) and dental offices) may not be exercised at the federal level but instead by individual states. Guidelines aimed at educating end users and physicians should be published and requirements to report tissue recipient adverse reactions should be implemented by state and federal regulators, as applicable, who have oversight of end users.

1. The AATB and EBAA note that documents providing guidance for the reporting of adverse events by physicians are not readily available. An AATB guidance document was drafted but it has not been finalized. The Working Group suggested including information gathered during the Transplant Transmission Sentinel Network (TTSN) project and seeking support from end user professional organizations (i.e., AAOS, AOSSM) to encourage wide use of the guidance document.
2. The EBAA generates twice-yearly reports for its membership regarding rates of infection and graft failures.
3. Statistics indicate that adverse events may be under-reported. AATB is currently promoting a tissue product tracking and tracing system that would enable hospitals to electronically report adverse events into a system that is accessible to organ procurement organizations, processors, and distributors, which could help address under-reporting.
    a. Instances of under-reporting may be influenced by concerns that those who report may face repercussions, be scrutinized, or be viewed as perpetuating unsafe practices. These concerns were identified in reports produced by the TTSN and in a report on biovigilance from the U.S. Department of Health and Human Services Office of Inspector General (OIG).
    b. Under-reporting may also be influenced by patient non-compliance, including patients not reporting events to overseeing physicians or to the FDA, and non-cooperation by end user clinicians with FDA representatives investigating a report of a tissue recipient adverse reaction (i.e., a MedWatch report).
    c. Working Group members recommend fostering a culture of safety among physicians and healthcare centers, rather than focusing on punitive measures in response to adverse events.
4. The EBAA indicated that ambulatory surgical centers (ASCs) where corneal transplants take place appear to be regulated by individual states rather than at the federal level (such as by CMS). A CMS representative agreed that ASCs are not under their oversight. also confirmed that dental offices where tissue products are used daily do not appear to be under federal oversight but might be required to follow state laws.

5. The group resolved that the following information indicates that tissue recipient adverse reactions might be under-reported :
    a. It is estimated that approximately 2.5 million tissue transplants occur annually in the United States.
    b. FDA reports that, in 2022, it received 267 reports of adverse reactions involving tissue products regulated solely under section 361 of the PHS Act.
    c. The CDC indicates that it has received a few referrals of infectious outbreaks related to tissue products and that each outbreak represents a significant public health safety concern.

Other Important Information – Not Gaps

The EBAA monitors its international and domestic allocation of products and has found that approximately one third of finished products are exported internationally.

The AATB has not assessed its finished product distribution allocation on a domestic and international basis.

AATB's accredited member tissue banks utilize primarily GS1 barcoding, with a minority of products utilizing ISBT128 barcodes.

The following resources identify concerns regarding tissue recipient informed consent:

- Fishman JA, Strong DM, Kuehnert MJ. Organ and tissue safety workshop 2007: advances and challenges. *Cell Tissue Bank*. 2009;10(3):271-280. doi:10.1007/s10561-008-9114-z (https://pubmed.ncbi.nlm.nih.gov/19016348/)
- Workshop on preventing organ and tissue allograft-transmitted infection: priorities for public health intervention. June 2-3, 2005. (https://www.cdc.gov/transplantsafety/pdfs/boots-workshop-2005-final-report.pdf)
- Previous ACBTSA meeting where recipient informed consent for blood transfusion, organ transplantation, and tissue transplantation was discussed. https://www.hhs.gov/sites/default/files/ash/bloodsafety/advisorycommittee/recommendations/april2015-recommendations.pdf