Guidance Document for Investigating and Reporting Adverse Reactions to the EBAA

Version 3

July 2017

Contents

INTRODUCTION

The EBAA initiated an adverse reaction reporting system in 1990. EBAA Medical Standard M1.500 requires each distributing establishment to seek postoperative outcome information between three and six months after transplant. MS G1.000 requires the investigation and reporting of adverse reactions to the EBAA for review by the Medical Review Subcommittee of the Medical Advisory Board. Reporting of adverse reactions was redesigned in 2004 for online use, utilizing the EBAA Online Adverse Reaction Reporting System (OARRS). OARRS enables easy reporting of adverse reactions, surgery, microbiological results, tissue-mate status, tissue source, transportation and comments.

The EBAA Medical Advisory Board (MAB) recently approved a number of significant changes to the OARRS system: (a) In June 2012, the MAB voted to standardize the surgical procedure and cause of

death categories to match the statistical report; (b) OARRS was updated to capture the Genus and species of any culture positive organism; (c) In June 2013, the MAB voted to harmonize our adverse reporting categories with the European SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) categories, recognized by the World Health Organization (WHO) Project NOTIFY; (d) A data element was added in OARRS to delineate between domestic and internationally-placed tissue.; (e) The MAB voted in November 2013 to add a new reporting category called "Early Regraft" for regrafts prior to 8 weeks. These changes necessitated a major revision of the Guidance Document for Adverse Reaction Reporting to the EBAA, previously published in 2009. OARRS was again updated in 2017 in response to member requests and a review by the Medical Review Subcommittee and version 3 of this guidance reflects those changes.

OARRS may be accessed through the following link: OARRS

The Medical Review Subcommittee is responsible for reviewing adverse reaction submissions once they are complete. Officially, the subcommittee's charge is to: review adverse events and document their occurrence; and monitor the efficacy of medical standards and their effectiveness regarding disease transmission. The subcommittee develops outcome measures to monitor areas for performance and outcome improvement. This subcommittee reports directly to the Medical Advisory Board.

GENERAL GUIDANCE FOR INVESTIGATING ADVERSE REACTIONS

Reports of adverse reactions may be received by any entity performing an eye banking function. However, the source eye bank is ultimately responsible for coordinating adverse reaction investigations. The source bank must notify all entities involved in the recovery, processing, storage, final distribution, tissue evaluation, and donor eligibility determination of the results of the investigation. Each of the involved entities must participate in the investigation and maintain documentation of the adverse event and results of the investigation forwarded to it by the source bank.

Here is a typical scenario for investigating a reported adverse reaction:

1. Surgeon reports an adverse reaction to the Distributing Eye Bank
2. Distributing Eye Bank notifies Source Eye Bank (unless same entity); Source Eye Bank coordinates investigation.
3. Quarantine other ocular tissue not yet transplanted from same donor and investigate status of mate tissue.
4. Source Eye Bank contacts surgeon (or designates Distributing Eye Bank to contact surgeon) to determine whether pre-existing/pre-disposing conditions, intraoperative complications, or possible sources of contamination may have influenced outcome. (See EBAA Adverse Reaction Inquiry Sample Form) If pre-existing or pre-disposing conditions exist, the Source Eye Bank Medical Director must determine if further investigation is necessary (see examples below).
5. Source Eye Bank initiates and coordinates investigation to review records produced by its staff, as well as records produced by the Recovery Establishment, Processing Establishment, Storage Establishment, and others involved with the tissue before it was distributed to the consignee.

6. Source Eye Bank submits to Medical Director a summary of records reviewed (including donor information form and tissue evaluation form), information obtained from transplanting surgeon (include post-op report, inquiry information), and mate status. Medical Director contacts surgeon for further follow up if necessary.
7. Medical Director establishes imputability, the likelihood that the adverse reaction in the recipient can be attributed to the tissue. Only Possible, Likely/Probable or Definite/Certain graft-transmitted adverse reactions are reportable via OARRS.
8. Source Eye Bank notifies all entities involved in the recovery, processing, storage, final distribution, tissue evaluation, and donor eligibility determination of the results of the investigation.
9. EBAA reporting is required within 30 days of the first report to an eye bank, via the OARRS website http://education.restoresight.org/arr/login.php.
10. If the adverse reaction involved a communicable disease and there is a reasonable possibility that the tissue caused the response, the bank which made the tissue available for distribution must report to the FDA within 15 days of the initial receipt of the information. The FDA MedWatch mandatory reporting form (Form FDA-3500A) should be used to report adverse reactions involving a communicable disease if it: a) is fatal; b) is life-threatening; c) results in permanent impairment of a body function or permanent damage to body structure; or d) necessitates medical or surgical intervention, including hospitalization.

Imputability Level Explanation (Adapted from SOHO V&S Guidance)*

Level of Attribution	Description	OARRS Reportable?
Not Assessable	Insufficient data for imputability assessment	**No**
Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes	**No**
Unlikely	Evidence clearly in favor of attribution to alternative causes	**No**
Possible	Evidence is indeterminate	**Yes**
Likely, Probable	Evidence in favor of attribution to the tissues/cells	**Yes**
Definite, Certain	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells	**Yes**

*Any systemic infection in a recipient due to a relevant communicable disease agent or disease (RCDAD) must be reported regardless of level of attribution.

FIVE TYPES OF ADVERSE REACTION INVESTIGATIONS

1. Graft Failure

Graft failure may occur early or late. Reportable graft failures are those that occur early and that conform to the criteria for Primary Graft Failure or Early Regraft listed below. Grafts that have been clear for a period of time after surgery and then fail are not reportable as adverse reactions under the Graft Failure category.

Criteria to determine Primary Graft Failure:

- Corneal edema present from the time of keratoplasty **and**
- Does not clear after eight weeks **and**
- No known operative or postoperative complications or underlying recipient conditions that would explain the biologic dysfunction

Criteria for determining Early Regraft:

- Corneal edema present from the time of keratoplasty **and**
- Does not clear prior to the time of regraft **and**
- No known operative or postoperative complications or underlying recipient conditions that would explain the biologic dysfunction **and**
- Regrafted in less than eight weeks
- In endothelial keratoplasty cases this may include failure of graft to attach, despite confirmation of correct graft orientation (e.g. by S-stamp)

Guidance for investigating reports of graft failure:

- Review storage conditions
- Review recovery records
- Review processing records
- Review mate status
- Review potential operative contributing factors.

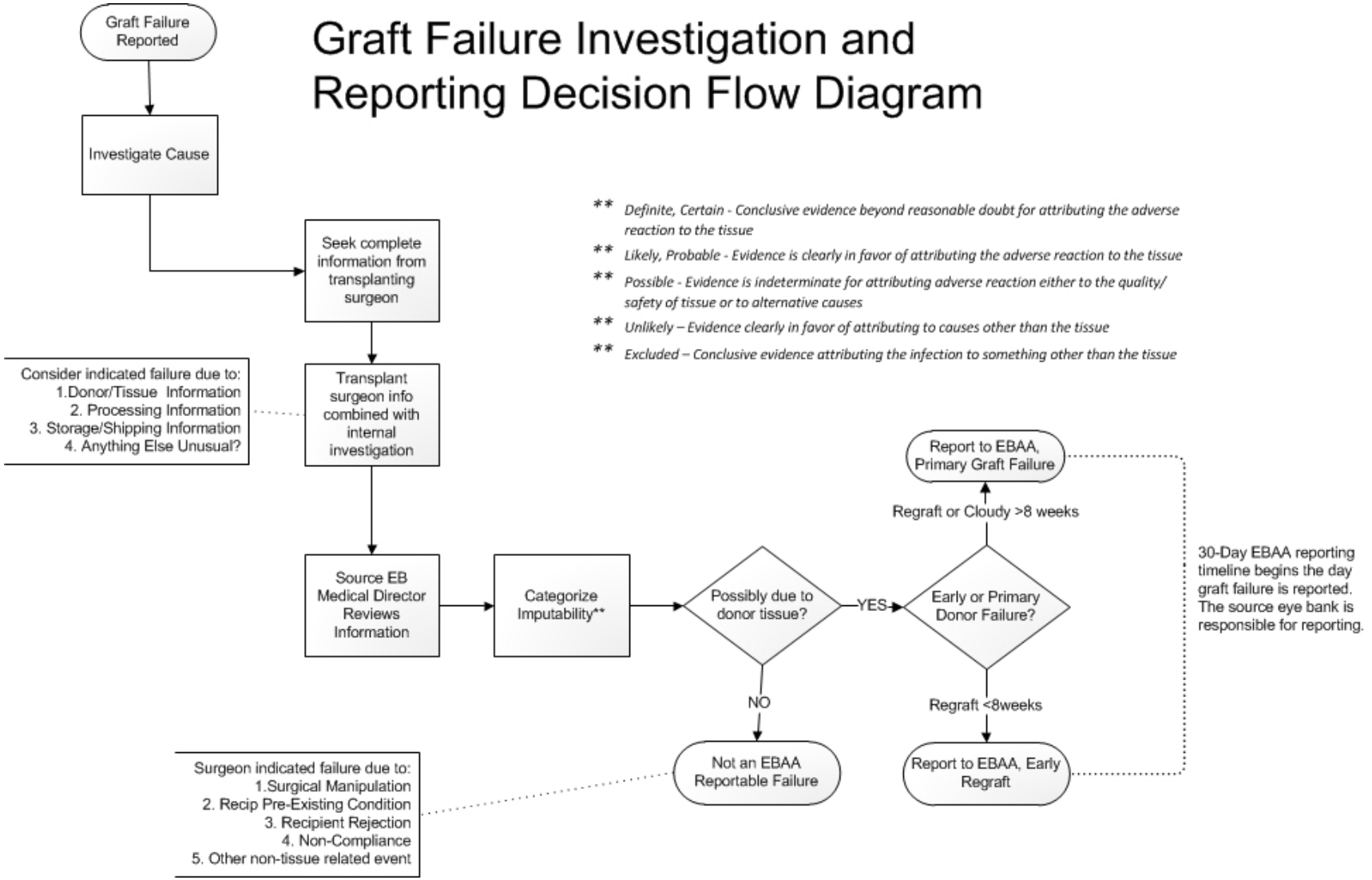
  Examples: Endothelial trauma, chamber collapse, intracameral injection of toxic or preservative containing fluids, Toxic Anterior Segment Syndrome (TASS), known intraoperative Descemet trauma, prolonged vitrectomy,

  For endothelial keratoplasty: tissue manipulation intraoperatively (e.g. upside down), re-bubbling, surgeon experience is less than ten cases, poor surgeon cut, presence of anterior chamber IOL, incision size, number of folds, insertion/folding technique, use of forceps, dislocation.

- Review potential recipient contributing factors.

  Examples: Persistent epithelial defect, persistent elevated IOP, marked post-operative inflammation, choroidal hemorrhage, IOL dislocation, flat anterior chamber, ocular surface disease, recurrence or persistence of pre-operative infectious keratitis, persistent wound leak.

Graft Failure Investigation and Reporting Decision Flow Diagram



2. Ocular Infections

A graft-transmitted ocular infection exhibits signs and symptoms of infection consistent with the infectious agent (e.g. pain, redness, loss of vision, hypopyon, corneal infiltrates, vitritis, etc.) from, or near, the operative site.

A **"Possible"** graft-transmitted infection is reported when the evidence is indeterminate:

- Surgeon reports an ocular infection believed to be due to donor tissue.
- No pre-implant donor culture was performed.
- No pre-existing or pre-disposing conditions, intraoperative complications, or possible sources of contamination are identified to exclude imputability.

A "**Likely/Probable"** graft-transmitted ocular infection may be attributed to the graft if there is:

- A match between the pre-implant donor and recipient culture findings in a recipient with no known or identified risk factors for the disease.
- A report of graft-associated infection in one or more recipients of tissues from the same donor.
- Evidence of failure to comply with SOP for aseptic technique prior to distribution of tissue.

A **"Definite/Certain"** graft-transmitted ocular infection may be attributed to the graft if there is:

- Confirmation by appropriate laboratory testing (e.g., genotyping, PCR, wet prep) that demonstrates scientific evidence linking the infectious agent in the recipient with donor samples, or
- A report of graft-associated infection with the same organism (genus and species) in two or more recipients of tissues from the same donor. In cases of coagulase-negative staphylococcus where the possibility of contaminants may be considerable from either the donor rim or from the recipient, a matching genus and species (such as *Staphylococcus epidermidis*) may not change a "Likely / Probable assessment to a "Definite / Certain" assessment. The Medical Director would need to make such an assessment.

Note: Only Possible, Likely/Probable and Definite/Certain graft-transmitted ocular infections are to be reported to OARRS

Guidance for investigating reports of ocular infection:

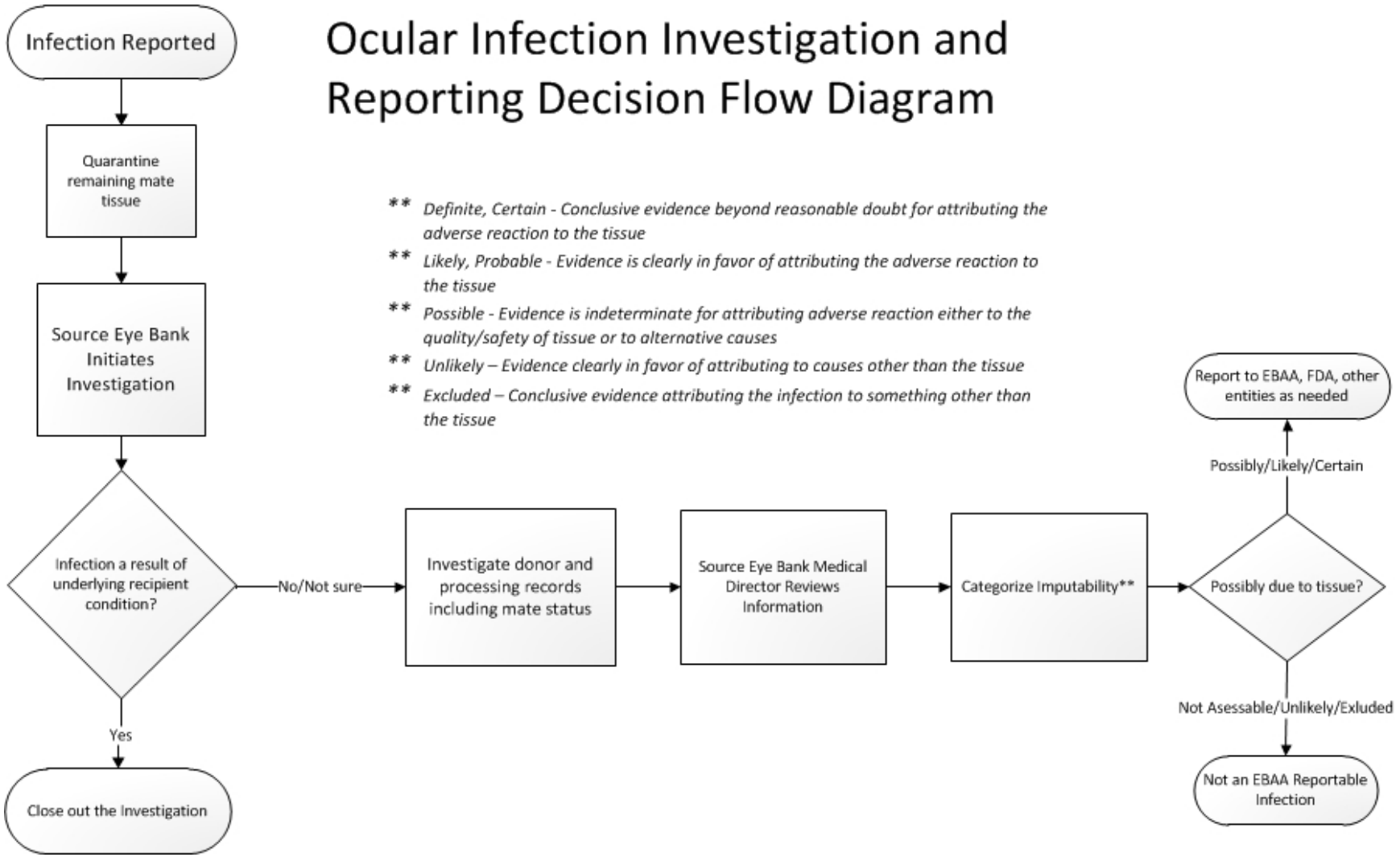
As part of the investigation, review records for possible sources of contamination

Examples: Breaks in aseptic technique during handling of tissue, improper sterilization of instruments, improper maintenance of equipment, contamination or expiration of storage solution, inadequate maintenance of sterile field in tissue preparation

- Review culture results pre and post-op
- Review donor screening records
- Review tissue evaluation
- Review recovery records
- Review processing records
- Review storage conditions
- Review mate tissue status, if applicable
- Review tissue bank donor cultures, if applicable
- Review potential intraoperative contributing factors

The Appendix contains a list of microorganism selections available on the OARRS website.

Ocular Infection Investigation and Reporting Decision Flow Diagram



** *Definite, Certain - Conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the tissue*

** *Likely, Probable - Evidence is clearly in favor of attributing the adverse reaction to the tissue*

** *Possible - Evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissue or to alternative causes*

** *Unlikely – Evidence clearly in favor of attributing to causes other than the tissue*

** *Excluded – Conclusive evidence attributing the infection to something other than the tissue*

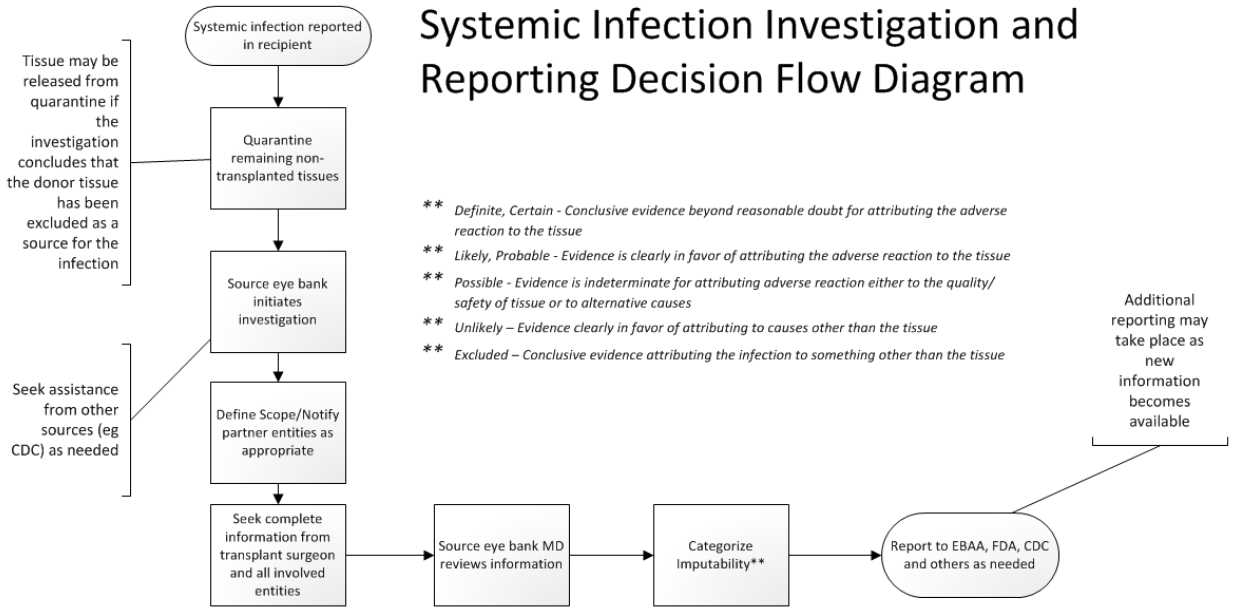
3. Systemic Infection in a Recipient

Any systemic infection due to a relevant communicable disease agent or disease (RCDAD) such as HIV, hepatitis, syphilis, West Nile Virus (WNV), or Creutzfeldt Jakob Disease (CJD) that develops in a recipient, whether or not it is suspected to be due to donor tissue, must be reported to the EBAA. The investigation should include:

- Report to EBAA via OARRS
- Review donor screening records from all sources
- Review serology and NAT infectious disease testing
    - Additional testing on archived serum may be warranted as part of the investigation with the most sensitive testing available
- Review mate recipient status, if applicable
- Contact other known recovery and distributing agencies

If an infection of a systemic nature is determined to be possible, likely/probably, or definitely due to donor tissue, communicate to all entities that recovered organs or received or recovered tissues from that donor.

Reporting may take place before the investigation is complete due to the lengthy investigations that can take place. Investigations may require coordination with the Centers for Disease Control (CDC) Office of Blood, Organ and Other Tissue Safety, FDA, and local health authorities. Other expert help may be required from reference laboratories and infectious disease experts.



4. Corneal Dystrophy

A donor derived corneal dystrophy is a dystrophy diagnosed in a recipient, which may possibly, probably or definitively be derived from the transplanted tissue and may or may not have been present in the tissue at the time of donation. This includes ectatic disease, such as keratoconus, which has been reported to affect 2 cases since 2007.

Tips for investigating a reported corneal dystrophy:

- Review donor records including ophthalmology records, if available
- Review tissue evaluation
- Review mate tissue status

5. Ocular Malignancy

A donor derived ocular malignancy is a malignant disease diagnosed in a recipient, which may possibly, probably or definitively be derived from the transplanted tissue and may or may not have been present in the tissue at the time of donation. Local ocular malignancies are usually related to metastatic disease to the anterior segment of the donor's eye (e.g. adenocarcinoma and melanoma). These donors typically would be deferred by proper eye evaluation prior to tissue collection. However, if malignancy transmission is reported, detailed investigation and reporting is appropriate, as follows:

- Review of recipients clinical symptoms, test results and any alternative risk factors for the malignancy in the donor's medical history
- Review tissue evaluation
- Review mate tissue status
- Histological examination and immunohistochemistry to help identify the pathology for comparison of tumors in the donor and recipient(s)

- Determination of the genetic identity of donor and recipient tumors can provide a high degree of confidence regarding imputability
- The temporal sequence is also an important factor in investigating imputability. Most transmitted tumors appear within the first 14 months after transplantation. Therefore, it is unlikely that an aggressive tumor diagnosed in the recipient five years after transplantation is donor-transmitted

6. Refractive Surgery in the Donor Tissue

Evidence suggestive of prior refractive surgery in the donor tissue inadvertently utilized for full thickness or anterior lamellar keratoplasty is an EBAA-reportable adverse reaction. This significant adverse event (SAE) is reportable through OARRS, regardless of whether the recipient has an adverse outcome, because inappropriate tissue has been released for clinical use. Tissues with a history of refractive surgery knowingly released by the eye bank for tectonic or emergency uses would not be reportable.

DEFINITIONS

Adverse Reaction: Any communicable or other disease that is possibly, reasonably likely/probable or definite/certain to have been transmitted by transplantation of donor eye tissue, including infection (as manifested by endophthalmitis, keratitis, or systemic disease) and biologic dysfunction (such as immediate endothelial failure, donor corneal dystrophy, malignancy, or evidence suggestive of prior refractive surgery).

Aseptic Technique: Method by which contamination with microorganisms is prevented.

Complaint: Any written or oral communication concerning dissatisfaction with the identity, quality, packaging, durability, reliability, safety, effectiveness, or performance of tissue.

Consignee: Any eye bank, eye banking intermediary or transplanting surgeon (whether individual, agency, institution, or organization) that receives tissue and assumes responsibility for any step in the processing, storage, distribution and/or use of such tissue.

Distributing Establishment: An entity that is reimbursed for or invoices for providing tissue to the end user. Shall be responsible for tracking recipient or consignee information, post-op follow-up and reporting any adverse reaction to the source establishment.

End User: A hospital, surgeon, surgical center, research center or any entity that utilizes tissue provided by an eye bank.

FDA: An abbreviation for the United States Food and Drug Administration.

Graft: Tissues prepared for use in transplantation

HIV: An abbreviation for human immunodeficiency virus

Imputability: The likelihood that a serious adverse reaction in a recipient can be attributed to the tissue or cells applied or that a serious adverse reaction in a living donor can be attributed to the donation process.

OARRS: An abbreviation for Online Adverse Reaction Reporting System.

Processing Establishment: The entity that performs post-recovery tissue preparation.

Processing: Any activity performed on the eye tissue, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as: testing for microorganisms; preparation; sterilization; steps to inactivate or remove adventitious agents; preservation for storage; manipulation/sizing; and removal from storage. Any manipulation of the ocular tissue intended for transplant that involves opening a previously sealed container after recovery.

Quarantine: The identification of ocular tissue as not currently eligible for transplantation, including ocular tissue that has not yet been characterized as being eligible for transplantation. Quarantine includes the storage of such tissue in an area clearly identified for such use, or other procedures, such as automated designation, to prevent the premature release of such ocular tissue for transplantation.

Recovery Establishment: The entity that recovers tissue from a donor.

Relevant Communicable Disease: Any communicable disease relevant to transplantation of tissue in humans as defined by FDA regulations, FDA guidance documents or U.S. law.

SOP: An abbreviation for standard operating procedures.

Source Establishment (or Facility): The entity that releases tissue following donor eligibility determination, and is responsible for maintaining donor records and evaluating adverse reaction reports.

Sterile: The absence of detectable, viable, microorganisms (refer to ANSI/AAMI ST79).

Sterilization: A validated method used to render instrumentation and ocular tissue free from viable microorganisms, including spores (refer to ANSI/AAMI ST79:2010/A4:2013).

Storage Establishment: The entity that stores tissue at any time prior to distribution to the end user.

REFERENCES

Medical Standards. Eye Bank Association of America. Washington, DC: November 2013. http://www.restoresight.org/wp-content/uploads/2014/01/Medical-Standards-November-2013.pdf

SOHO V&S Guidance For Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions Associated with Human Tissues and Cells. EU Public Health Programme, Project #20091110. January 2013. http://www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf

NOTIFY: Exploring Vigilance Notification for Organs, Tissues and Cells. Organs, Tissues, & Cells, 2011, November, 14, 3: Suppl. http://www.notifylibrary.org/sites/default/files/BOOK%20NOTIFY.pdf

Guidance for Industry: Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely under Section 361 of the Public Health Service Act and 21 CFR Part 1271, March 2016.

https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM434834.pdf

USEFUL LINKS

Notify Library
http://www.notifylibrary.org/

FDA's HCT/P Adverse Reaction Reporting
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/ucm152576.htm
Form: Form FDA 3500A - Mandatory Reporting (2/2013)

OARRS Website
http://education.restoresight.org/arr/login.php

OARRS Organism Listing (Genus and Species)

Bacteria

Achromobacter (formerly Alcaligenes)
Acinetobacter spp.
Citrobacter spp.
Clostridium perfringens
Corynebacterium spp.
Enterococcus species

- Enterococcus faecalis
- Enterococcus faecium
- Other Enterococcus spp.
- Enterococcus unspecified

If known, include Vancomycin resistance in the comments (VRE)

Enterobacter spp.
Escherichia coli
Flavobacterium spp.
Haemophilus influenzae
Klebsiella spp.
Mycobacterium species

- Mycobacterium avium
- Mycobacterium chelonae
- Mycobacterium fortuitum
- Other Mycobacterium spp.

Pseudomonas aeruginosa
Propionibacterium spp.
Serratia marcescans
Staphylococcus species

- Staphylococcus aureus
- Staphylococcus epidermidis / coagulase negative
- Staphylococcus unspecified
- If known, include methicillin resistance in the comments (MRSA)

Streptococcus species

- Streptococcus pyogenes (Group A Strep)
- Streptococcus agalactiae (Group B Strep)
- Streptococcus pneumoniae
- Viridans streptococci (alpha hemolytic)
- Streptococcus unspecified

Stenotrophomonas maltophilia

Fungi

Aspergillus spp.
Candida species

- Candida albicans
- Candida glabrata
- Candida parapsilosis
- Candida tropicalis
- Candida other
- Candida unspecified

Cephalosporium spp.
Curvularia spp.
Fusarium spp.
Penicillum spp.
Yeast – non-specified

Virus

Herpes simplex
Cytomegalovirus

Parasites

Acanthamoeba spp. (if known, add the species to the comments)

Other

REVISION HISTORY

2009
Marion Macsai, MD
Amanda Nerone, CEBT

2014
Jennifer DeMatteo, MCM, CIC
Sean Edelstein, MD
Thomas D. Lindquist, MD, PhD
Amanda Nerone, CEBT
Edwin Roberts, CEBT
Chris Stoeger, MBA, CEBT

2017
Jennifer DeMatteo, MCM, CIC
Sean Edelstein, MD
Susan Hurlbert, CEBT
Marian Macsai, MD
Edwin Roberts, CEBT
Chris Stoeger, MBA, CEBT