Development of the Transplantation Transmission Sentinel Network: Progress On Biovigilance

10th European Haemovigilance Seminar

29 Feb 2008

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Centers for Disease Control and Prevention

I have no financial relationships with commercial interests to disclose.

The opinions presented are those of the speaker and do not represent official policy of CDC.

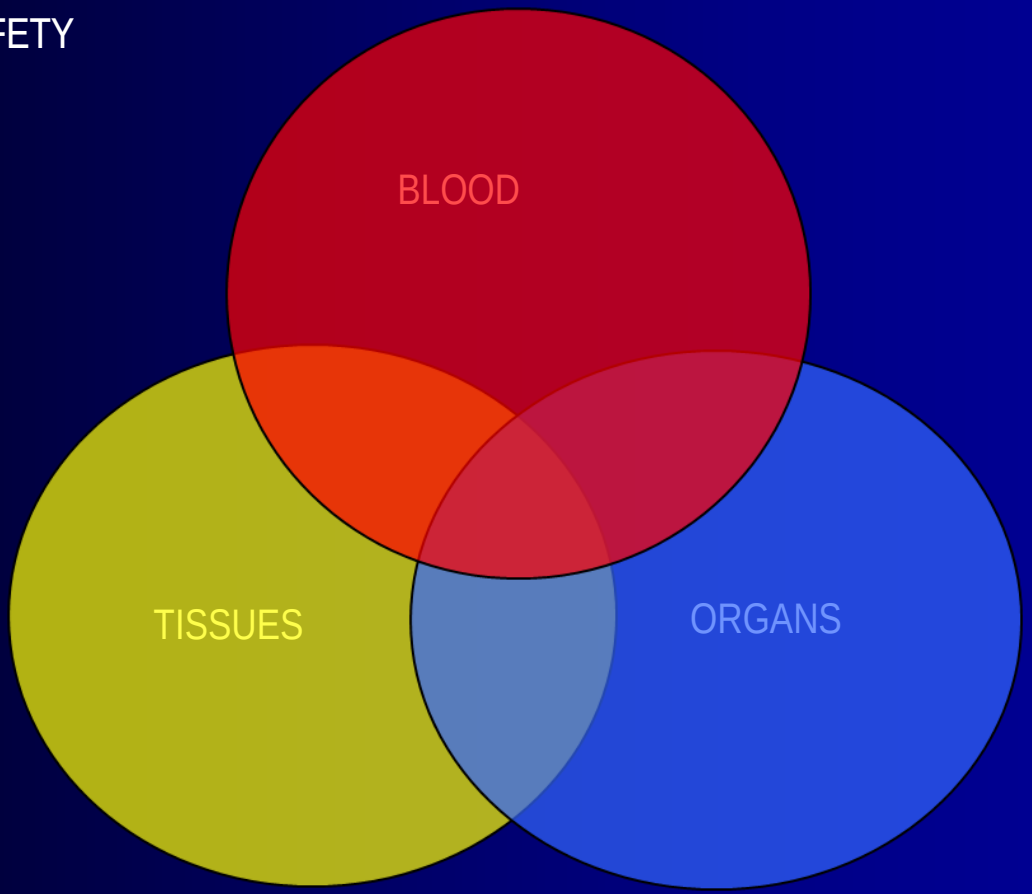
Bio-vigilance: A convergence of products

PATIENT SAFETY

VACCINES

DRUGS

DEVICES



Notable Organ Transplant-Transmitted Infections

- HIV, 1985
- Hepatitis C (HCV), 2000
- Chagas Disease, 2001
- West Nile Virus (WNV), GA 2002
- Lymphocytic Choriomeningitis Virus (LCMV), WI 2003
- Rabies, 2004
- LCMV, MA/RI 2005
- WNV, NY/PA 2005
- Chagas, CA 2006
- In 2007…

HIV and Hepatitis C virus (HCV)

- October 2007
  - Recipient tested positive for HIV and HCV
    - had tested negative pre-transplant
  - Donor
    - tested negative by serology
    - considered “high risk” based on behavoiral questionnaire
  - Other organs (heart, liver, kidney) had been transplanted
    - all reportedly “doing well”
  - Investigation
    - donor serum tested positive for HIV and HCV by nucleic acid testing
    - all 4 organ recipients infected with HIV and HCV

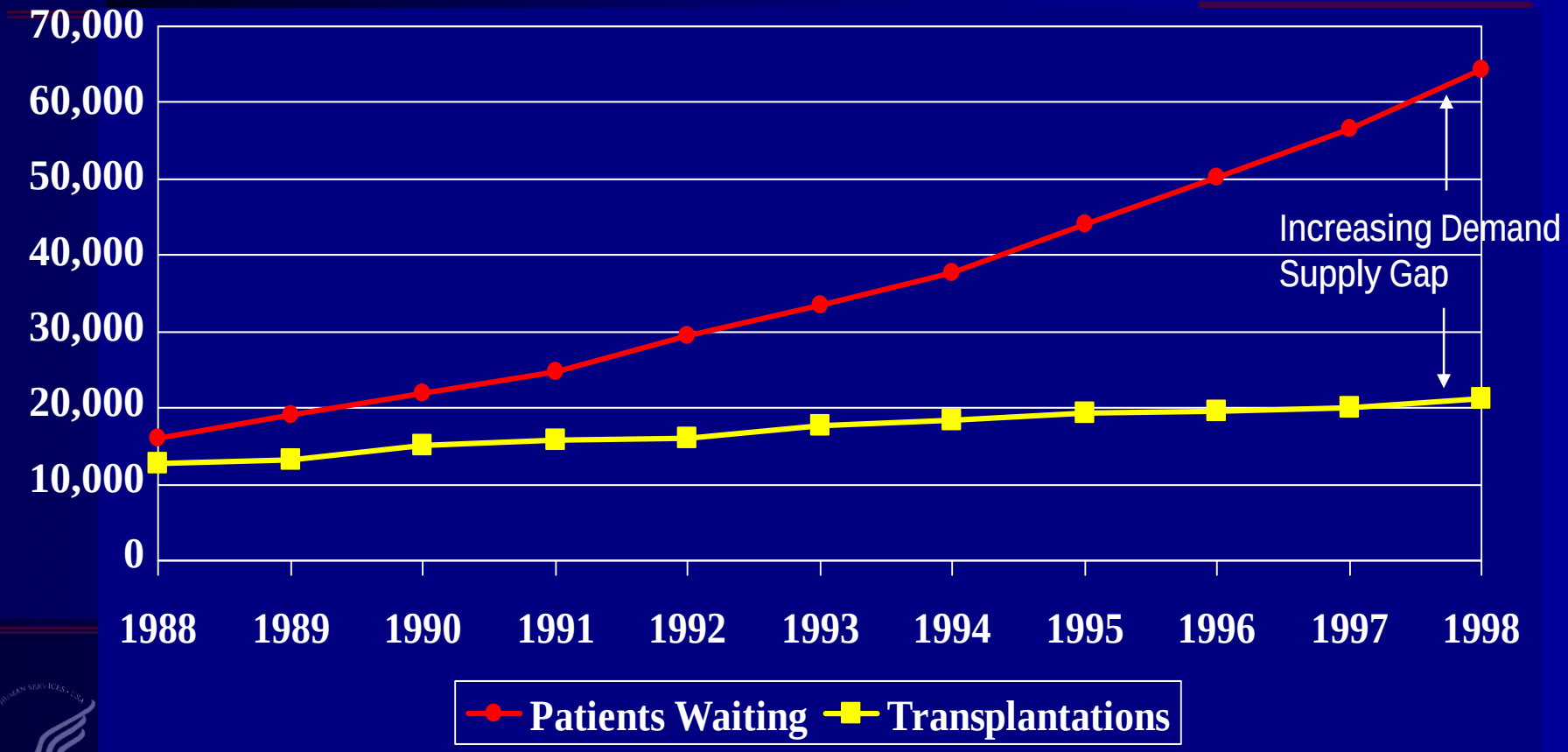
Transplant-transmitted tuberculosis (TB)

- April 2007
  - Report of TB in an organ donor from OK state health dept
  - Patient with hx pneumonia, fever with seizures, progresses to brain death and becomes organ donor
  - Cultures performed on CSF, +TB months post-mortem
  - Recipients
    - Kidney - disseminated TB – died after septic-like illness
    - Kidney – unknown status
    - Liver – unknown status
  - On followup, the surviving kidney recipient, a 23 year old black female, presented with fever 6 weeks after transplant
    - Upon notification of events, put on 4 anti-TB therapy and survived
  - Liver recipient treated expectantly
  - Extensive contact investigations required
  - MMWR planned

Organ Transplantation

Year-end Waiting Lists vs. Transplanted

(kidney, liver, pancreas, heart, lung)

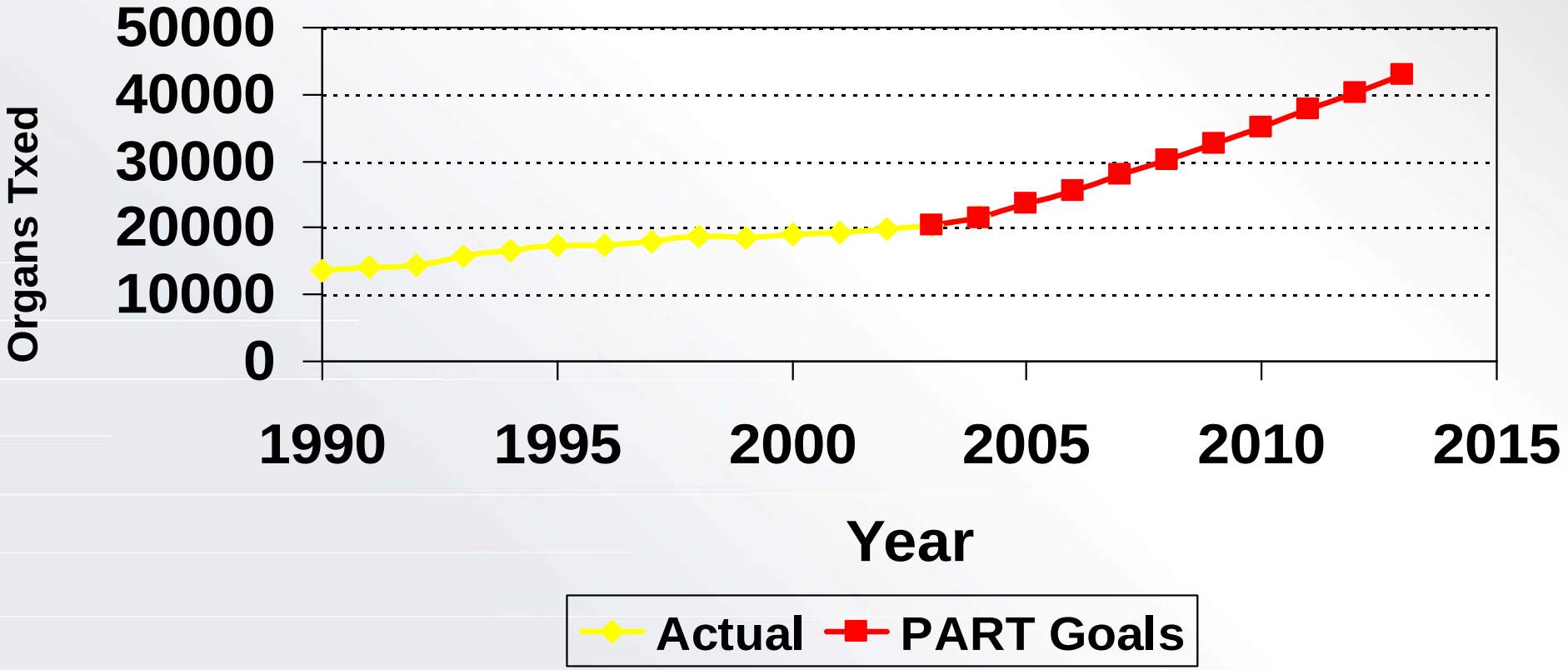


Source: UNOS

As of 2008, over 25,000 transplants, with 95,000 on the waiting list.

Program Goals: Increase Organ Availability

Increase number of deceased donor organs transplanted each year until 42,800 are transplanted in 2013



Balancing Resources

Differences between blood, organs, and tissues

SAFETY

Blood?

AVAILABILITY

Organs?

Tissues?

The explosive growth of tissue allograft use

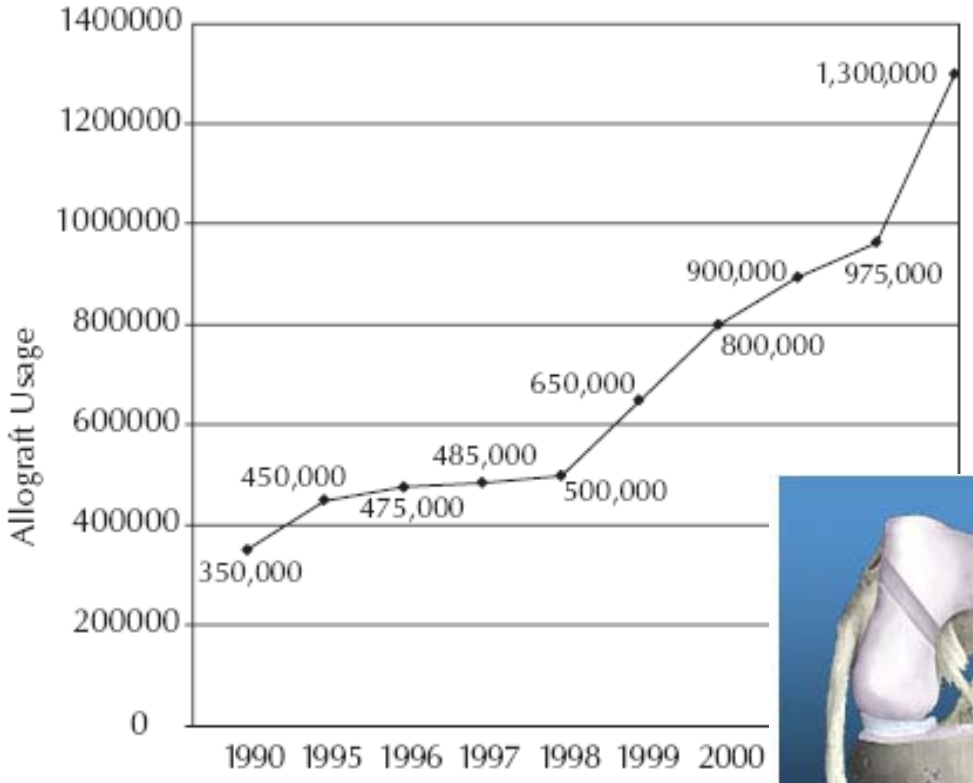
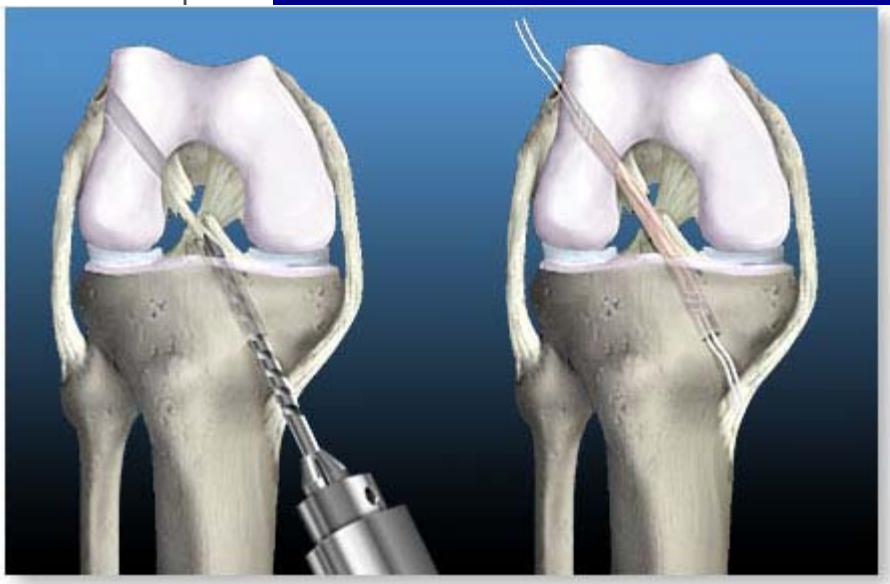


Figure 1: Musculoskeletal allograft distribution. Source: AATB Annual Survey.



Increasing Use of Allografts: Technological advances and challenges

- >2,000,000 allografts implanted annually
- ~50,000 corneas
- Investigations of tissue-transmitted infxn
  - *Candida albicans*
  - Hepatitis C virus
  - Group A Streptococcus
  - *Clostridium sordellii*
  - Clostridial endophthalmitis
  - *Chryseobacterium meningosepticum*
  - Improper donor screening or tissue processing (BTS, DRS)

A few facts…and a few challenges

- As many as 100 allografts can be processed and distributed from one person's donation
- A donor's tissues can be recovered by multiple recovery entities, and tissues sent to multiple banks for processing (skin, musculoskeletal, cardiac valves, eyes)
- ~13% of all tissue donors are organ donors*
- ~36% of all organ donors are tissue donors*

*Scott Brubaker, AATB

HIV from organ and tissue donor 1985

- Transmitted by organs, unprocessed frozen tendon, two unprocessed frozen femoral heads,
- Not transmitted by freeze-dried tendon (blood, cells removed from bone ends, antibiotic soaked), freeze-dried bone (blood, cells removed, ETOH soaked) or irradiated dura

- Six recipients not able to be identified by hospitals during epidemiologic investigation in 1991.
  - Inadequate hospital recordkeeping!

Simonds et al NEJM 1992;326:726

Organ and Tissue Safety
Reporting - current systems and gaps

- Organs and tissues have systems for adverse event reporting, but are passive, with multiple pathways
  - Organs – HRSA/UNOS DTAG (hospitals, OPOs)
  - Tissues – FDA (hospitals, tissue banks, OPOs)
  - MedWatch
- Adverse event reporting systems do not ensure participation of clinician
- Tissue regulations extend only to “hospital door”
- Outcome reporting needed

CDC/FDA/HRSA Organ and Tissue Safety Workshop Priorities – 2005

- ✓ 1. Unique donor ID linking organs and tissues
- ✓ 2. Notification algorithm for trace-back and trace-forward tracking
- ✓ 3. Clear mechanisms for adverse event reporting by healthcare facilities
- ✓ 4. Better communication network within and between organ and tissue community
- ✓ 5. Stronger information dissemination to broad array of clinicians, health professionals and patients

Background

- In June 2005, CDC published a request for application (RFA) for federal funds for the development of a sentinel network for detecting emerging infections among allograft donors and recipients.
- The United Network for Organ Sharing (UNOS), in an alliance with multiple partners, was awarded the cooperative agreement with CDC.
- The objective of the network is to detect and prevent disease transmission through improved communication among those in the organ, eye, and tissue community (e.g., tissue recovery organizations, OPOs, eye banks, tissue banks and processors, tissue distributors), healthcare facilities, and public health officials.
- The project was named the Transplantation Transmission Sentinel Network (TTSN).

Background

- In order to meet these requirements and to plan, direct and study the actions needed to accomplish these requirements, a TTSN Advisory Group was established.

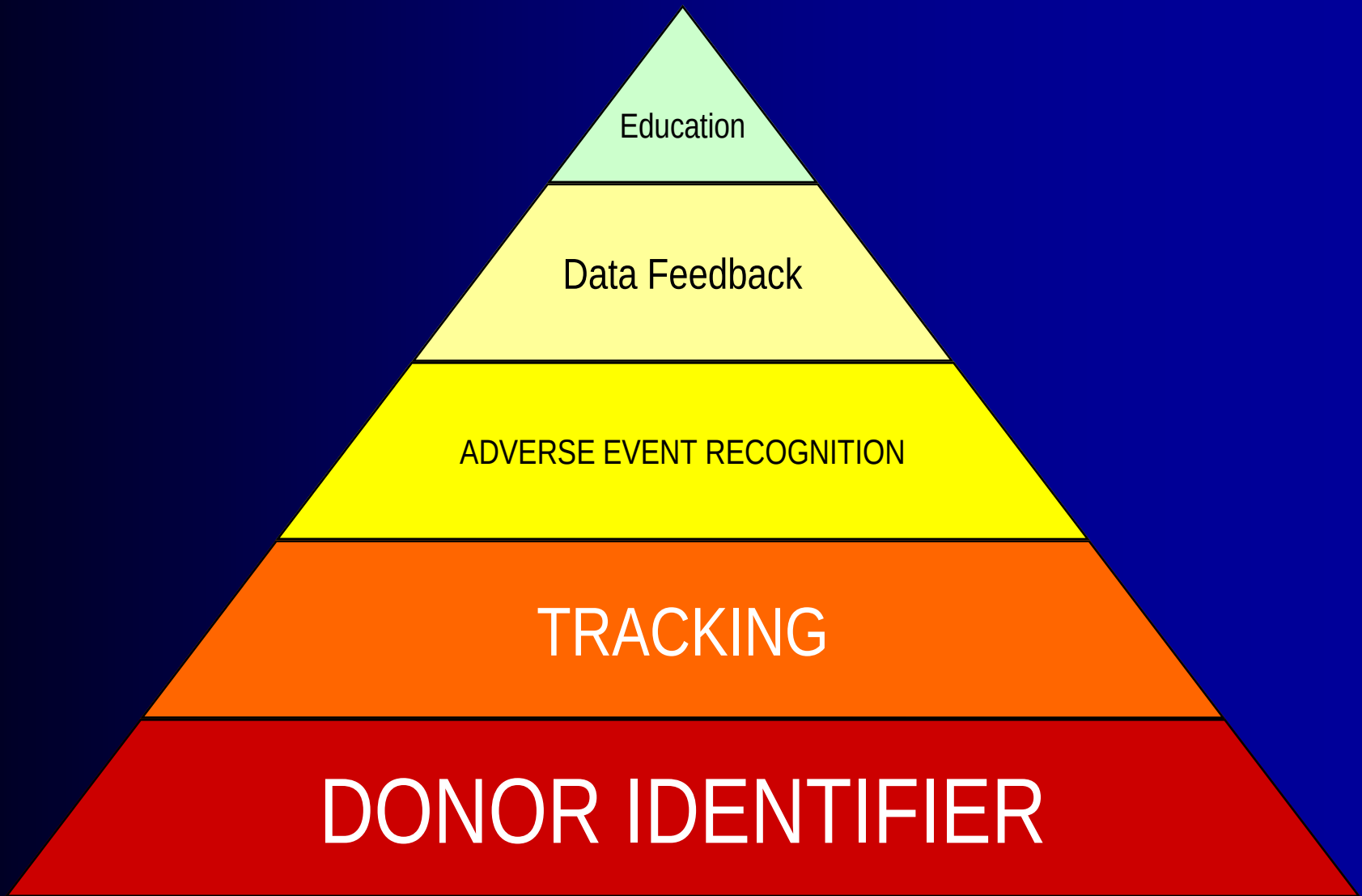
- The TTSN Advisory Group includes representatives of the major stakeholder organizations representing organ and tissue procurement and use and regulatory agencies of the Federal government.

Background

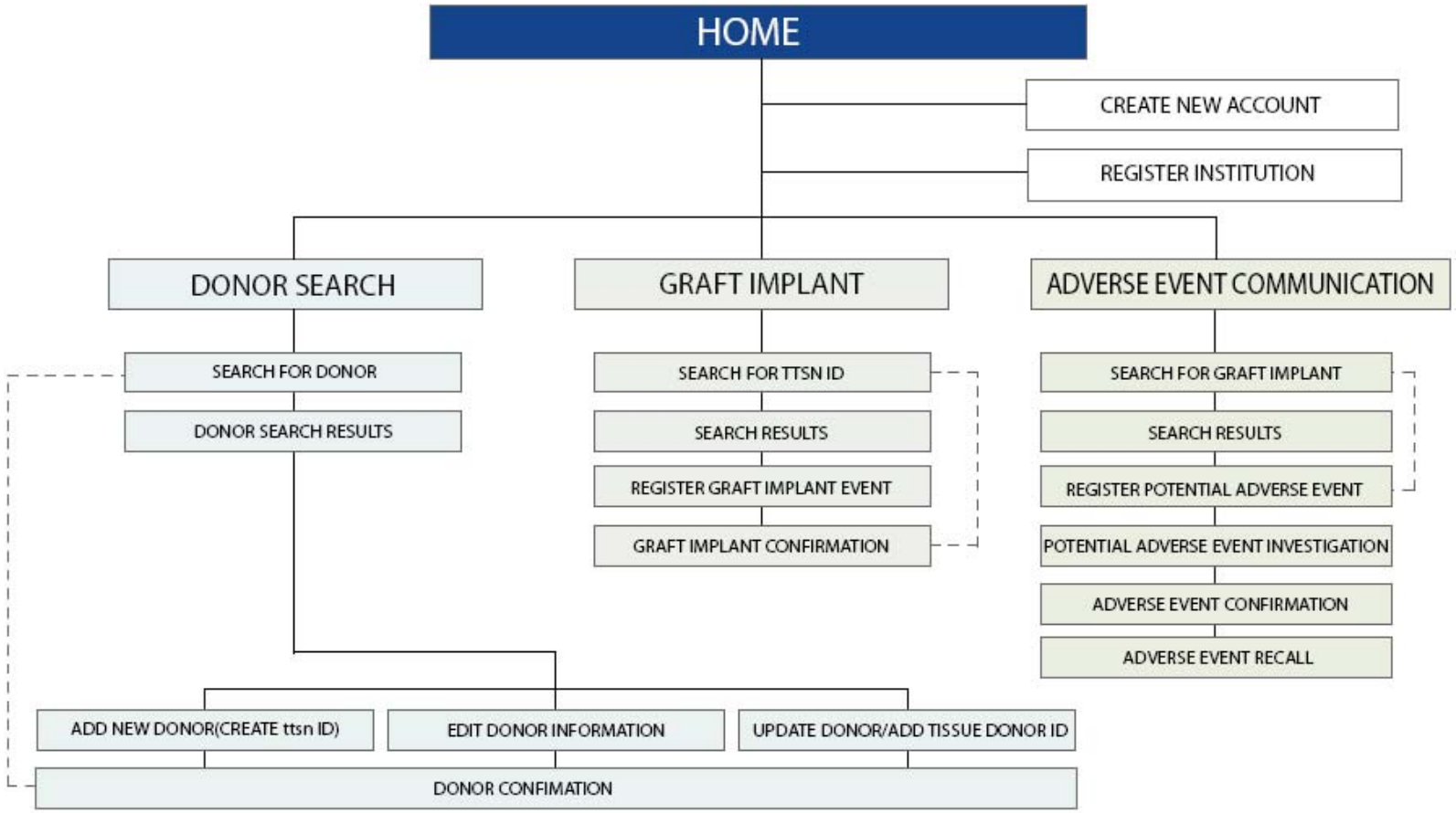
- The following organizations are represented:
  - **AATB** - American Association of Tissue Banks
  - **EBAA** - Eye Bank Association of America
  - **AOPO** - Association of Organ Procurement Organizations
  - **ASTS** - American Society of Transplant Surgeons
  - **AST** - American Society of Transplantation
  - **STS** – Society of Thoracic Surgeons
  - **AAO** - American Academy of Ophthalmology
  - **AAOS** - American Association of Orthopedic Surgeons
  - **AOSSM** - American Orthopaedic Society for Sports Medicine
  - **AABB** – formerly known as the American Association of Blood Banks

  - **FDA** – Food and Drug Administration
  - **HRSA** – Health Resources and Services Administration
  - **CMS** - Centers for Medicare and Medicaid Services
  - **CDC** – Centers for Disease Control and Prevention

The TTSN Task Pyramid



ttsn SITE MAP



TTSN Process Flow

Register Donor	Register Graft Implant	Register Potential Adverse Event	Investigate Potential Adverse Event	Notify Network of Recall
TTSN ID				
A Donor is registered in through the Donor Registration Event. This event generates a unique TTSN ID and associates an Institution specific Donor ID with it.	A Graft implant is registered in the TTSN through a Graft Implant Event when an Institution uses a Graft.	If a potential Adverse Event occurs, it is registered by the Institution which placed the Graft into the recipient. The Graft recovery Institution is notified and initiates a transmission investigation.	Each Recovery Institution will investigate all potential adverse events reported for their institution as required by the appropriate regulatory authorities and will determine if further action is necessary. If a Potential Adverse Event is determined to be probable or proven, the eye, organ or tissue recovery institution will determine which flags are posted on the TTSN record.	If the responsible graft recovery institution determines that the Potential Adverse Event reported warrants a recall the user will fill out the Recall Information form which will display an alert of recall for any tissues acquired from that particular donor.

ttsn TRANSPLANTATION TRANSMISSION SENTINEL NETWORK

Welcome to the TTSN Web site

Please login to get started

SECURE LOGIN

Username

Password

Login

This section is password-protected for secure data entry by authorized users. Contact your site administrator for information on becoming an authorized user of this system or click the following link to create a new account.

About TTSN

The Transplantation Transmission Sentinel Network (TTSN) was established by a CDC cooperative agreement in September 2005. The United Network for Organ Sharing (UNOS), in an alliance with Association of Organ Procurement Organizations (AOPO); American Association of Tissue Banks (AATB); Eye Bank Association of America (EBAA); American Society of Transplantation (AST); and American Society of Transplant Surgeons (ASTS), was awarded the cooperative agreement. The purpose of the Sentinel Network is to establish a network for detecting, communicating, and tracking allograft donors to recipients.

Important Links

Register Institution
Create User Account
Link 3
Link 4
Link 5

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Donor Search

ADMIN | LOGOUT

ttsn TRANSPLANTATION TRANSMISSION SENTINEL NETWORK

DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

3 ways to search

This is where the system explanation or instructions will be displayed for the user...

1 Search by ID:

TTSN ID: | or | UNOS Donor ID: | Search

2 Search by Institution:

Institution: * AAUNOSCORP | Donor ID: * | Search

3 Search by Donor Info:

Last Name: * | First Name: *

Date of Birth: | Date of Death: | Recovery Date: | Search

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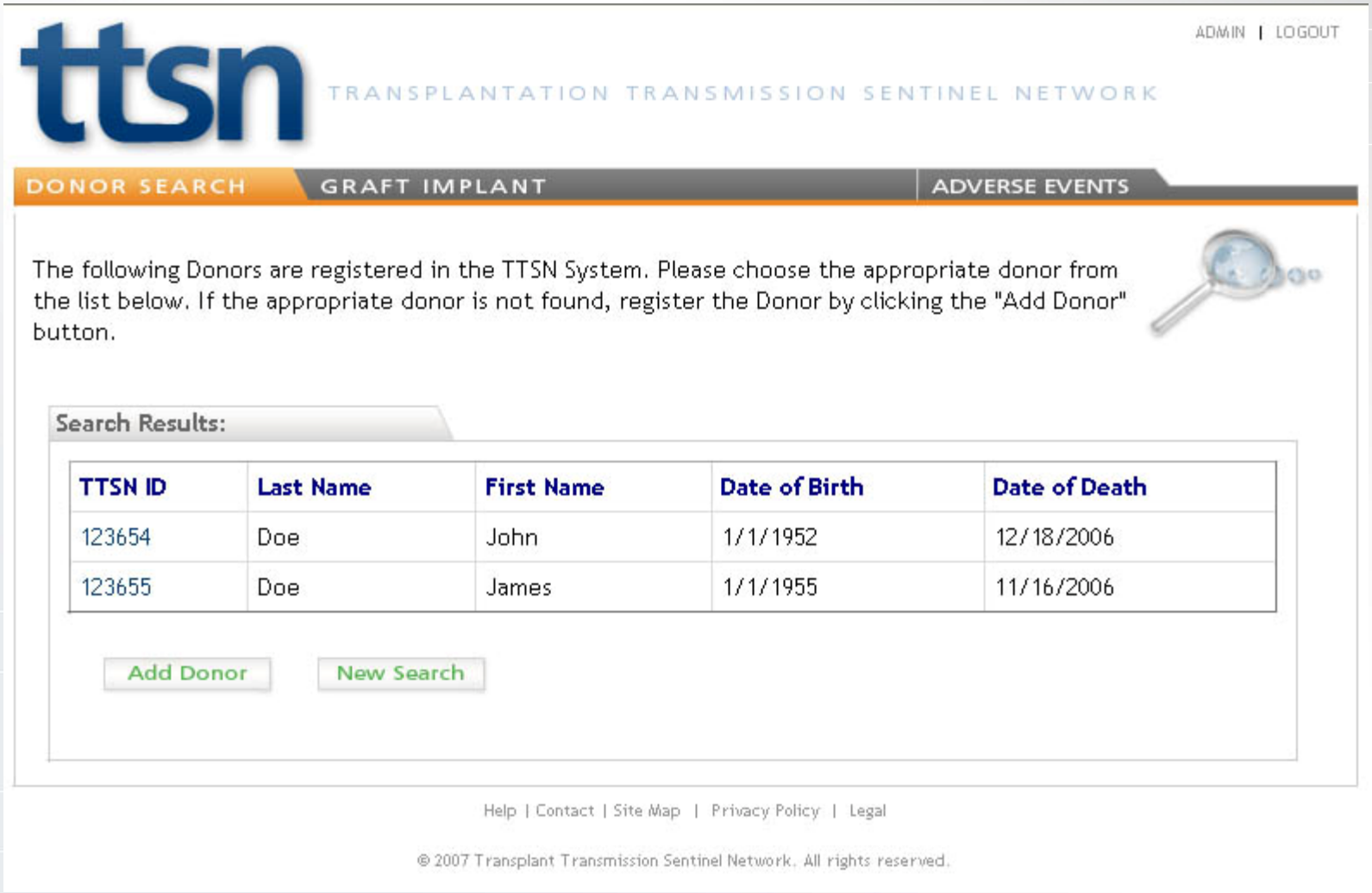
ttsn
TRANSPLANTATION TRANSMISSION SENTINEL NETWORK
ADMIN | LOGOUT
DONOR SEARCH
GRAFT IMPLANT
ADVERSE EVENTS
The following Donors are registered in the TTSN System. Please choose the appropriate donor from the list below. If the appropriate donor is not found, register the Donor by clicking the "Add Donor" button.
Search Results:
TTSN ID | Last Name | First Name | Date of Birth | Date of Death
123654 | Doe | John | 1/1/1952 | 12/18/2006
123655 | Doe | James | 1/1/1955 | 11/16/2006
Add Donor
New Search
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ADMIN | LOGOUT

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DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Below is the information for the donor you selected, including all related / associated institutional Donor IDs that have been assigned to this TTSN ID. You may print this information by clicking on the "Print" button. Editing of this Donor Information is reserved for users of the institution which created the donor record. Thank you.

Donor Information:

Print

TTSN ID
123654

Last Name *
Doe

First Name *
John

Date of Birth *
01/01/1952

Date of Death *
12/18/2006

Recovery Date *
01/19/2007

Associated Donor IDs:

Institution Name	Donor ID	Graft Types Collected
UNOSCORP	U09867899888777	Cornea, CV - Cardio Vascular
New Tissue Bank	NTB4569877754	Cornea, CV - Cardio Vascular
New Tissue Bank		Cornea CV - Cardio Vascular MS - Muscular Skeletal Sclera Skin

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Register Graft Identifier (Link Graft to Donor Identifier)

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DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Search for TTSN ID

Use the form below to search to search for a TTSN ID. If you have the TTSN ID, use the "Search by ID" search, if you have a graft ID and Institution, use the "Search by Institution" search

1 Search by ID:

TTSN ID: *

Search For Donor

2 Search by Institution:

Institution: *

UNOSCORP

Graft ID: *

Search For Donor

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DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Search Results

Use the form below to search to search for a TTSN ID. If you have the TTSN ID, use the "Search by ID" search, if you have a graft ID and Institution, use the "Search by Institution" search

Search Results:

TTSN ID	Institution Name	Institution Donor ID
123654	UNOSCORP	U09867899888777
123654	New Tissue Bank	NTB4569877754

Add | New Search

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Graft Implant Registration

ADMIN | LOGOUT

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DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Welcome to the graft implant page. Use the form below to enter a graft implant. When you have filled out the form completely, click the "Save" button to save the information.

Save

1 Graft Information:

TTSN ID: 123654

Graft ID:

Graft Type:

2 Procedure Information:

Procedure Date:

Procedure Type:

3 Recipient Information:

Medical Record #:

Last Name:

First Name:

Date of Birth:

Age:

4 Institution Information:

Implanting Institution:

Implanting Surgeon

Last Name:

First Name:

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Potential Adverse Event Entry

Clinical Recognition Criteria Possible Allograft-Transmitted Adverse Reactions

- Infection
- Malignancy
- Graft Failure/Rejection

- Clinical diagnosis
- Confirmatory diagnostic test
- Outcome

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ADMIN | LOGOUT

Welcome Will

DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Welcome to the Adverse Event Reporting page.

Recipient Information:

Recipient Last Name: Recipient	Recipient First Name: Eye	Recipient D.O.B. 1/25/1964
Medical Record Number: 987456987777999	Implanting Institution: UNOSCORP	
Surgeon Last Name Surgeon	Surgeon First Name Bob	
TTSN ID: 123654	Graft ID: 123654088556687	Graft Type: Bone
Procedure Date: 3/28/2007	Procedure Type: DALK: Deep Lamellar Anterior Keratoplasty	Diagnosis: diagnosis 2

Adverse Event Information:

Adverse Event Category:

Clinical Diagnosis:

Save

Patient Status:

Labratory Confirmed: ☑

Diagnostic Test:

Adverse Event Description:

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Potential Adverse Event Communication

- Entering an adverse event will:
  - Generate an email notification to the responsible allograft institution - eye or tissue bank, processor, distributor or OPO, who will
    - perform an investigation according to current institution practice/regulatory requirements

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ADMIN | LOGOUT

Welcome HospitalUser1

DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

Adverse Event Registration

The following information is necessary to register an Adverse Event. This information will be forwarded to your tissue bank.

Recipient Information:

Recipient Last Name: Recipient	Recipient First Name: Eye	Recipient D.O.B. 5/14/1945
Medical Record Number: HOS0001	Implanting Institution: New Hospital	
Surgeon Last Name Surgeon	Surgeon First Name Eye	
TTSN ID: 123654		
Graft Recovery Institution: New Tissue Bank	Graft ID: NEB000101	Graft Type: Cornea
Procedure Date: 1/21/2008	Procedure Type: OTH LARYNGEAL OPERATION	Diagnosis: diagnosis 2

Adverse Event Information:

Save

Adverse Event Category:

Clinical Diagnosis:

Pathogen Identified:

Patient Status:

Patient Hospitalized?: Yes No

Laboratory Confirmed:

Diagnostic Test:

Adverse Event Description:

Contact First Name:

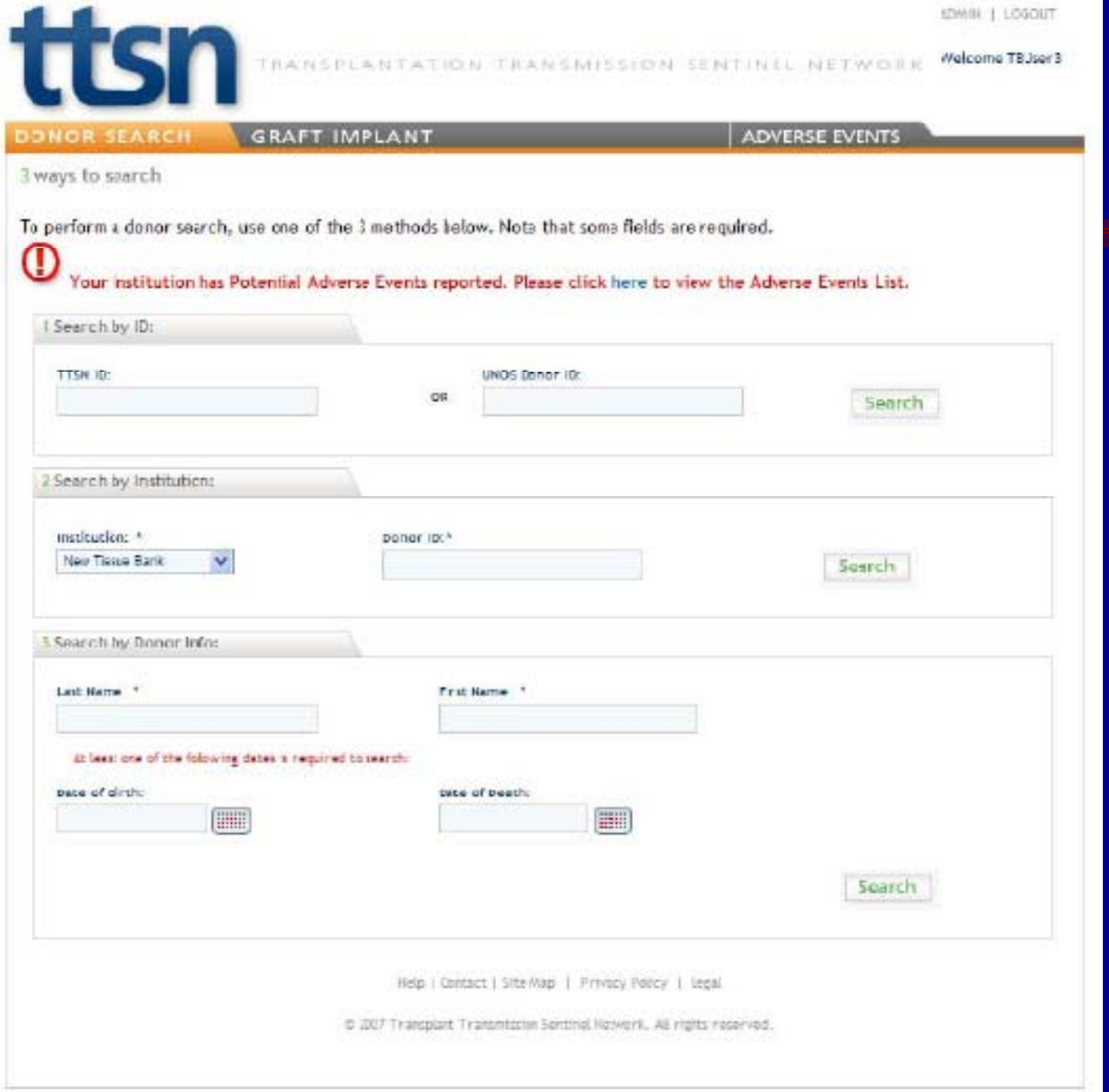
Contact Last Name:

Contact Email Address:

Contact Phone Number:

DEPARTMENT OF HEALTH AND HUMAN SERVICES - USA

CDC


ttsn
TRANSPLANTATION TRANSMISSION SENTINEL NETWORK
ADMIN | LOGOUT
Welcome TBUser3
DONOR SEARCH
GRAFT IMPLANT
ADVERSE EVENTS
3 ways to search
To perform a donor search, use one of the 3 methods below. Note that some fields are required.
Your institution has Potential Adverse Events reported. Please click here to view the Adverse Events List.
1 Search by ID:
TTSN ID:
OR
UNOS Donor ID:
Search
2 Search by Institution:
Institution: *
New Tissue Bank
Donor ID: *
Search
3 Search by Donor Info:
Last Name *
First Name *
At least one of the following dates is required to search:
Date of Birth:
Date of Death:
Search
Help | Contact | Site Map | Privacy Policy | Legal
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Recipient Information:

Recipient Last Name: Recipient	**Recipient First Name:** Eye	**Recipient D.O.B.** 5/14/1945
Medical Record Number: HOS0001	**Implanting Institution:** New Hospital	
Surgeon Last Name Surgeon	**Surgeon First Name** Eye	
TTSN ID: 123654		
Graft Recovery Institution: New Tissue Bank	**Graft ID:** NEB000101	**Graft Type:** Cornea
Procedure Date: 1/21/2008	**Procedure Type:** OTH LARYNGEAL OPERATION	**Diagnosis:** diagnosis 2

Adverse Event Information:

Adverse Event Category: Infection	**Clinical Diagnosis:** this one	**Pathogen Identified:** This Pathogen
Patient Status: Dead	**Patient Hospitalized?:** No	**Laboratory Confirmed:** No **Diagnostic Test:** Not Reported
Contact First Name: Moly	**Contact Last Name:** Blue	
Contact Email Address: mblue@tresa.com	**Contact Phone Number:** 4445556666	

Adverse Event Description:
The adverse EVent Description goes here

Investigation Information:

Investigation Status:

Save

Graft Related:

Add Comments:

Investigation Comments:


DONOR SEARCH
GRAFT IMPLANT
ADVERSE EVENTS
The following TTSN IDs are in the system. Please choose the appropriate record from the list below. If the appropriate TTSN ID is not found, register the Graft Implant Event by clicking the "Add" button.
A recall has been issued by the following institution(s):
New Tissue Bank <click here for more information>
New Eve Bank <click here for more information>
Search Results:
TTSN ID
Institution Name
Institution Donor ID
Institution ID
New Tissue Bank
Add
New Search

Steps for Input

- June 2007 UNOS Workshop
  - emphasized need to integrate and interface with existing systems (e.g., eye adverse event surveillance)
  - feedback from organ and tissue community on TTSN system programming
  - continued input sought from OPOs, tissue banks, and end users
- Recruitment of a “user” group
- Implementation workshop planned May 2008
- Pilot sites using system by mid-2008

TTSN Pilot Timeline

- The TTSN Pilot
  - Beginning April 2007 – August 2008
  - Approximately 9 institutions from eye, organ and tissue recovery, processing and distribution agencies and hospital allograft users
    - Each institution will choose users
  - Participating institutions will represent many stakeholders across the allograft community

Challenges

- Who will maintain the system once it is designed?
- Who will analyze the data in “real-time”?
- How will participation be assured?
- How will the system connect with existing reporting systems?
- What resources will be available to bear the cost?

Some tissues are not being monitored in TTSN

- Blood and blood products
- Stem cells
  - Bone marrow
  - Peripheral stem cells
  - Cord blood
- Reproductive cells
- If not included, how do we best interface with existing or planned parallel systems?

AABB's Interorganizational Task Force on Biovigilance

AABB Task Force in Talks with Government to Support Voluntary National Biovigilance Network

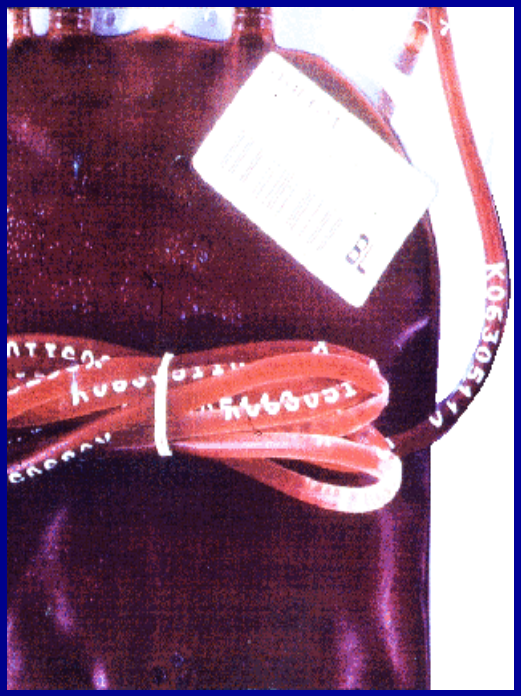
By Ashley Smith
AABB STAFF WRITER

The AABB Interorganizational Task Force on Biovigilance currently is in talks with the federal government to explore technical support options for the creation of a national biovigilance network that would help improve patient and donor safety. Under the plan, the biovigilance network — a central, coordinated system for identifying adverse events and near-miss incidents occurring at any point in the collection, processing, distribution, transfusion or transplantation of blood, tissue and cellular therapy products — would get technical support from the federal government, including software and a platform. The network itself would remain voluntary, nonpunitive and independent of governmental regulation.

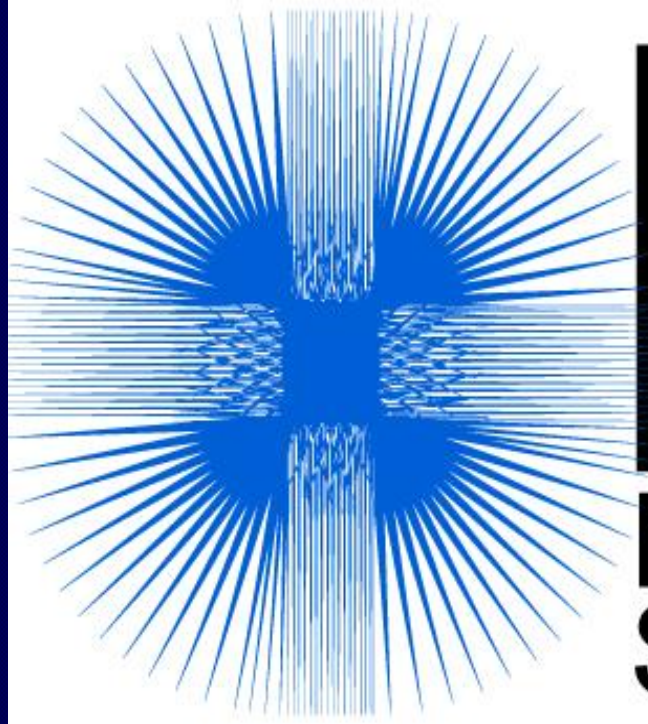
"While we originally envisioned this as solely a private initiative, the government's support will help us make this program a reality more quickly, and that could mean instituting safer practices sooner," said Barbee Whitaker, PhD, director of the Center for Data and Special Programs at AABB. While this contribution from the federal government will help expedite completion of the network, "support from the transfusion medicine and cellular therapies community remains a critical element for success," noted Whitaker.

The Challenge of “Hemovigilance”

- No national “hemovigilance” program exists in the U.S., comprising patchwork of programs
- Blood collection centers perform screening
- Hospital transfusion services report adverse events



A public-private partnership is born!



NHSN

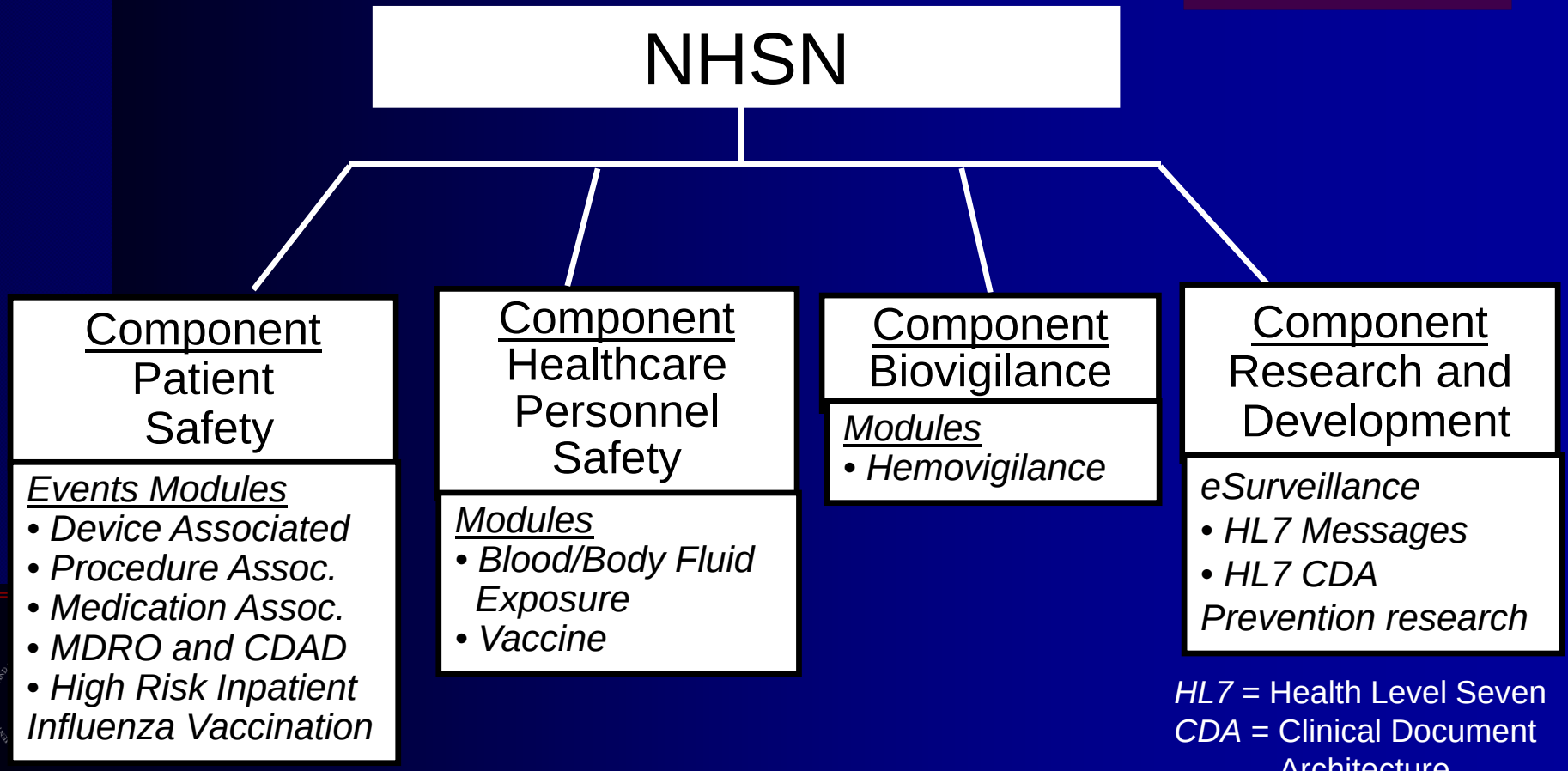
National Healthcare Safety Network

The National Healthcare Safety Network (NHSN) is a secure, internet-based surveillance system that integrates patient and healthcare personnel safety surveillance systems managed by the Division of Healthcare Quality Promotion (DHQP) at CDC.

What is the NHSN model?

- Provide standardized protocols and definitions
- Identify and monitor risk factors for adverse events/injuries
- Feedback risk-adjusted aggregated data for comparison
- Provide access to prevention guidelines and other prevention tools

NHSN Components and Modules



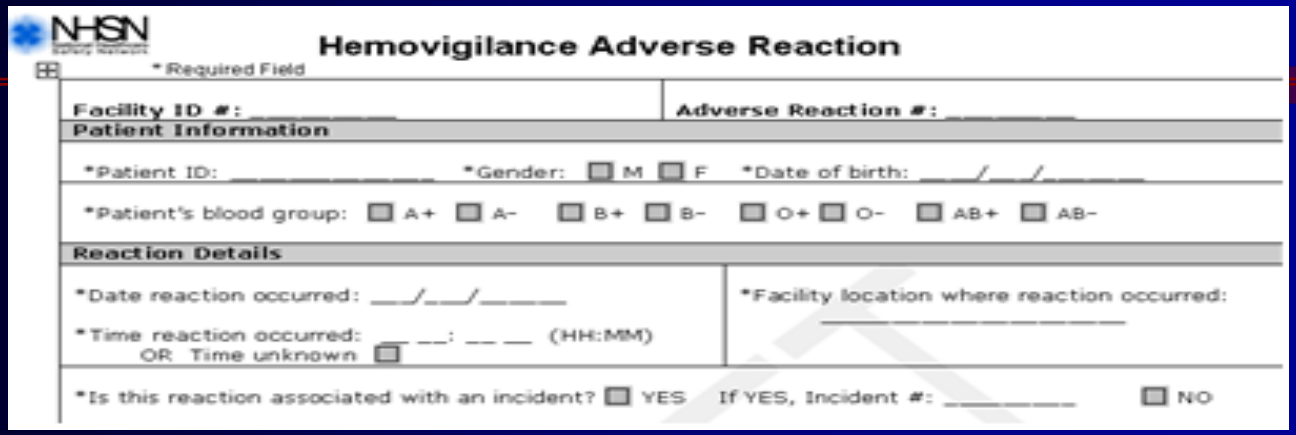
MDRO = Multidrug-resistant organism

CDAD = Clostridium difficile associated disease

HL7 = Health Level Seven

CDA = Clinical Document Architecture

Hemovigilance Module: Adverse Reactions



NHSN

Hemovigilance Adverse Reaction

*Required Field

Facility ID #: _____ Adverse Reaction #: _____

Patient Information

*Patient ID: _____ *Gender: ☐ M ☐ F *Date of birth: ___/___/_____

*Patient's blood group: ☐ A+ ☐ A- ☐ B+ ☐ B- ☐ O+ ☐ O- ☐ AB+ ☐ AB-

Reaction Details

*Date reaction occurred: ___/___/_____

*Time reaction occurred: __ __: __ __ (HH:MM)
OR Time unknown ☐

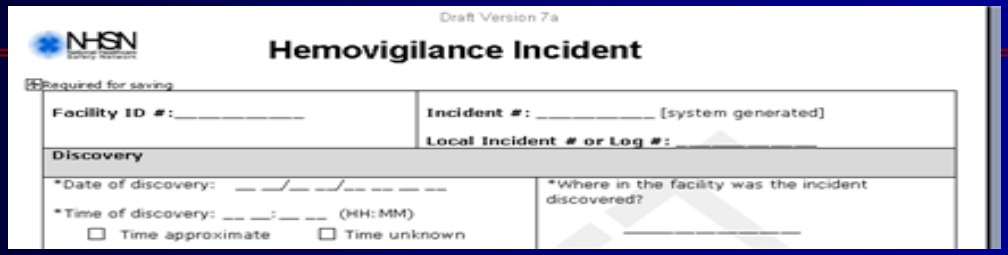
*Facility location where reaction occurred: _____

*Is this reaction associated with an incident? ☐ YES If YES, Incident #: _____ ☐ NO

Participating Facilities will report monthly:

- Each transfusion-associated adverse reaction in recipients
  - Pre-defined diagnostic criteria for:
    - Allergic, febrile, hemolytic, hypotensive reactions, infections, post transfusion purpura, transfusion associated circulatory overload (TACO), transfusion associated acute lung injury (TRALI), transfusion associated graft vs. host disease (TA-GVHD), others
  - Grade of severity and relationship to transfusion
  - Component and unit details
  - Outcome

Hemovigilance Module: Errors


Draft Version 7a

NHSN

Hemovigilance Incident

Required for saving

Facility ID #:_____

Incident #: _____ [system generated]

Local Incident # or Log #: _____

Discovery

*Date of discovery: __ __/__ __/__ __ __ __

*Time of discovery: __ __:__ __ (HH:MM)

☐ Time approximate ☐ Time unknown

*Where in the facility was the incident discovered?

_____

- Participating facilities will report monthly:
  - Incidents associated with blood products
    - All incidents reported to blood transfusion services from product check-in to product administration
  - Report discovery (date, time, how and where)
  - Occurrence (date, time, where, worker involved, MERS-TM codes for incidence)
  - Incident result, product action
  - Patient ID for any incident associated with an adverse reaction

Hemovigilance Module Status

- Completed:
  - Data collection forms development
  - Diagnostic criteria for adverse reactions
- In progress:
  - Protocol
  - Forms testing
  - Criteria for infection reporting
- To be done:
  - Identify pilot sites
  - Develop user training

"The US Biovigilance Network"

- 4 Modules
  - Blood Recipient System
    - Content – AABB Advisory Group
    - Electronic System – CDC/NHSN
  - Blood Donor System
    - Content – AABB Advisory Group
    - Electronic System – HHS
  - Tissue / Organs – ttsn
    - Content – UNOS Advisory Group
    - Electronic System – UNet-based
  - Cellular Therapies (TBD)

“Vigilance is an attitude.”

Dr Luc Noel, WHO

July 2007, EUSTITE Meeting,V&S MAC

Improvements to Surveillance & Reporting are occurring globally

- Cells and tissues
  - Canada
  - USA
  - Europe
    - The **EUSTITE** Project
      - European Union Standards & Training in the Inspection of Tissue Establishments

Biovigilance is not just an attitude - it is now a global movement!

Questions?

Bio-vigilance
Definitions

"Bio" – Comprehensive interpretation of biologic products

Blood/plasma derivatives, immunoglobulins, albumin…

Organs (e.g., kidney, liver, lung, heart…)

Other Tissues (e.g., musculoskeletal, heart valves, skin, eyes, dura, stem cells…)

Xenotransplants

Genes

Recombinant products

Parts of devices/ drugs/vaccines

Synthetics

Bio-vigilance
Definitions

"Vigilance" – numerous facets for discussion

- Donor surveillance
  - deferral and lab testing
- Recipient surveillance
  - adverse events
- Emerging Infectious Disease (EID) monitoring
- Product quality assurance (QA)
- Availability/Use Assessment

Biovigilance
Surveillance Needs Follow Two Models

- Comprehensive reporting model
  - For common, well-defined events and outcomes
  - Active surveillance approach
  - Selected site methodology
- Sentinel model
  - For uncommon, unusual events and outcomes
  - Passive or enhanced passive surveillance approach
  - Uniform national methodology
- For either model, need to determine intervention threshold (and what action should be)