European Homograft Bank

Kliniek SINT-JAN
Clinique SAINT-JEAN

TISSUES, INTERNATIONAL COLLABORATION AND VIGILANCE

R. Jashari, MD, FETCS
Cardiac Surgeon, Director of EHB
Saint Jean Clinic, Brussels, Belgium

TRIP Symposium 2017, Rotterdam, November 22, 2017

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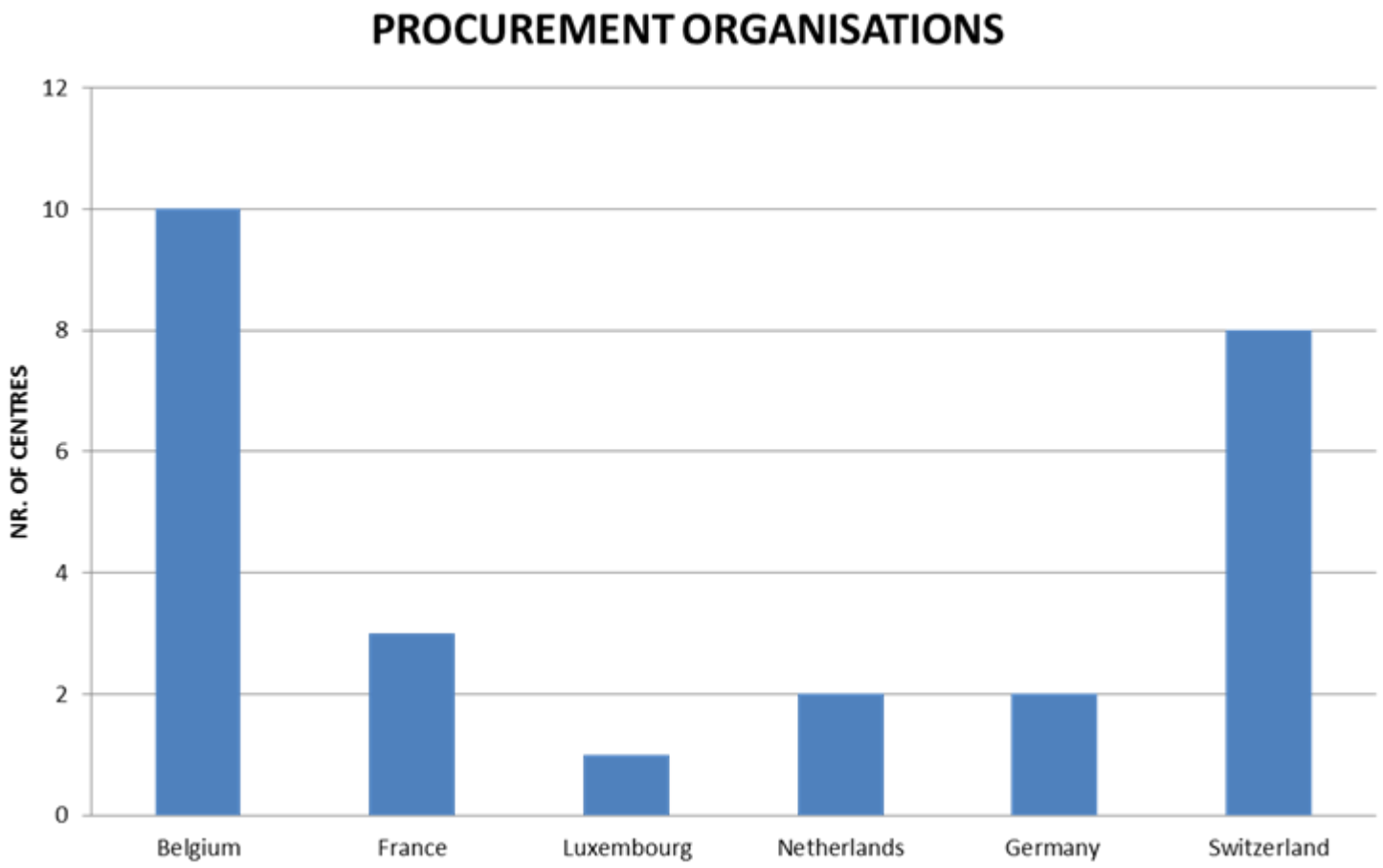
COOPERATION NETWORK OF EHB



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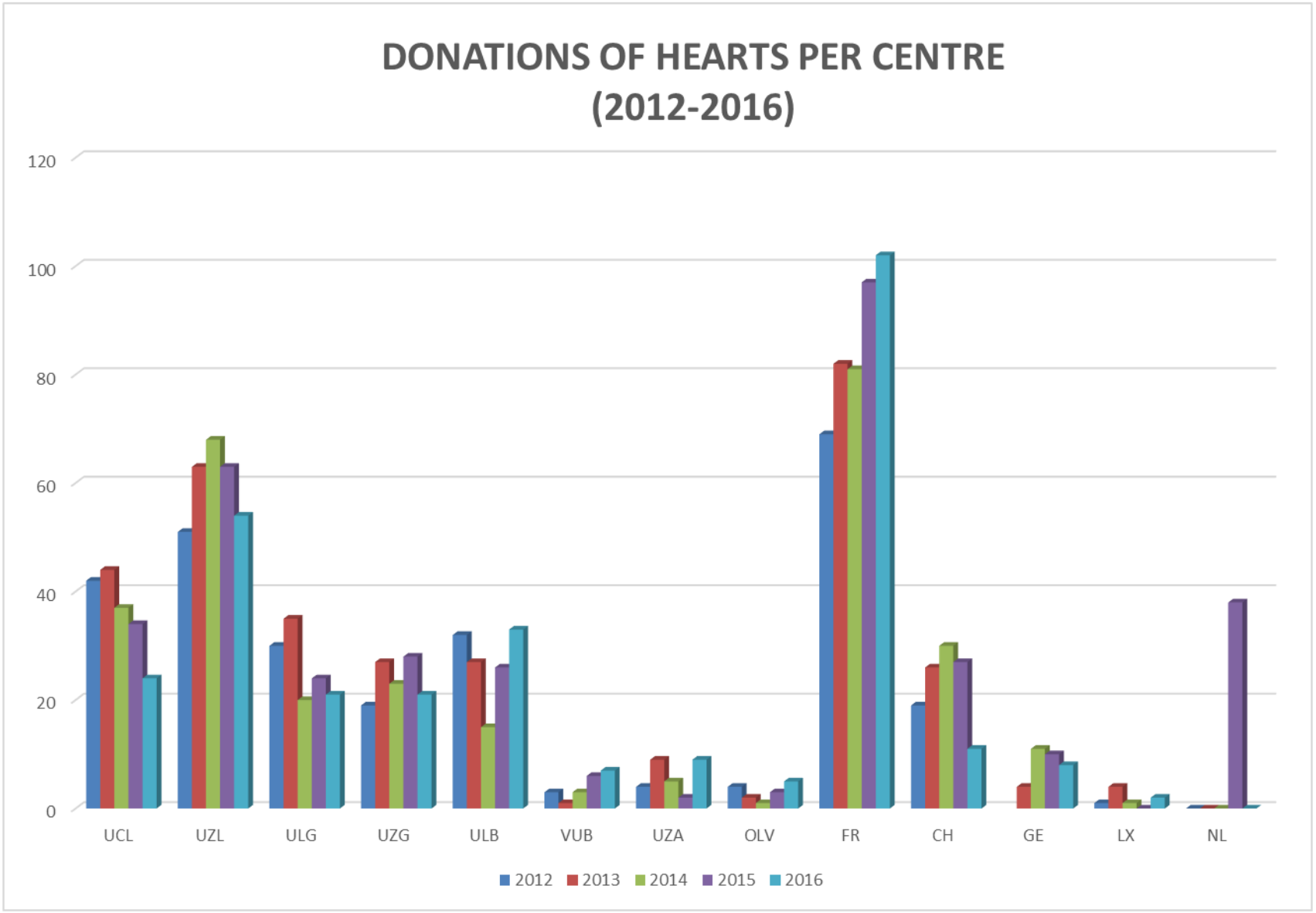

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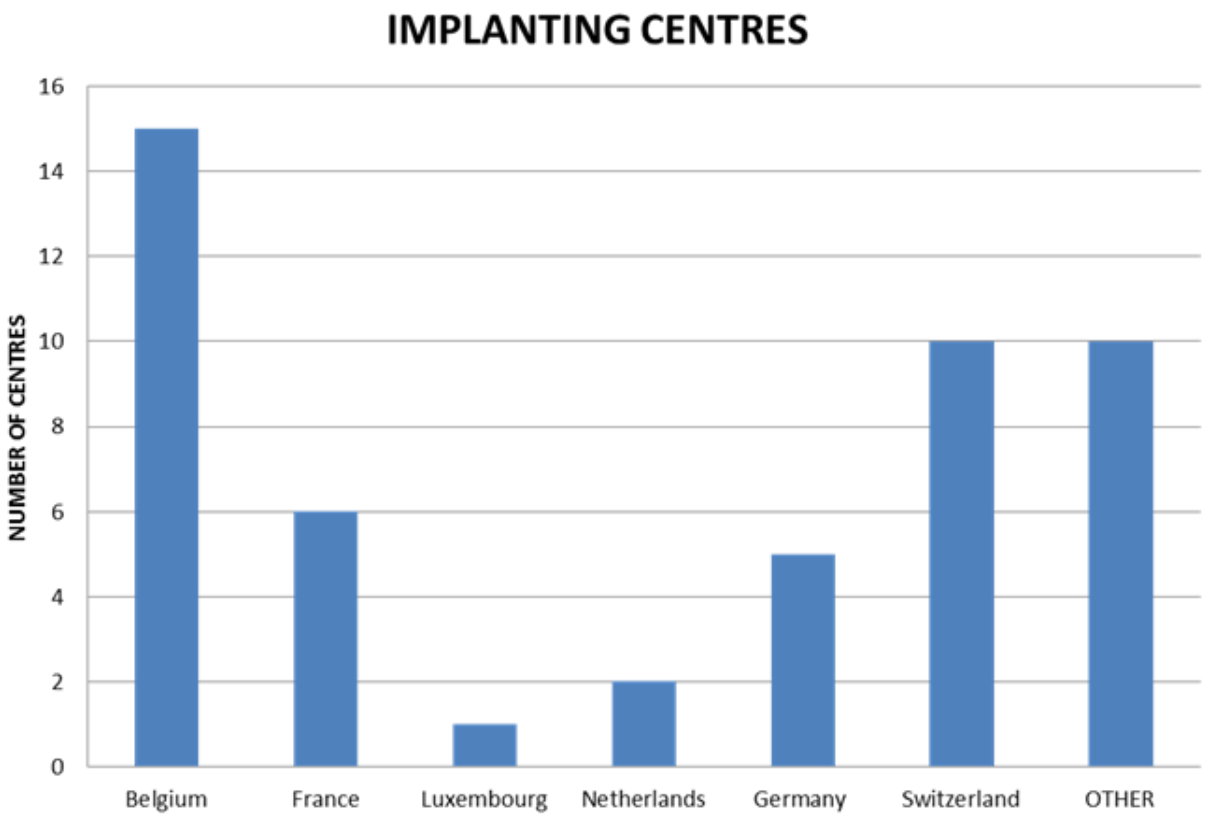

- **DISTRIBUTES TO WHOLE BE, CH, FR (MANY CARDIAC AND/VASCULAR CENTRES), GE, LX, NL,OCCASIONALLY IN OTHER CENTRES IN EU & WORLDWIDE**

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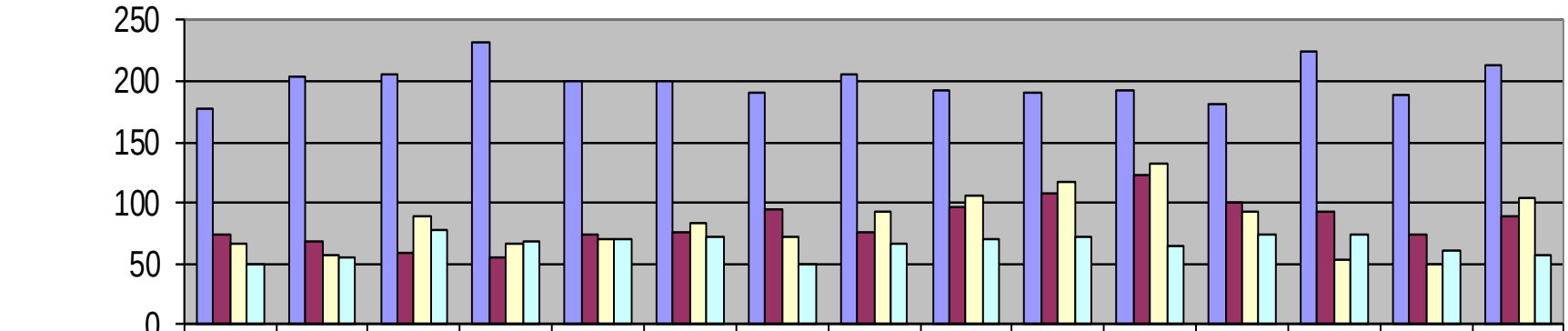
Distribution of allografts

ALLOGRAFTS (Valves + Ateries) IMPLANTED BY COUNTRY



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Belgique	177	203	205	232	200	200	190	206	193	191	192	181	225	188	213
France	75	68	60	56	75	76	94	76	97	108	123	100	93	75	89
Germany	66	58	89	66	70	83	72	93	106	117	132	92	53	49	105
Switzerland	49	56	77	69	71	72	49	67	71	72	65	75	75	61	58

Year

<u>OTHER COUNTRIES</u>: AUSTRIA, CROATIA, GREECE, HONG KONG, HUNGARY, LUXEMBURG, MOLDAVIA, NETHERLANDS, NEW ZEALAND, SAUDI ARABIA, SLOVENIA, SERBIA, TURKEY, UK,

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DIVERSE REGULATIONS WITHIN E.U. M.S.

- **COMPLEX (DIVERSITY IN) RULES** OF EXCHANGE (TRANSFER/EXPORT/IMPORT) OF TISSUES BETWEEN THE MS
  - DIFFERENCES IN DONOR ACCEPTABILITY (CAUSE OF DEATH, DURATION OF POSTMORTEM DELAY, DONOR AGE, ….)
  - DIFFERENCES IN SEROLOGY TESTS (HEPATITIS B IMMUNISATION, HTLV, NAT, CMV,…..)
- **COOPERATION** WITH THIRD COUNTRIES (NON E.U.M.S.)
  - THE ALLOGRAFT MAY BE TREATED IN EUROPE UNDER THE **“TRANSIT” STATUS**

European Homograft Bank, International Association, Brussels, Belgium.

INSIDE A TISSUE BANK QMS: Validation of transport and storage of Human Body Substances (HBS) for allograft preparation

NGAKAM N. R., AKANYI H. N., VAN HOEK B. and JASHARI R.
European Homograft Bank (EHB), International Association, Brussels, Belgium

INTRODUCTION/AIM

Tissues quality is highly dependent of HBS's storage and transport conditions while being transported from the procurement centre. The transport conditions of HBS from procurement until processing in the tissue establishment must be stable and accurate (i.e. sterilely, at a temperature between 0.3 and 8.0°C, for 24h max.).Goal of these experiments was to ensure, taking into account the worse case scenarios (transport and storage below 0°C or above 30°C), that the materials and procedures used daily are able to ensure the latter 2 conditions. Procedures consist in putting the box or bag containing HBS and physiological solution inside 2 different types of insulated polystyrene boxes (coefficient of thermal conduction = 0.034 W/m.K) containing ice: a big one (volume 31.07L; thickness 3 cm) and a smaller one (20.45L; thickness 4 cm).

MATERIAL AND METHODS

Material :

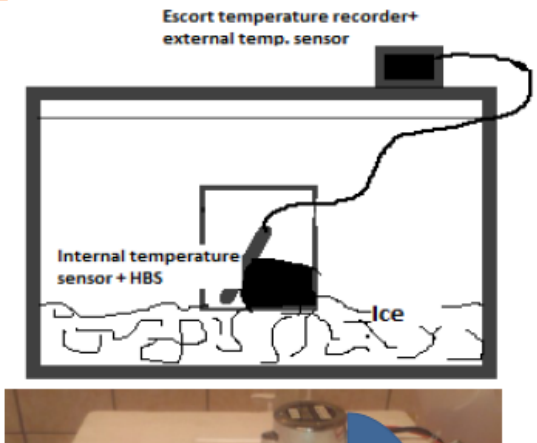
- **Insulated boxes in polystyrene:**

-Type 1: Size : 41x31x31 cm Thickness: 3 cm
-Type 2: Size : 37,5x24, 5x25, 5 cm Thickness: 4 cm

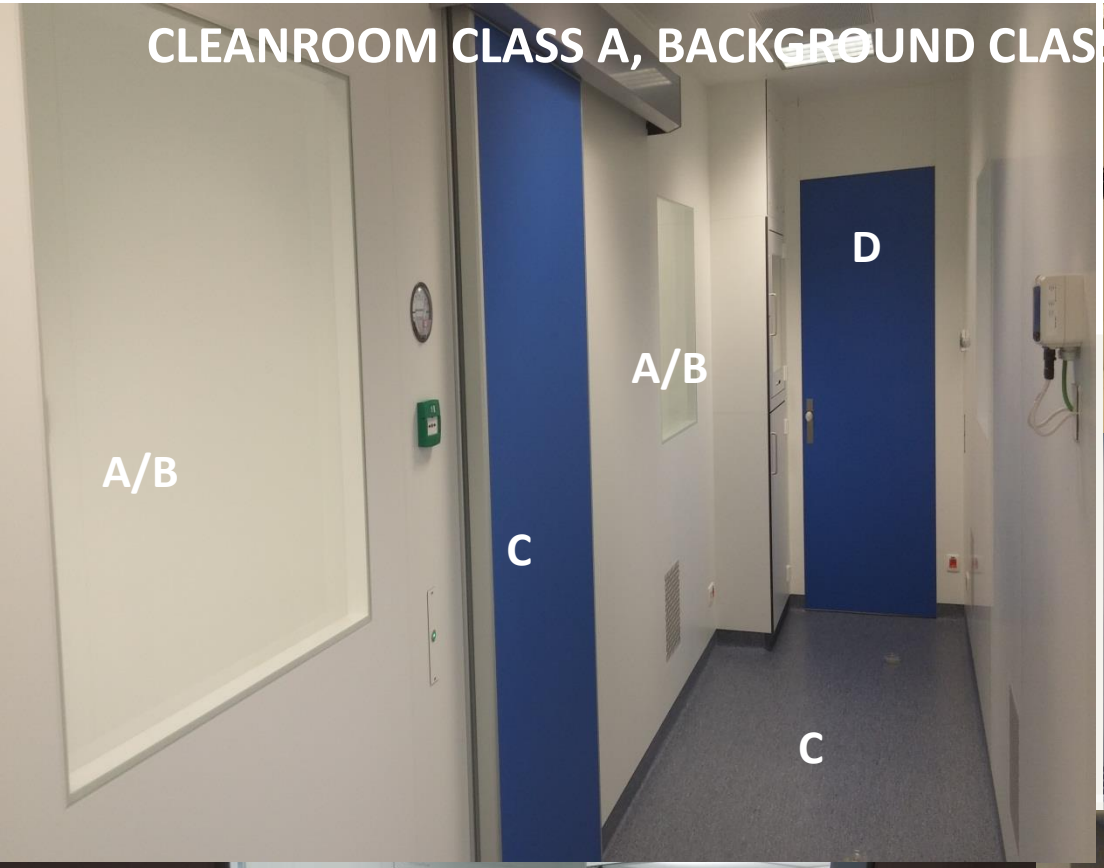
- **Escort temperature recorder**
- **Wet ice:** solid form of water, melting point= 0°C under atmospheric pressure

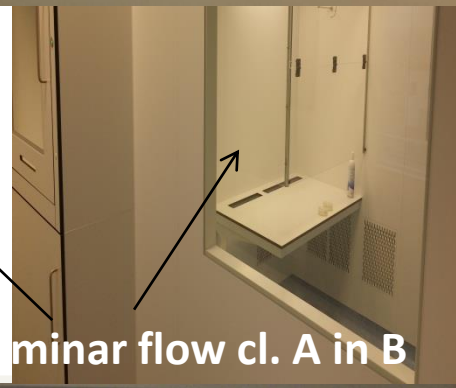
Methods:

- **Scenarios:** transport/storage round -18°C (i.e. winter), 5°C (i.e. fridge), 24°C (i.e. room temperature) and 30°C (i.e. heat wave)
- **Estimation of the theoretical amount** of ice needed (in each scenario and taking



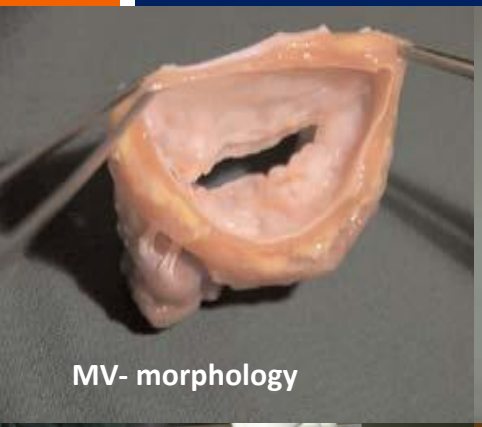
CLEANROOM CLASS A, BACKGROUND CLASS B/C, SURROUNDING CLASS D





Vertical laminar flow cl. A in B

PROCESSING, CONTROL, CRYOPRESERVATION& STORAGE

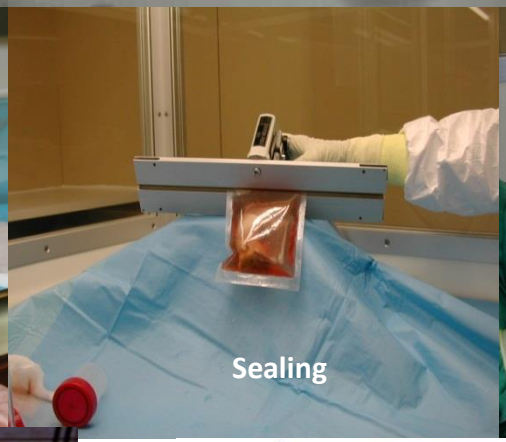

MV- morphology


PV- Competence test


AV- Competence test


Measuring of diameter

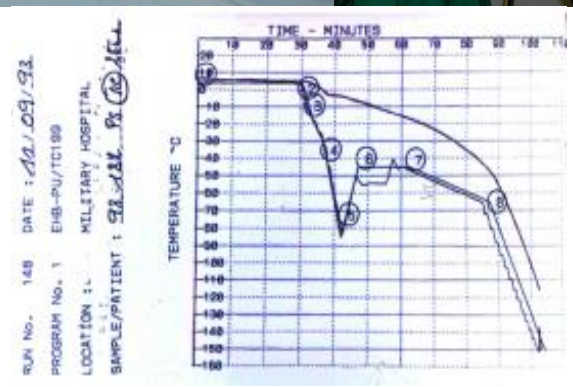

Internal pouch with 10%DMSO


Sealing


External 3-laminary pouch


Cryopreservation

Planer 560-16



Storage (≤-135°C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Banque de MCH cardiovasculaire
Bank van het cardiovasculaire MLM
Bank of cardiovascular HBM
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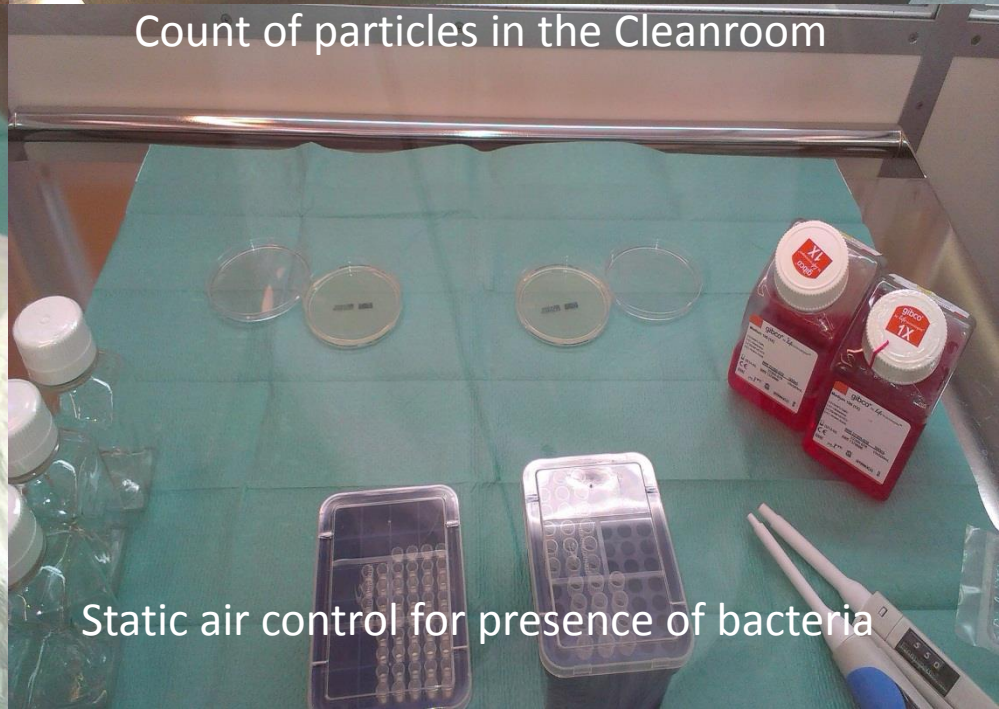
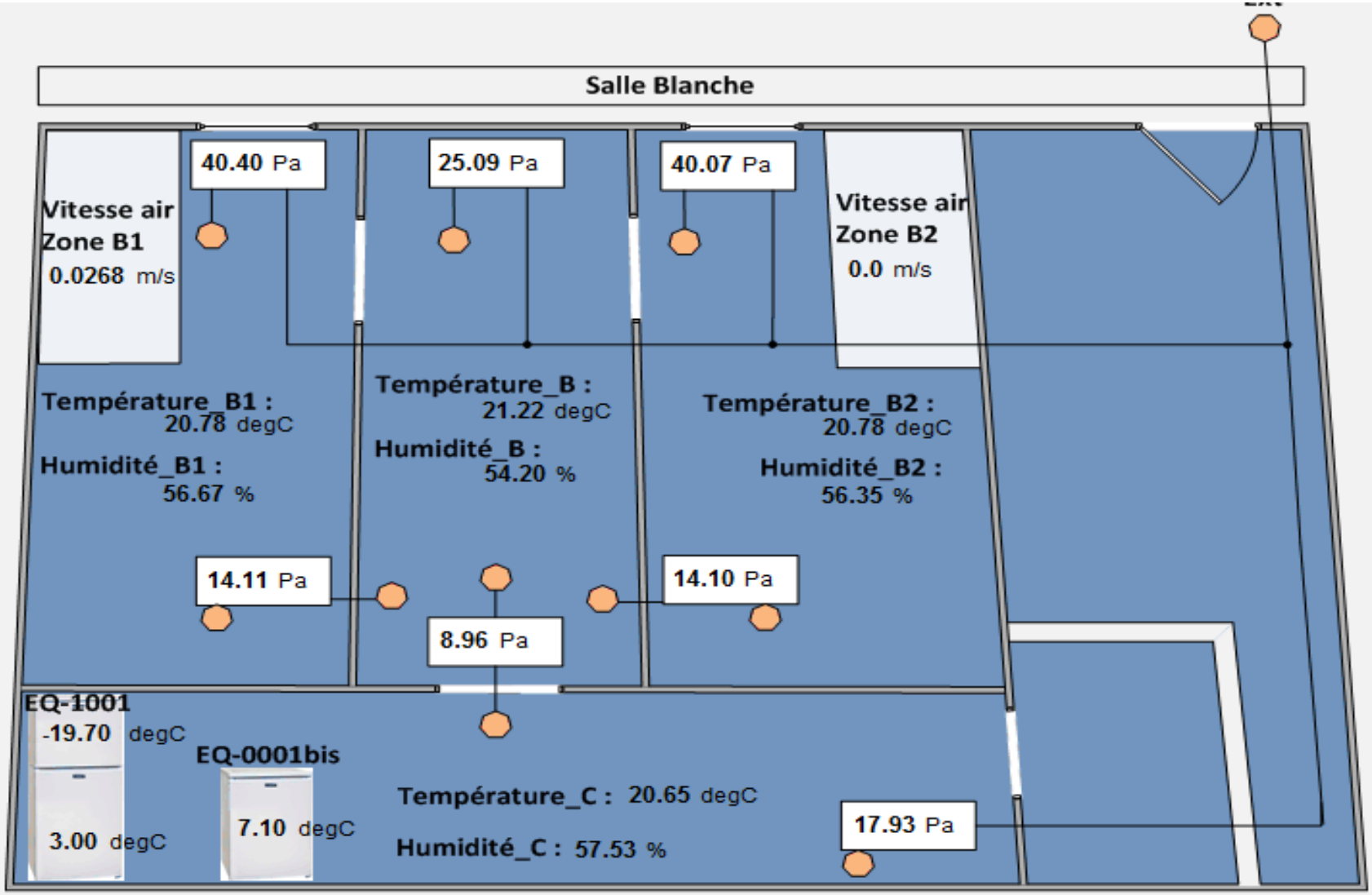
Biocolector for dynamic air control

Count of particles in the Cleanroom

« Finger print » after allograft manipulation



Static air control for presence of bacteria


Salle Blanche
40.40 Pa
25.09 Pa
40.07 Pa
Vitesse air
Zone B1
0.0268 m/s
Vitesse air
Zone B2
0.0 m/s
Température_B1 :
20.78 degC
Humidité_B1 :
56.67 %
Température_B :
21.22 degC
Humidité_B :
54.20 %
Température_B2 :
20.78 degC
Humidité_B2 :
56.35 %
14.11 Pa
14.10 Pa
8.96 Pa
EQ-1001
-19.70 degC
EQ-0001bis
3.00 degC
7.10 degC
Température_C : 20.65 degC
Humidité_C : 57.53 %
17.93 Pa

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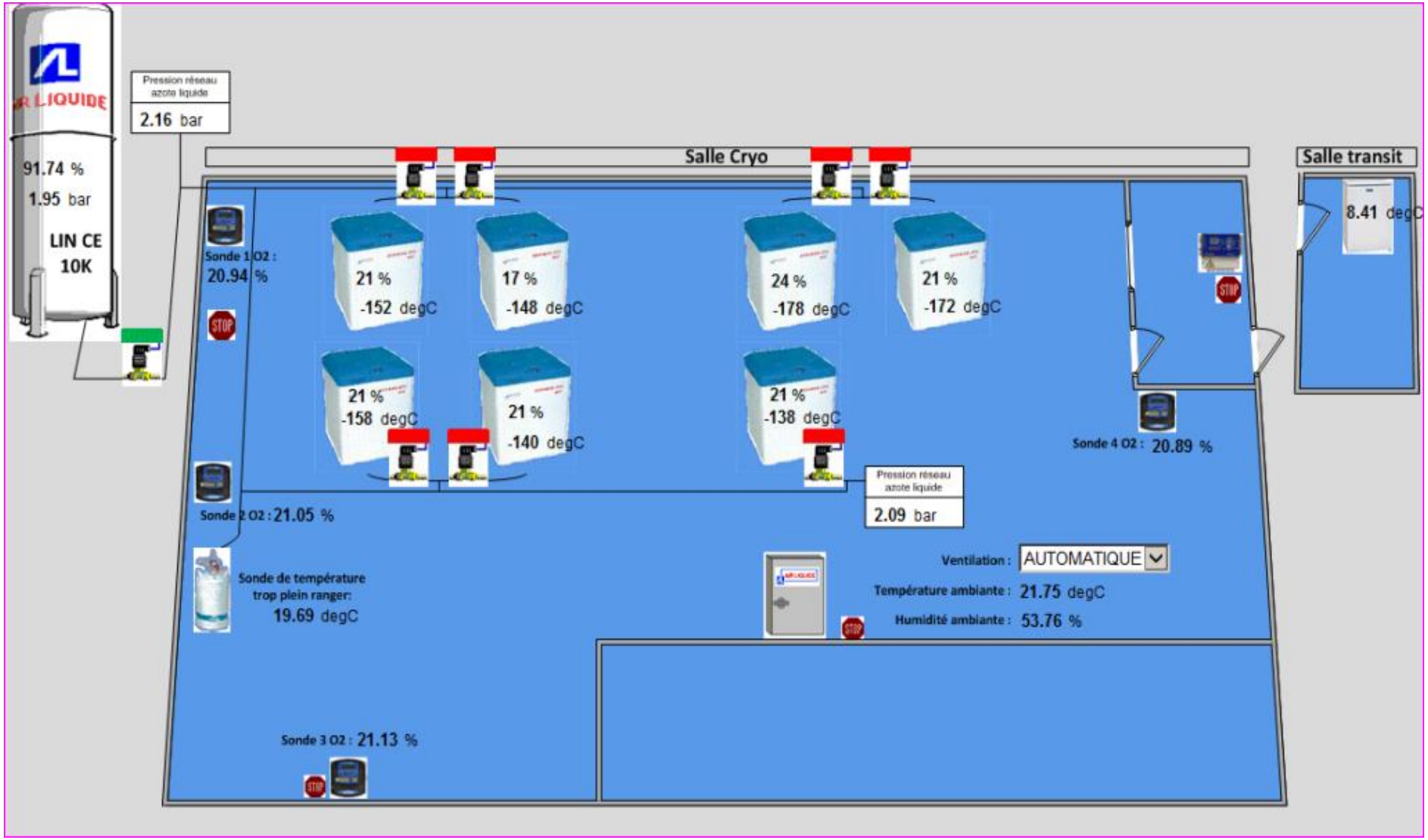

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In LNV (DS); temp ≤ -130°C

In Dry Ice (DI), -76°C

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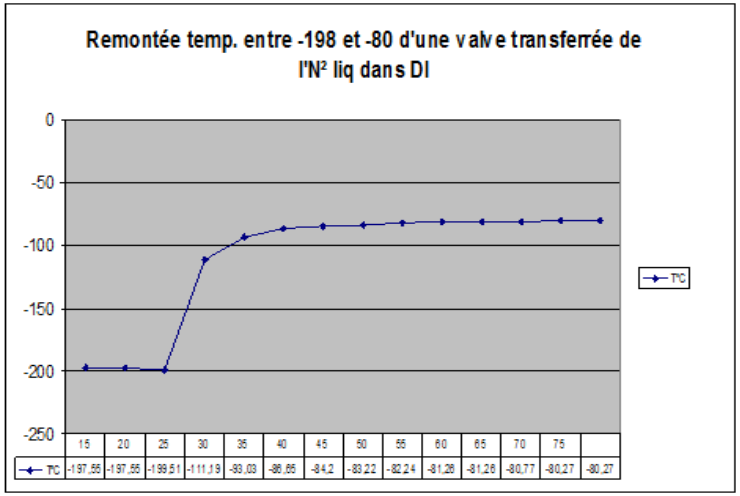
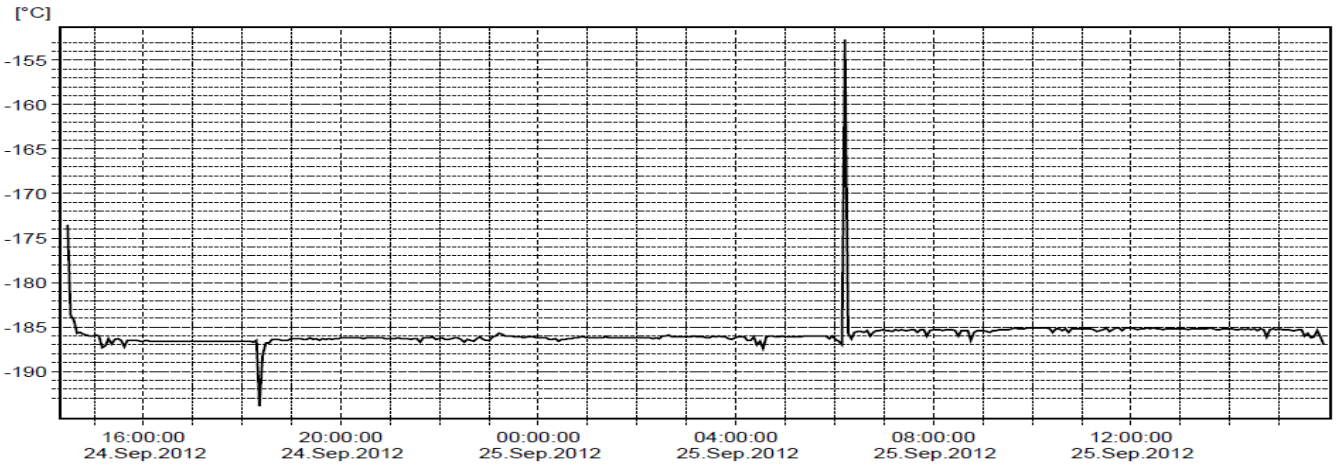


Validation of shipment in Dry Ice (DI), -76°C

Résultats de l'enregistrement

Température maximum:	-152.7 °C; 25.Sep.2012 06:10:59	Démarrage transit:	24.Sep.2012 14:25:59
Température minimum:	-193.9 °C; 24.Sep.2012 18:22:59	Arrivé:	25.Sep.2012 15:55:25
Température moyenne:	-185.8 °C	Alarme à:	aucun
MKT	-161.1 °C	Fichier créé:	25.Sep.2012 15:57:36



Monitoring during the shipment in LNV (DS); temp ≤ -130°C

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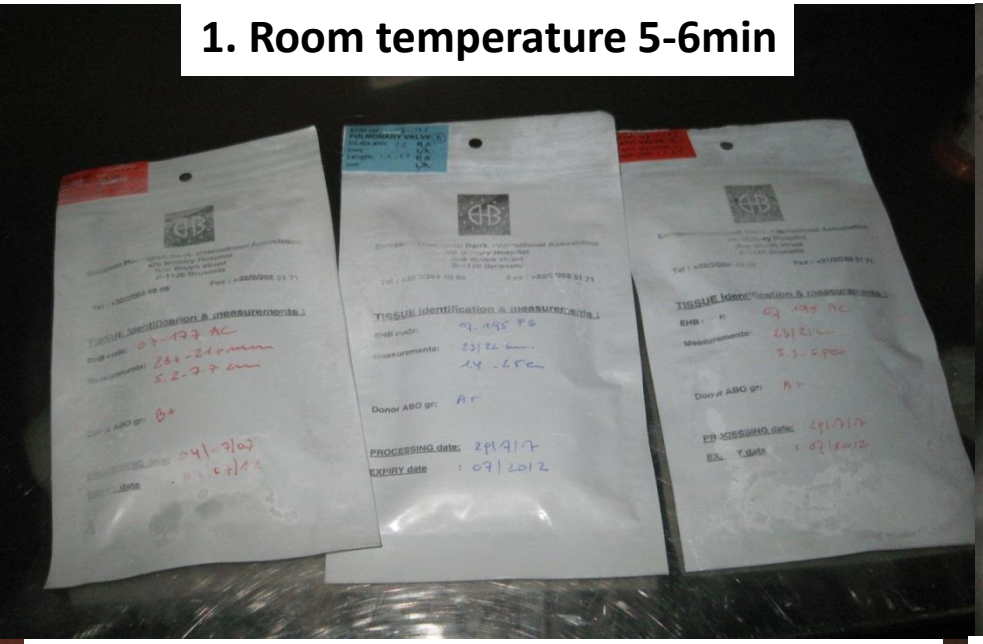
ALLOGRFT THAWING AND DMSO DILUTION

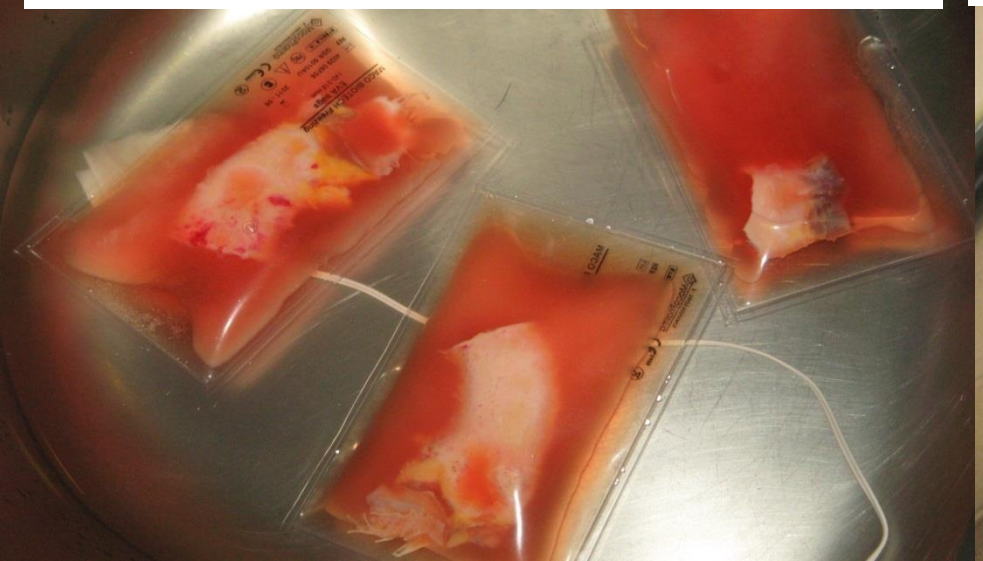
INSTRUCTIONS

1. Room temperature 5-6min

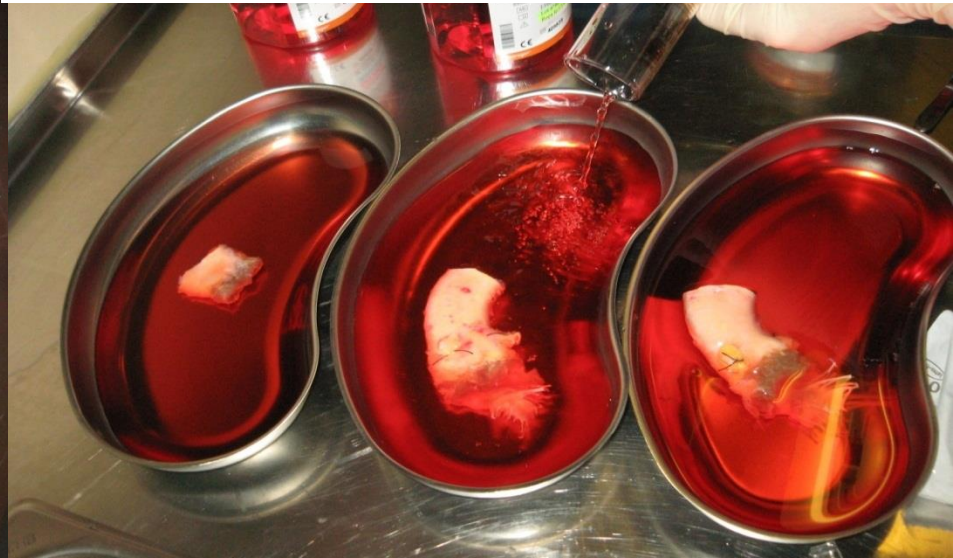


2. Water Bath (37-42°C), 5-6min

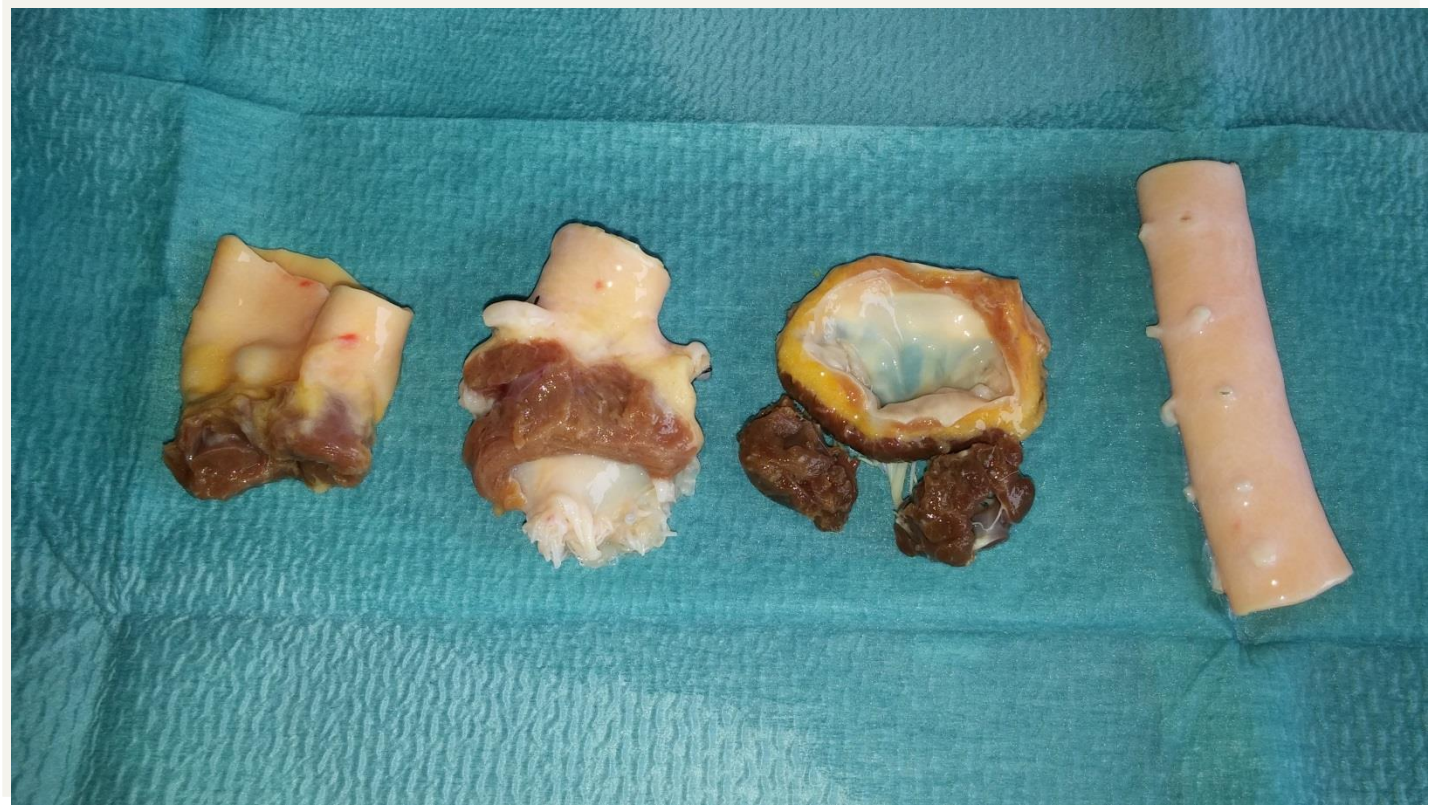
3. Sterile warm (37-42°C) NaCl 0,9%, 5-6min



4. Dilution of DMSO in 3 steps from 10% to 1%



CONTROL OF ALLOGRAFT AFTER THAWING



CORRECTLY PRESERVED ALLOGRAFTS (FROM LEFT TO RIGHT: PV, AV, MV, DA)

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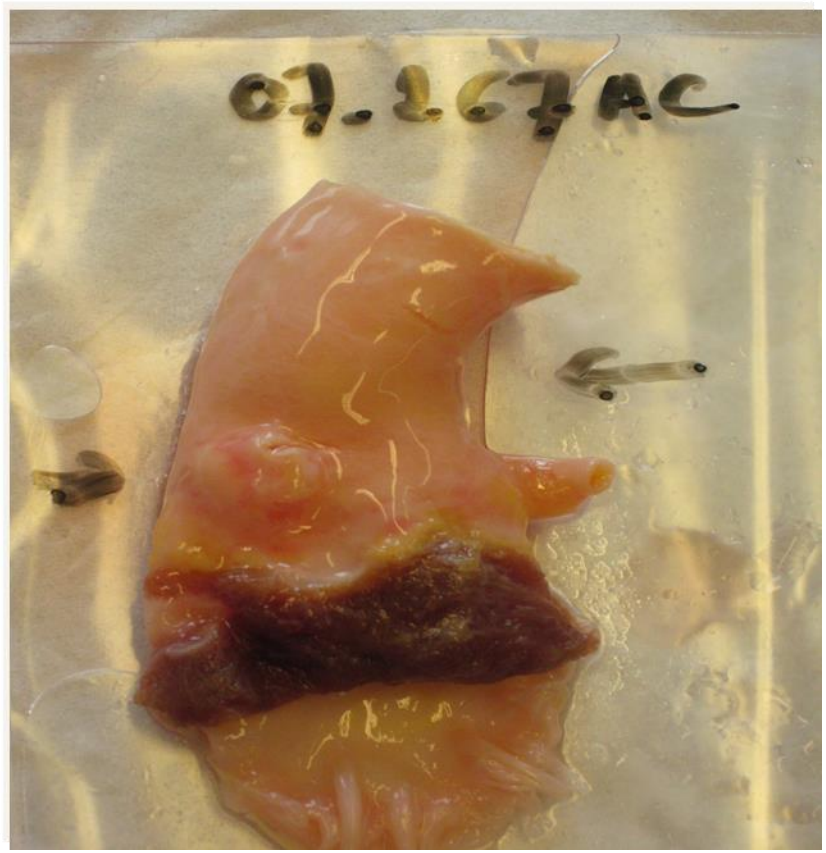
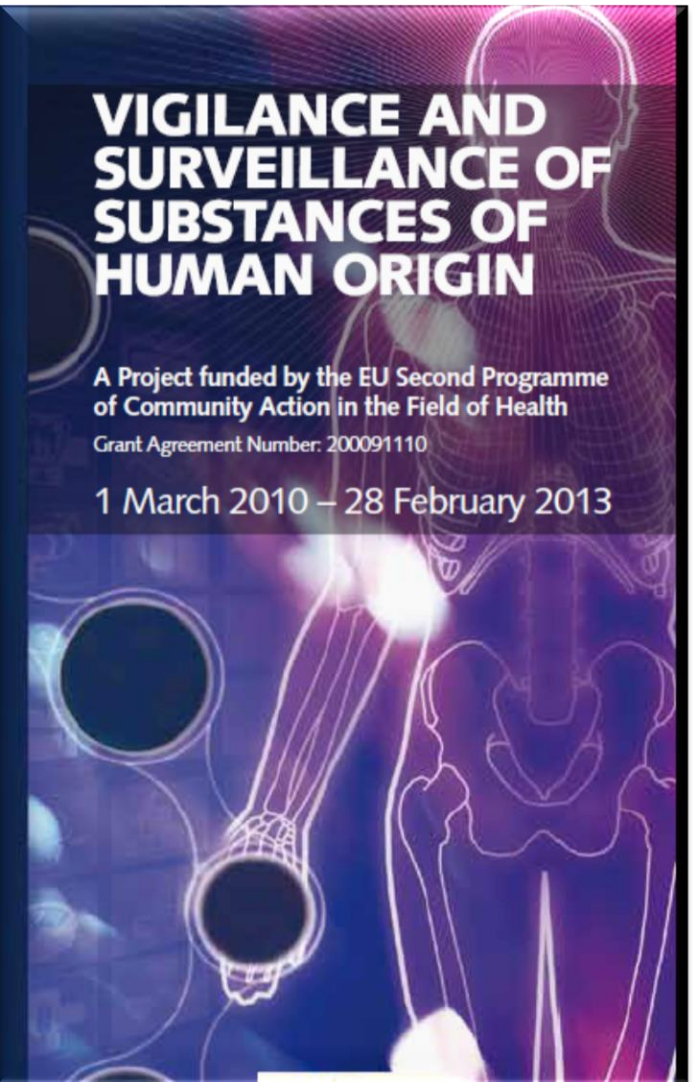


INCORRECTLY PRESERVED ALLOGRAFT: CRYOPRESERVATION, STORAGE, TRANSPORT OR THAWING PROBLEM?

SERIOUS ADVERSE EVENTS/REACTIONS

- CAN HAPPEN/APPEAR IN ANY STEP OF THE TB ACTIVITY
  - *FROM THE DONOR SELECTION TO THE ALLOGRAFT CLINICAL APPLICATION*
  - *NEED FOR TRACEABILITY OF ALL STEPS, MATERIALS, PERSONS INVOLVED IN EACH STEP*
- INVESTIGATION OF ALL STEPS AND PERSONS
  - *FIND OUT THE REASONS*
- EVALUATION OF THE IMPUTABILITY& CONSEQUENCES
  - *ESTIMATE THE CONSEQUENCES FOR THE PATIENT*
- ASSURE THE NON-RECURRENCE OF THE EVENT
- REPORTING OF THE EVENT/REACTION

VIGILANCE INVESTIGATION



SERIOUS ADVERSE REACTIONS

INVESTIGATION SHOULD ESTABLISH **IMPUTABILITY**

SERIOUS ADVERSE EVENTS

INVESTIGATION SHOULD ESTABLISH **ROOT CAUSE**

INVESTIGATING SAES

- **GATHERING DATA** – TO INCLUDE FULL DETAILS OF WHAT HAPPENED, AS WELL AS RELEVANT POLICIES AND PROCEDURES
- **MAPPING THE INFORMATION** – POSSIBLY IN TIMELINES, FLOWCHARTS OR A CHRONOLOGICAL NARRATIVE OF THE CHAIN OF EVENTS ALLOWING THE IDENTIFICATION OF ANY INFORMATION GAPS AND SHOWING CONTRIBUTING FACTORS
- **IDENTIFICATION OF THE PROBLEM(S) THAT CONTRIBUTED TO THE OCCURRENCE** – THIS COULD REQUIRE A REVIEW MEETING WITH RELEVANT PERSONNEL INVOLVED.
- **ANALYSIS OF THE CONTRIBUTING FACTORS** WITH PRIORITIZATION
- **IDENTIFICATION AND AGREEMENT ON THE ROOT CAUSES** – THE FUNDAMENTAL CONTRIBUTORY FACTORS WHICH, IF RESOLVED, WILL ERADICATE OR HAVE THE MOST SIGNIFICANT EFFECT ON REDUCING LIKELIHOOD OF RECURRENCE
- **REPORTING**.

IMPUTABILITY

IMPUTABILITY CAN BE DEFINED AS

'THE LIKELIHOOD THAT A SERIOUS ADVERSE REACTION IN A RECIPIENT CAN BE ATTRIBUTED TO THE ORGAN, TISSUE OR CELLS APPLIED OR THAT A SERIOUS ADVERSE REACTION IN A LIVING DONOR CAN BE ATTRIBUTED TO THE DONATION PROCESS.'

IMPUTABILITY OF A SAR MAY CHANGE IN THE COURSE OF THE INVESTIGATION, AS EVIDENCE IS GATHERED.

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Eustite

Public Health

World Health Organization

Serious Adverse Event (SAE): *any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.*

Serious Adverse Reaction (SAR): *an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.*

EUSTITE V&S TOOLS V2.1

SAEs - Criteria

CRITERIA FOR REPORTING SAEs
Inappropriate tissues/cells have been distributed for clinical use, even if not used;
The event could have implications for other patients or donors because of shared practices, services, supplies or donors;
The event resulted in a mix-up of gametes or embryos;
The event resulted in loss of any irrep autologous tissues or cells or any high matched (i.e. recipient specific) alloge or cells;
The event resulted in the loss of a sig quantity of unmatched allogeneic tiss

Severity (SARs)

Non serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability
Serious	- hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with donor gametes or embryos.

Report

Imputability (SARs)

NA Not assessable	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes.
1. Unlikely	Evidence clearly in favour of attributing to other causes.
2.	Evidence is indeterminate.
	ce in favour of attributing to the s/cells.
	usive evidence beyond reaonable doubt for ting to the tissues/cells

FIRST WE NEED TO CHECK SEVERITY AND IMPUTABLITY

Impact (SARs and SAEs)

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to happen but possible
3	Possible	May occur occasionally
4	Likely	Probable but not persistent
5	Almost certain	Likely to occur on many occasions

Step 1 – Probability of recurrence

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage	Some applications postponed
2	Significant	Serious	Damage to system – services will be affected for short period	Many applications cancelled or postponed
3	Major	Life threatening	Major damage to system – significant time needed to repair	Significant no. of procedures cancelled - importation required to make-up short-fall
4	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled

Step 2– Consequences of Recurrence

Recurrence probability → / Consequences ↓	Rare 1	Unlikely 2	Possible 3	Likely 4	Almost certain 5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

Step 3 - Impact

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CASE 1

- DONATION IN FRANCE (MOD &TISSUES) ON **14/07/2015**
- F/18Y, 50KG, ASTHMATIC ATTACK; 24HRS AT ICU, 4RBC, 4FFP, 1PLATES (HEMODILUTION CALCULATION: **NO HEMODILUTION**)
  - HEART HARVESTED FOR HEART VALVE ALLOGRAFTS, ARTERIES FOR ANOTHER (FRENCH) T.E.
- AV & PV ACCEPTED AND CRYOPRESERVED

CASE 1

- SEROLOGY EVALUATION OF THE DONOR: **NEGATIVE**
- BACTERIOLOGY ASSESSMENT OF THE DONATED TISSUES/TRANSPORT SOLUTION IN THREE STEPS OF PROCESSING: **ALL NEGATIVE**
- HISTOLOGY EVALUATION (LV, RV, IVS, MV, P-WALL, A-WALL): **NORMAL**
- **BOTH VALVES RELEASED** FOR CLINICAL APPLICATION AFTER RECEIVING THE **ASSIGNMENT DOCUMENT (DONOR)** FROM THE "EXPORTING" T.E. IN FRANCE
  - *ONLY FRENCH T.E. AUTHORIZED FOR EXPORT OR IMPORT OF THE DONATED HBM AIMED FOR CLINICAL APPLICATION*

CASE 1

- **PV IMPLANTED ON 9/10/2015** (IN A BELGIAN CENTER) IN A MALE PATIENT OF 2 YEARS
- **AV STILL IN STOCK**
- **4 MONTHS AFTER DONATION** (NOVEMBER 2015) WE GET THE INFORMATION FROM THE "EXPORTING" FRENCH T.E. THAT THE ABM (FRENCH COMPETENT AUTHORITY) HAS **RE-CALCULATED** THE BLOOD TRANSFUSION AND THAT **HEMODILUTION** WAS RETROACTIVELY CONFIRMED
- FRENCH T.E. WAS INFORMED IMMADIATELY AFTER THE MODIFICATION OF DECISION; **EHB NOT!**
- OUR CALCULATION OF HEMODILUTION: **NO HEMODILUTION**

WHAT TO DO?

INVESTIGATING SUSPECTED VIRAL TRANSMISSIONS

- FULL REVIEW OF THE RECIPIENT'S CLINICAL SYMPTOMS AND TEST RESULTS
- CAREFUL CONSIDERATION OF ALTERNATIVE RISK FACTORS (LIFE-STYLE RISK, RELEVANT MEDICAL HISTORY, EXPOSURE TO OTHER SOHO ESPECIALLY BLOOD OR PLASMA COMPONENTS/PRODUCTS) INCLUDING EXPOSURE TO POSSIBLE NOSOCOMIAL SOURCES OF INFECTION;
- IF IT IS STILL CONSIDERED POSSIBLE THAT THE DONOR WAS THE SOURCE OF THE INFECTION
  - CHECK/TEST OTHER RECIPIENTS OF MATERIAL FROM THAT DONOR
  - REVIEW DONOR HISTORY FOR RISK FACTORS OR OTHER RELEVANT INFORMATION
  - CHECK AUTOPSY FINDINGS
  - REVIEW THE TESTING PROTOCOLS FOR DONOR SCREENING AND PERFORM ADDITIONAL TESTING, AS IF RELEVANT AND POSSIBLE.

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CASE 1

- **REVIEW THE DONOR RECORD AND ALL BLOOD TESTS PRIOR TO DONATION**
- **CONTACT THE IMPLANTING SURGEON (**PATIENT **IN ANOTHER** INSTITUTION)
- CONTACT THE **TREATING CARDIOLOGIST** AT THE OTHER HOSPITAL AND ASK ABOUT THE CLINICAL STATE OF THE PATIENT
  - REQUEST FOR **A SEROLOGY TESTS 4 MTHS AFTER IMPLANTATION(BS)**
  - CONTACT THE PARENTS OF THE CHILD (VIA TREATING MD): PATIENT IS CLINICALLY OK; **BLOOD TEST PERFORMED**
  - **COMPLETE SEROLOGY EVALUATION: NEGATIVE**
- **INFORMED THE BELGIAN COMPETEBNT AUTHORITY (BIOVIGILANCE)**
- **DESTROY THE AV (IN STOCK)**
- INFORMED THE FRENCH RESPONSIBLE T.E. ABOUT ALL ACTIONS
- INFORMED FRENCH COMPETENT AUTHORITY (FRENCH T.E.)
- INFORMED THE IMPLANTING SURGEON ABOUT THE RESULT OF THE INVESTIGATION

SoHO V&S Tool

HTA Human Tissue Authority

Serious Adverse Event (SAE): any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

Serious Adverse Reaction (SAR): an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

SAE Reporting Criteria

Inappropriate tissues/cells have been distributed for clinical use, even if not used
The event could have implications for other patients or donors because of shared practices, services, supplies or donors
The event resulted in a mix-up of tissues or cells
The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells
The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells

Reaction Severity (SAR)

	Nil	▪ No harm, no risk, patient not informed as there was no risk of harm
	Non-serious	▪ Mild clinical / psychological consequences ▪ No hospitalisation ▪ No anticipated long term consequence / disability
Report to HTA	**Serious**	▪ Hospitalisation or prolonged hospitalisation ▪ Persistent or significant disability or incapacity ▪ Intervention to preclude permanent damage ▪ Evidence of a serious transmitted infection
Report to HTA	**Life-threatening**	▪ Major intervention to prevent death ▪ Evidence of a life-threatening transmitted infection
Report to HTA	**Death**	▪ Death

Reaction Imputability (SAR)

N/A	**Not assessable**	Insufficient data for imputability assessment
N/A	**Excluded**	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
N/A	**Unlikely**	Evidence clearly in favour of attribution to alternative causes
1	**Possible**	Evidence if indeterminate
2	**Likely / probable**	Evidence in favour of attribution to the tissues/cells
3	**Definite / certain**	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

Impact (SARs and SAEs)

Step 1 - Likelihood of recurrence

Score	Classif-ication	Description
1	**Rare**	Difficult to believe it could occur again
2	**Unlikely**	Not expected to occur again
3	**Possible**	May occur occasionally
4	**Likely**	Expected to occur again but not persistent
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Step 2 - Impact/consequences of recurrence

	Impact level	On individuals		On system		On tissue / cell supply
0	**Insign-ificant**	Nil	**or**	No effect	**or**	Insignificant
1	**Minor**	Non-serious	**or**	Minor damage	**or**	Some applications postponed
2	**Moder-ate**	Serious	**or**	Damage for short period	**or**	Many cancellations or postponements
3	**Major**	Life-threatening	**or**	Major damage to system - significant delay to repair	**or**	Significant cancellations - importation required
4	**Catast-rophic/ extreme**	Death	**or**	System destroyed - need to rebuild	**or**	All allogeneic applications cancelled

Step 3 - Applying the Impact Matrix

Impact of recurrence \ Likelihood of recurrence	1. Rare	2. Unlikely	3. Possible	4. Likely	5. Probable (almost certain)
0. Insignificant	0	0	0	0	0
1. Minor	1	2	3	4	5
2. Moderate	2	4	6	8	10
3. Major	3	6	9	12	15
4. Catastrophic / extreme	4	8	12	16	20

0-3 Green	Establishment to manage the corrective and preventative actions; HTA to file the report and keep a 'watching brief'.
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SAE Reporting Criteria

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The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells

Reaction Severity (SAR)

	Nil	▪ No harm, no risk, patient not informed as there was no risk of harm
	Non-serious	▪ Mild clinical / psychological consequences ▪ No hospitalisation ▪ No anticipated long term consequence / disability
Report to HTA	**Serious**	▪ Hospitalisation or prolonged hospitalisation ▪ Persistent or significant disability or incapacity ▪ Intervention to preclude permanent damage ▪ Evidence of a serious transmitted infection
Report to HTA	**Life-threatening**	▪ Major intervention to prevent death ▪ Evidence of a life-threatening transmitted infection
Report to HTA	**Death**	▪ Death

Reaction Imputability (SAR)

N/A	**Not assessable**	Insufficient data for imputability assessment
N/A	**Excluded**	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
N/A	**Unlikely**	Evidence clearly in favour of attribution to alternative causes
1	**Possible**	Evidence if indeterminate
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	Life-threatening	▪ Major intervention to prevent death ▪ Evidence of a life-threatening transmitted infection
	Death	▪ Death

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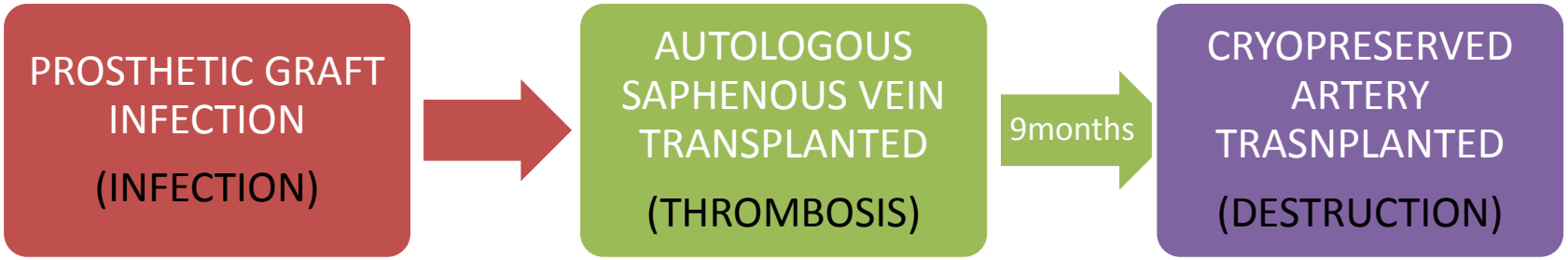
CASE 2

52Y OLD MALE PATIENT, RECEIVED **2 CRYOPRESERVED FA** (FROM SAME DONOR) AT FEMORO-POPLITEAL REGION

- 1° OP: FEM-POP BYPASS WITH PROSTHESIS ⟹ **INFECTION**
- 2° OP: REPLACEMENTR OF PROSTHESIS WITH AUTOLOGOUS VEIN ⟹ **THROMBOSIS**
- 3° OP: CRYOPRESERVED ARTERY ⟹ MULTIPLE **ANEURYSM DILATION** ONLY **1MTH** AFTER IMPLANTATION (DONOR: 49Y OLD MALE, DIED OF BRAIN TRAUMA; NHBD)



European Homograft Bank

Kliniek SINT-JAN Clinique SAINT-JEAN

Step 1: Serious Adverse Reaction SEVERITY

SEVERITY	▪COMMENTS
Non serious	▪Mild clinical / psychological consequences ▪No hospitalisation ▪No anticipated long-term consequence/disability
Serious	▪Hospitalisation or prolonged hospitalisation ▪Persistent or significant disability or incapacity ▪Intervention to preclude permanent damage ▪Evidence of a serious transmitted disease
Life-threatening	▪Major intervention to prevent death ▪Evidence of a life-threatening transmitted disease
Death	▪Death

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CASE 2

- NO PROBLEMS OCCURRED DURING THAWING NOR IMPLANTATION OF THIS ALLOGRAFT. THE PATIENT WAS DISCHARGED FROM THE HOSPITAL 1 WEEK LATER AFTER A GOOD RESULT OF A DOPPLER ULTRASONOGRAPHY

- THE PATIENT WAS REFERRED TO VASCULAR SURGERY DEPARTMENT 1 MONTH LATER BECAUSE OF THE PALPATION OF A BEATING FEMORAL MASS

- A CT SCAN SHOWED MULTIPLE PSEUDOANEURYSMS OF THE FPB OVER ITS ENTIRE LENGTH, WITH THE LARGEST ONE MEASURED AT 33 MM IN ITS DISTAL PART (FIG. 1)

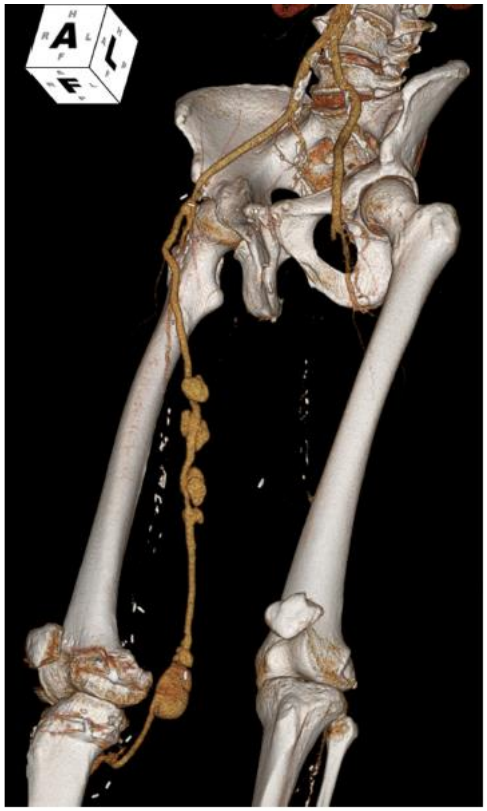

Fig. 1 3D reconstruction of a contrast-enhanced arterial phase CT scan, showing multiple pseudoaneurysms of the right femoropopliteal bypass with the first cryopreserved arterial homograft. Native femoral arteries are not patent due to severe peripheral arteriopathy

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CASE 2

- THE FIRST CRYOPRESERVED ARTERIAL ALLOGRAFT WAS RAPIDLY REPLACED BY A SECOND ONE BECAUSE OF THE RISK OF RUPTURE OF THE GRAFT.
- BACTERIOLOGICAL ANALYSES OF THE EXPLANTED ALLOGRAFT AND BLOOD CULTURES OF THE PATIENT WERE NEGATIVE. THUS FAILURE OF THE GRAFT DUE TO INFECTION WAS EXCLUDED
- RESULTS OF THE CT WERE CONFIRMED AT MACROSCOPIC INSPECTION AFTER EXPLANTATION (FIG. 2).

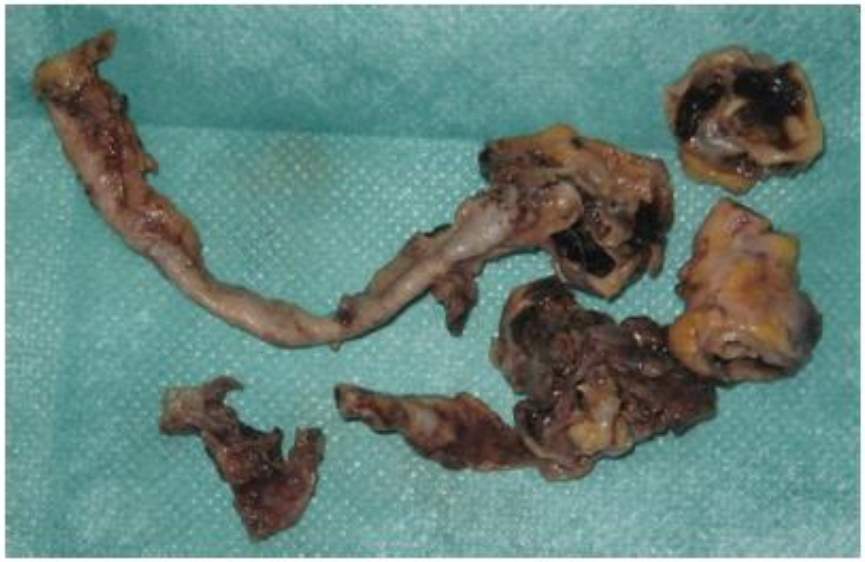

Fig. 2 Macroscopic study, showing the degradation of the femoral homograft with pseudoaneurysms and hematomas

WHAT TO DO?

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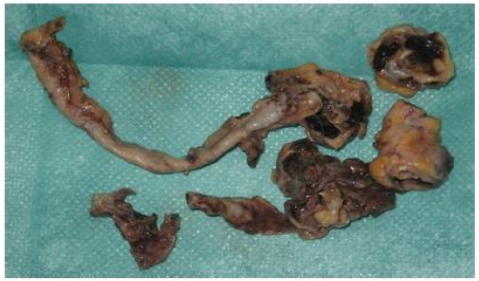
ISSUE:

THE PATIENT WAS REFERRED TO THE DEPARTMENT OF VASCULAR SURGERY 1 MONTH AFTER ALLOGRAFT IMPLANTATION BECAUSE OF THE PALPATION OF A BEATING FEMORAL MAS



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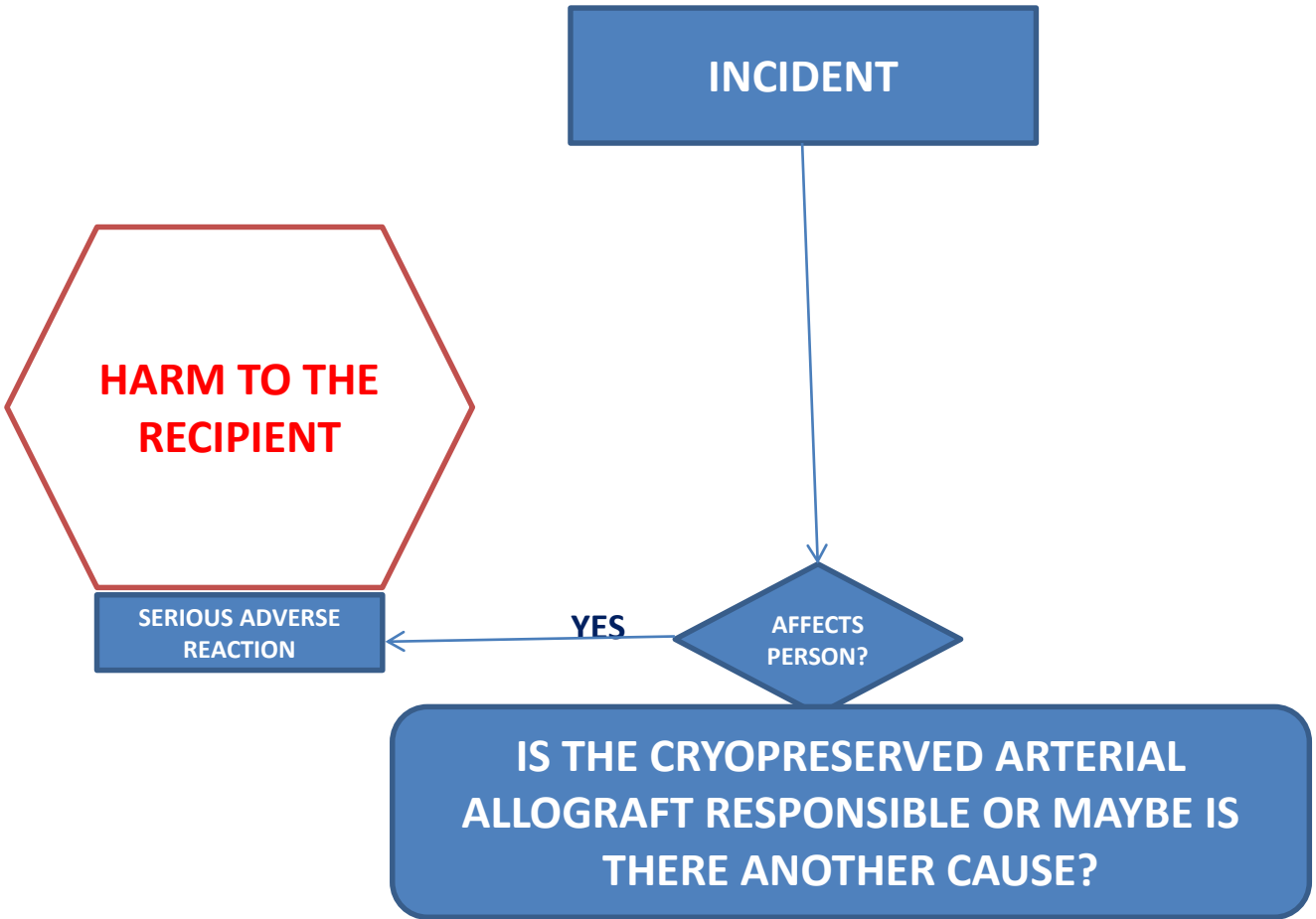

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1	**Possible**	Evidence if indeterminate
2	**Likely / probable**	Evidence in favour of attribution to the tissues/cells
3	**Definite / certain**	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

Impact (SARs and SAEs)

Step 1 - Likelihood of recurrence

Score	Classif-ication	Description
1	**Rare**	Difficult to believe it could occur again
2	**Unlikely**	Not expected to occur again
3	**Possible**	May occur occasionally
4	**Likely**	Expected to occur again but not persistent
5	**Probable**	Expected to occur again on many occasions

Step 2 - Impact/consequences of recurrence

	Impact level	On individuals		On system		On tissue / cell supply
0	**Insign-ificant**	Nil	**or**	No effect	**or**	Insignificant
1	**Minor**	Non-serious	**or**	Minor damage	**or**	Some applications postponed
2	**Moder-ate**	Serious	**or**	Damage for short period	**or**	Many cancellations or postponements
3	**Major**	Life-threatening	**or**	Major damage to system - significant delay to repair	**or**	Significant cancellations - importation required
4	**Catast-rophic/ extreme**	Death	**or**	System destroyed - need to rebuild	**or**	All allogeneic applications cancelled

Step 3 - Applying the Impact Matrix

Impact of recurrence \ Likelihood of recurrence	1. Rare	2. Unlikely	3. Possible	4. Likely	5. Probable (almost certain)
0. Insignificant	0	0	0	0	0
1. Minor	1	2	3	4	5
2. Moderate	2	4	6	8	10
3. Major	3	6	9	12	15
4. Catastrophic / extreme	4	8	12	16	20

0-3 Green	Establishment to manage the corrective and preventative actions; HTA to file the report and keep a 'watching brief'.
4-9 Amber	Interaction required between establishment and HTA which may request an inspection that focuses on the event or reaction and CAPAs, including evidence of effective recall as necessary. Written communication to professionals in field might be appropriate.
10-20 Red	HTA will generally develop or approve the CAPA and possibly set up a task force to address broader implications. Inspection, follow up and written communication and RATC where relevant.

Serious Adverse Event (SAE): *any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.*

EUSTITE V&S TOOLS V2.1

Serious Adverse Reaction (SAR): *an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.*

SAEs - Criteria

CRITERIA FOR REPORTING SAEs
Inappropriate tissues/cells have been distributed for clinical use, even if not used;
The event could have implications for other patients or donors because of shared practices, services, supplies or donors;
The event resulted in a mix-up of gametes or embryos;
The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;
The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

Severity (SARs)

Non serious	Mild clinical/psychological consequences. No hospitalisation. No anticipated long term consequence/disability
Serious	- hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with donor gametes or embryos.
Life-threatening	- major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following ART with donor gametes or embryos.
Death	Death

Report to CA

Imputability (SARs)

NA Not assessable	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes.
1. Unlikely	Evidence clearly in favour of attributing to other causes.
2. Possible	Evidence is indeterminate.
3. Likely, Probable	Evidence in favour of attributing to the tissues/cells.
4. Definite, Certain	Conclusive evidence beyond reaonable doubt for attributing to the tissues/cells

Impact (SARs and SAEs)

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to happen but possible
3	Possible	May occur occasionally
4	Likely	Probable but not persistent
5	Almost	Likely to occur on many

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage	Some applications postponed
2	Significant	Serious	Damage to system – services will be affected for short period	Many applications cancelled or postponed
3	Major	Life threatening	Major damage to system – significant time needed to repair	Significant no. of procedures cancelled - importation required to make-up short-fall

Recurrence probability → / Consequences ↓	Rare 1	Unlikely 2	Possible 3	Likely 4	Almost certain 5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15

Serious Adverse Event (SAE): *any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.*

Public Health

World Health Organization

Serious Adverse Reaction (SAR): *an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.*

EUSTITE V&S TOOLS V2.1

SAEs - Criteria

CRITERIA FOR REPORTING SAEs
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The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

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Report to CA

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4	Likely	Probable but not persistent
5	Almost certain	Likely to occur on many occasions

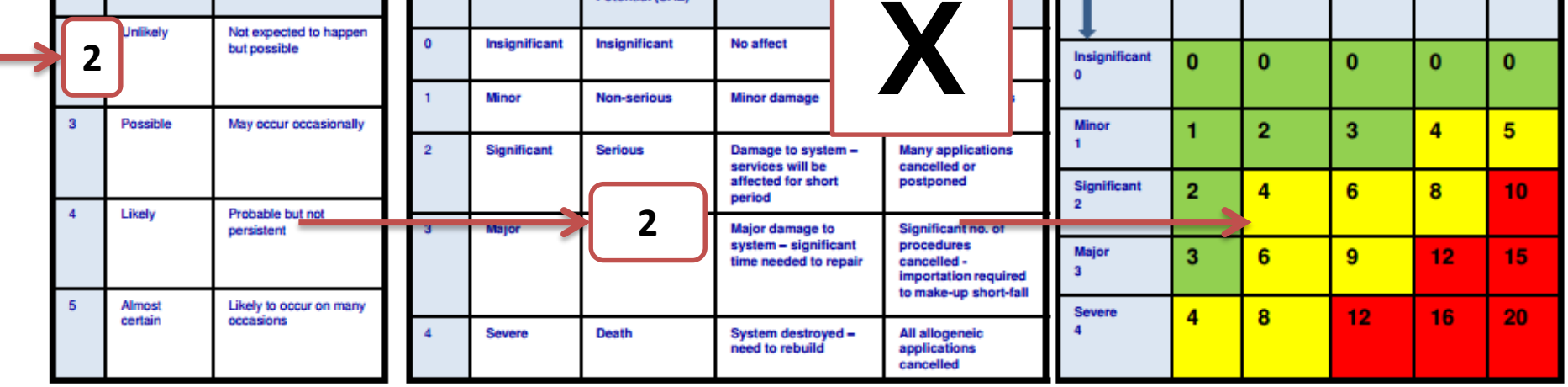
Step 1 – Probability of recurrence

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on Transplant or Fertility Syste	Impact on
0	Insignificant	Insignificant	No affect	
1	Minor	Non-serious	Minor damage	
2	Significant	Serious	Damage to system – services will be affected for short period	Many applications cancelled or postponed
3	Major		Major damage to system – significant time needed to repair	Significant no. of procedures cancelled - importation required to make-up short-fall
4	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled

Step 2– Consequences of Recurrence

Recurrence probability → / Consequences ↓	Rare 1	Unlikely 2	Possible 3	Likely 4	Almost certain 5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

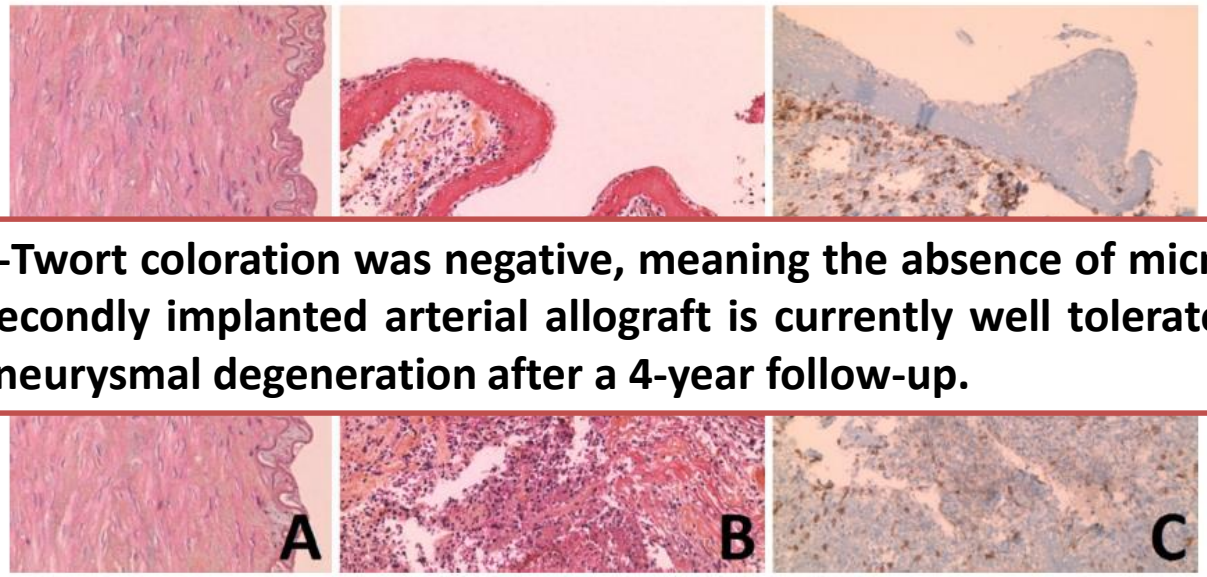
Step 3 - Impact



CASE 2

- HISTOLOGICAL OBSERVATIONS OF THE EXPLANTED ARTERY SHOWED A MASSIVE T CELL INFILTRATION, A SUBTOTAL NECROSIS OF THE ARTERIAL WALL WITH MULTIPLE RUPTURES, ASSOCIATED WITH PSEUDOANEURYSMS AND HEMATOMAS (FIG. 3), LEADING TO THE CONCLUSION THAT THIS ARTERIAL ALLOGRAFT WAS THE SEAT OF AN ACUTE **CELLULAR REJECTION**.

Cell Tissue Bank



Gram-Twort coloration was negative, meaning the absence of microorganism. The secondly implanted arterial allograft is currently well tolerated, without any aneurysmal degeneration after a 4-year follow-up.

Fig. 3 Histology of the femoral homograft at procurement showing a normal arterial wall before implantation (a). Histology (b) and immunohistochemistry (c) of the edge of a pseudoaneurysm at surgery after 1 month, showing a rupture of the arterial wall and the identification of the T-cells by anti-CD8. The inner surface of the pseudoaneurysm is covered with fibrin exudation (Obj. ×10)

CASE 2: CONLCUSIONS

- ACUTE CELLULAR REJECTION IS MORE FREQUENT IN TRANSPLANTED **ORGANS** SUCH AS HEART, KIDNEY, AND LIVER, AND THE CRITERIA FOR ITS DEFINITION ARE WELL ESTABLISHED (DEMETRIS ET AL. 1997. 2).

- ACUTE REJECTION OF CRYOPRESERVED ALLOGRAFTS HAS BEEN SPARSELY REPORTED, AND DESCRIBED IN TISSUES SUCH AS **MENISCUS** (HAMLET ET AL. 1997) AND **VEINOUS GRAFTS** (NEGLE´N AND RAJU 2003).

- IN THIS CASE, THERE WAS **NO ABO MISMATCH** BETWEEN THE PATIENT AND THE FIRST DONOR. HLA TYPING REVEALED NO COMMON HLA MARKER AND ANTI-HLA ANTIBODIES WERE FOUND AFTER EXPLANTATION OF THE FIRST ALLOGRAFT

- HISTOLOGICAL FINDINGS ARE **IN FAVOR OF AN ACUTE REJECTION,** WHICH TO OUR KNOWLEDGE HAS NEVER BEEN SO WELL DOCUMENTED AS IN THIS CASE OF A CRYOPRESERVED VASCULAR ALLOGRAFT IMPLANT.

CORRECTIVE ACTION: **RAPID ARTERY REPLACEMENT**

***LEARNING POINTS*:**

- **CRYOPRESERVED ARTERIAL ALLOGRAFT IS A GRAFT OF CHOICE IN CASES OF ARTERIAL INFECTIONS, BUT THE PROBLEM OF ITS IMMUNOGENICITY IS RAISED**
- **MORE STUDIES TO ANALYZE KEY FACTORS FOR TISSUE REJECTION SHOULD BE DONE**

Cell Tissue Bank. 2015 Sep;16(3):331-3. doi: 10.1007/s10561-014-9489-y. Epub 2014 Dec 16.

Acute rejection of a cryopreserved arterial homograft.

Soquet J[1], Chambon JP, Goffin Y, Jashari R.

Author information

Abstract

The use of arterial homograft is indicated especially in case of prosthetic graft infections after bypass surgery. We report the case of a patient who experienced the loss of a cryopreserved femoral artery caused by an acute rejection. This homograft had to be explanted 1 month after implantation because of an acute aneurysmal deterioration. Histology of the explanted artery showed inflammatory cells infiltration, pseudoaneurysms and necrosis. It was then replaced by a second cryopreserved femoral artery which is currently well tolerated. This first case of acute rejection of a cryopreserved artery, to our knowledge, raises again the question of the immunogenicity of cryopreserved homografts. The case report is followed by a brief discussion.

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Welcome to the Notify Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the application of human organs, tissues and cells. We aim to support continued improvements in safety and efficacy in transplantation and in assisted reproduction.

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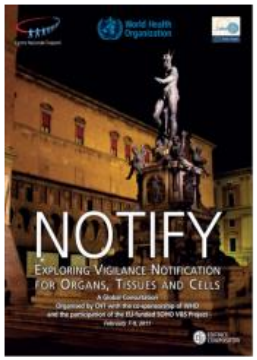
The database is continually updated and to date 100% of the cases collected (until 2010) by the BIG V&S were examined and uploaded. The next phase of the Notify Project will be to collect new cases (from 2010 to present) and increase the database volume.The search engine is accessible without username and password.

Click on this image to download the report of the Bologna Notify Meeting and 5 didactic papers developed by the Notify experts



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WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs

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