THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

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EDQM activities in the field of biovigilance

AFMPS Symposium – Brussels, 5 February 2024

Gabriela Bodea and Marie Emery – SoHO Division, EDQM, Council of Europe

Contents

- Introduction to the EDQM
- Standard setting: EDQM Guides
- Strengthening biovigilance programmes for organs, tissues and cells project
- Serious Adverse Reactions/Events Reporting (SARE Exercise)

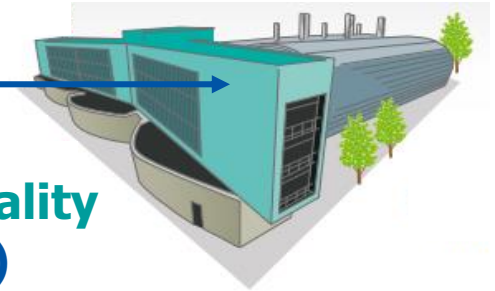
Introduction to the EDQM

The EDQM, a Directorate of the COUNCIL OF EUROPE

COUNCIL OF EUROPE

Founded in 1949
Intergovernmental organisation
46 Member States
Population more then 700 Millions

COMMITTEE OF MINISTERS | PARLIAMENTARY ASSEMBLY | CONGRESS OF LOCAL AND REGIONAL AUTHORITIES | EUROPEAN COURT OF HUMAN RIGHTS | COMMISSIONER OF HUMAN RIGHTS | CONFERENCE OF INGOS



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COUNCIL OF EUROPE
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The European Directorate for the Quality of Medicines and HealthCare (EDQM)

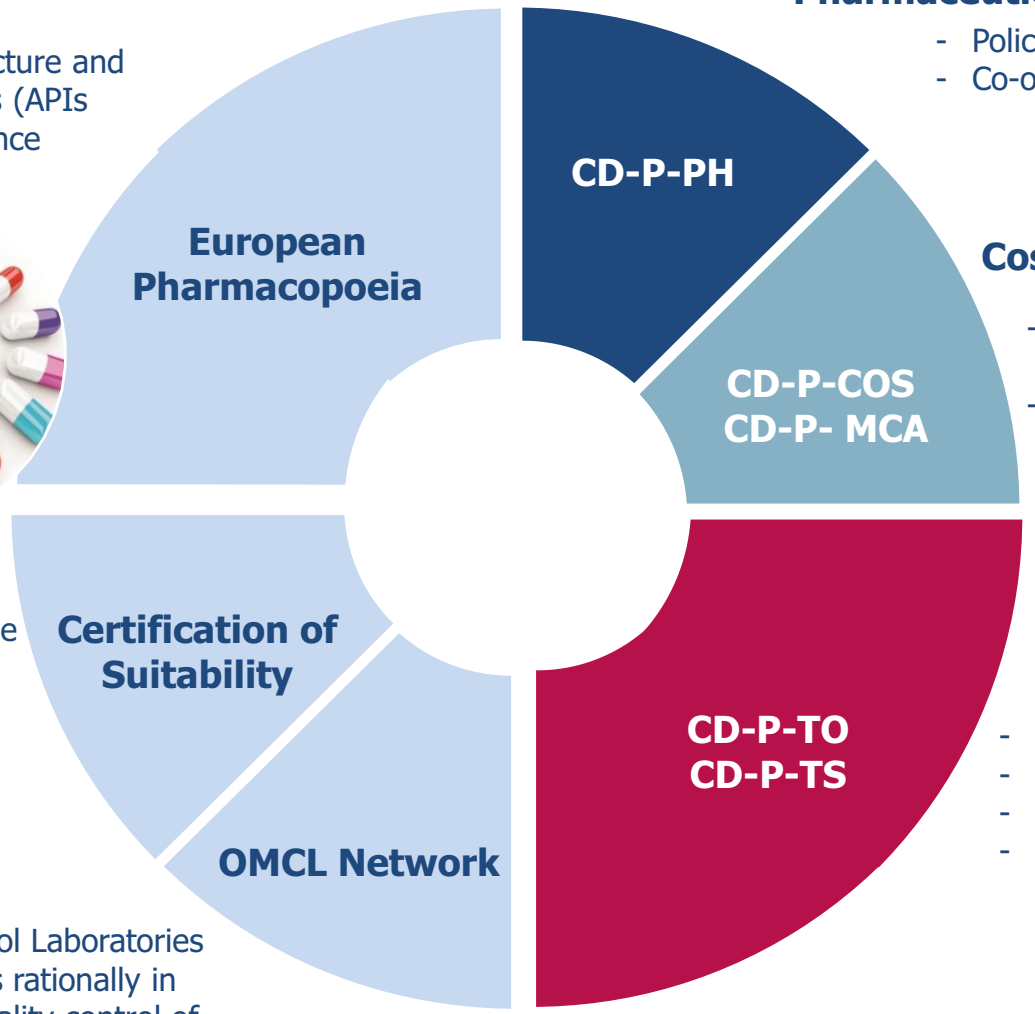
Founded in 1964
Based on the Convention on the Elaboration of a European Pharmacopoeia (partial agreement,1964)
39 Member States & the EU
Contribute to Public Health and enhance access to good quality medicines and healthcare in Europe

The EDQM: Mission & areas of work

- Official standards for the manufacture and quality control of pharmaceuticals (APIs and medicinal products) & reference standards

- Certificates of Suitability demonstrating compliance of pharmaceutical substances with pharmacopeial standards
- Inspections of manufacturers of these substances

- Network of Official Medicines Control Laboratories to pool expertise and use resources rationally in order to achieve effective public quality control of medicines



Pharmaceutical Care

- Policies & model approaches for the safe use of medicines
- Co-operation to combat falsification of medical products

Cosmetics & food contact materials

- Standards for cosmetics and food contact materials
- Coordinating control of cosmetics

Substances of Human Origin (SoHO)

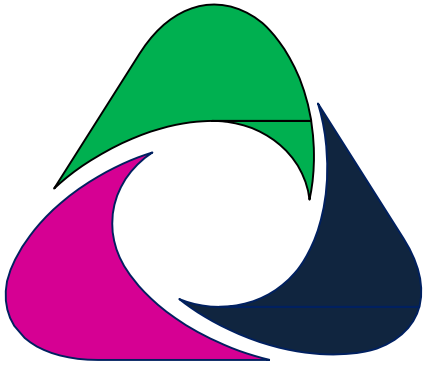
- Ethical, safety and quality standards
- Data collection
- Networks
- Co-operation and operational activities

CD-P-X: Intergovernmental Structure

The Council of Europe: Activity types

Standard-setting
Elaboration & adoption of standards and identification of best practices (*Conventions, recommendations, guidelines or policy recommendations)*

Technical co-operation
Activities aiming at raising awareness about standards and their implementation



Monitoring
Activities aimed at assessing compliance with standards

Governance of SoHO activities

*responsible for SoHO activities since 2007

EDQM*

Department of Biological Standardisation, OMCL Network & HealthCare
SoHO Division

COMMITTEES

CD-P-TO and CD-P-TS

Non-commercialisation of substances of human origin

Mutual assistance

Protection of donors & recipients

ACTIVITIES

Developing legal instruments, technical standards, policies

Monitoring data & practices

Operational activities supporting SoHO establishments in implementing CoE standards & EU legislation

Governance in the transplantation field

European Committee CD-P-TO

The intergovernmental committee appoints (ad hoc) working groups to elaborate quality and safety standards in technical guidelines (nominate experts, approves terms of reference of the working groups).

Working groups regularly report to the Committee

Final technical guidelines adopted by the CD-P-TO before publication.

Standard setting : EDQM Guides

Standard-Setting - Transfusion and Transplantation

EDQM Technical Guidance (SoHO)

Comprehensive guidelines **based on best available scientific evidence** to provide professionals with a useful overview of the most recent developments in the field

Ensure high level of **quality and safety standards**

Addressed to the **46 CoE member states**

Contribute to the **harmonisation** of these activities among European countries, facilitating uniform standards and practices

Consensus documents elaborated by ad hoc working groups (under the aegis of the CD-P-TO / CD-P-TS) composed of experts nominated by Member States and professional associations

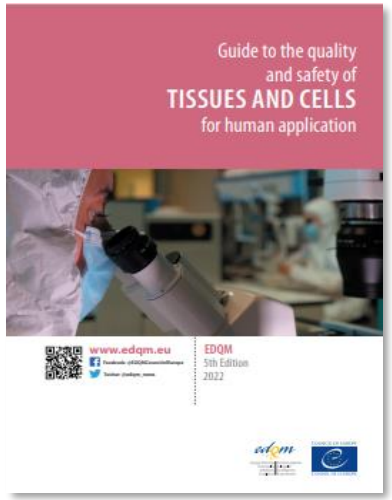
Continuous update and maintenance

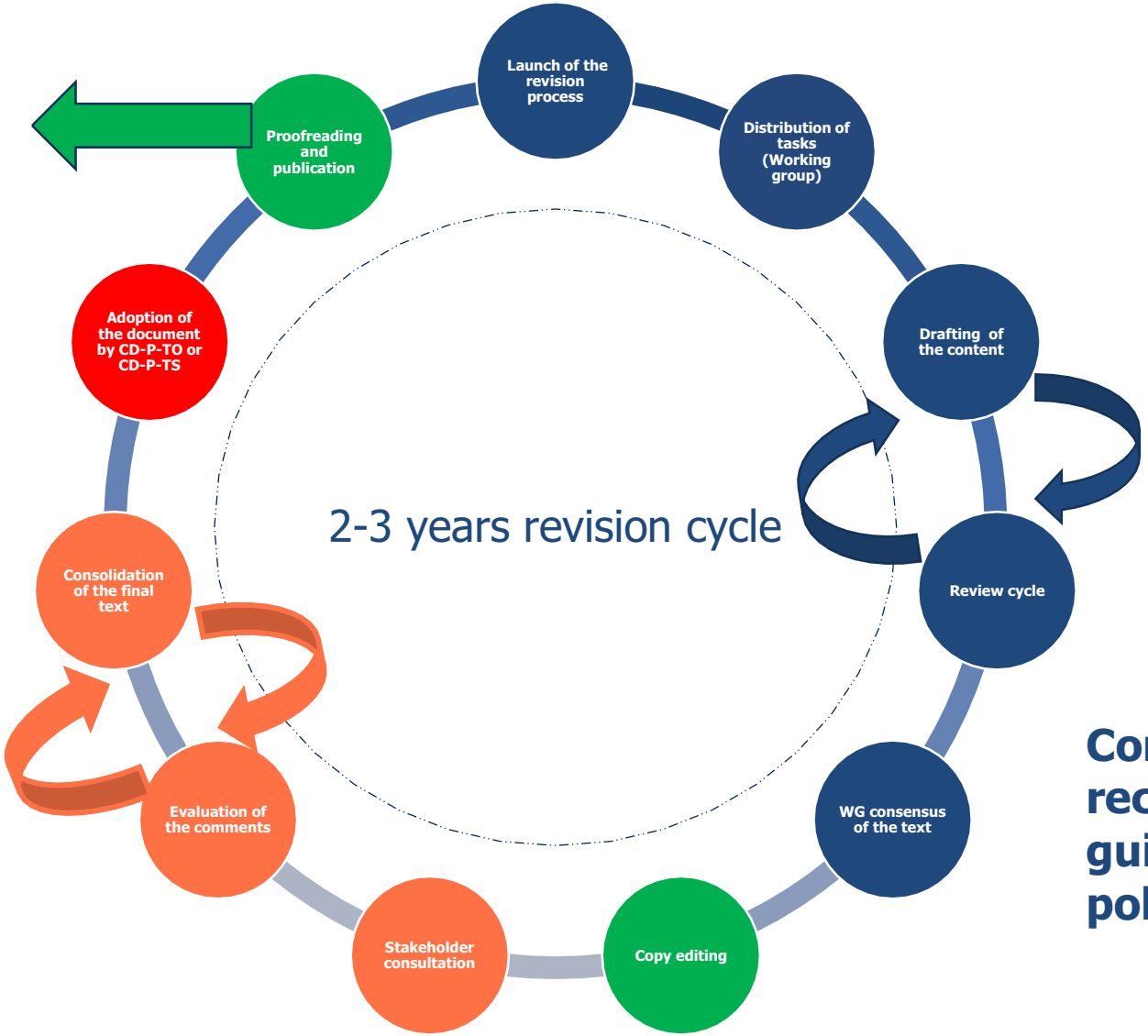
INCREASED QUALITY AND SAFETY OF BLOOD, ORGANS, TISSUES & CELLS

IMPROVED CLINICAL OUTCOMES

Guide elaboration and consultation process

EDQM Guide 5th edition



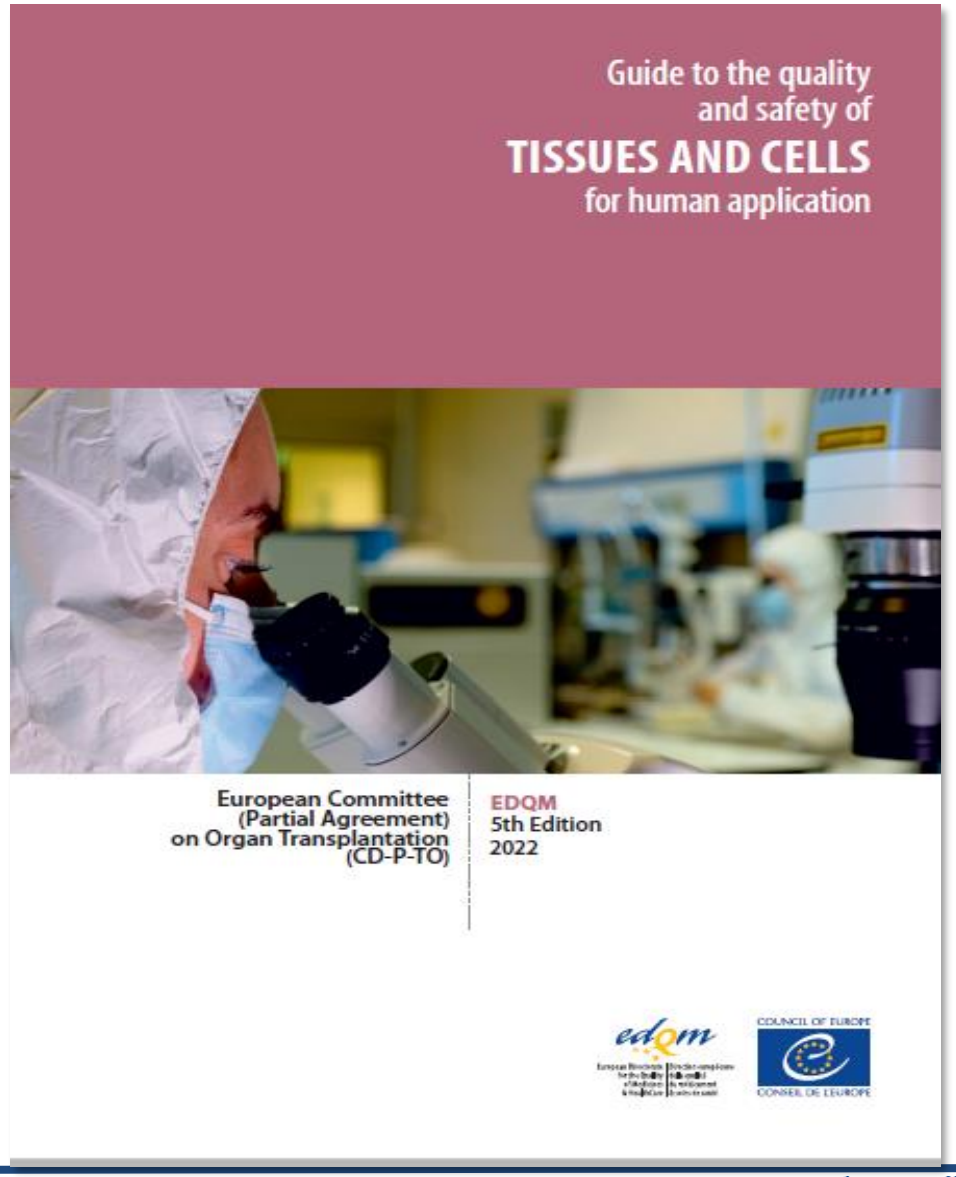


Conventions, recommendations, guidelines, policy recommendations

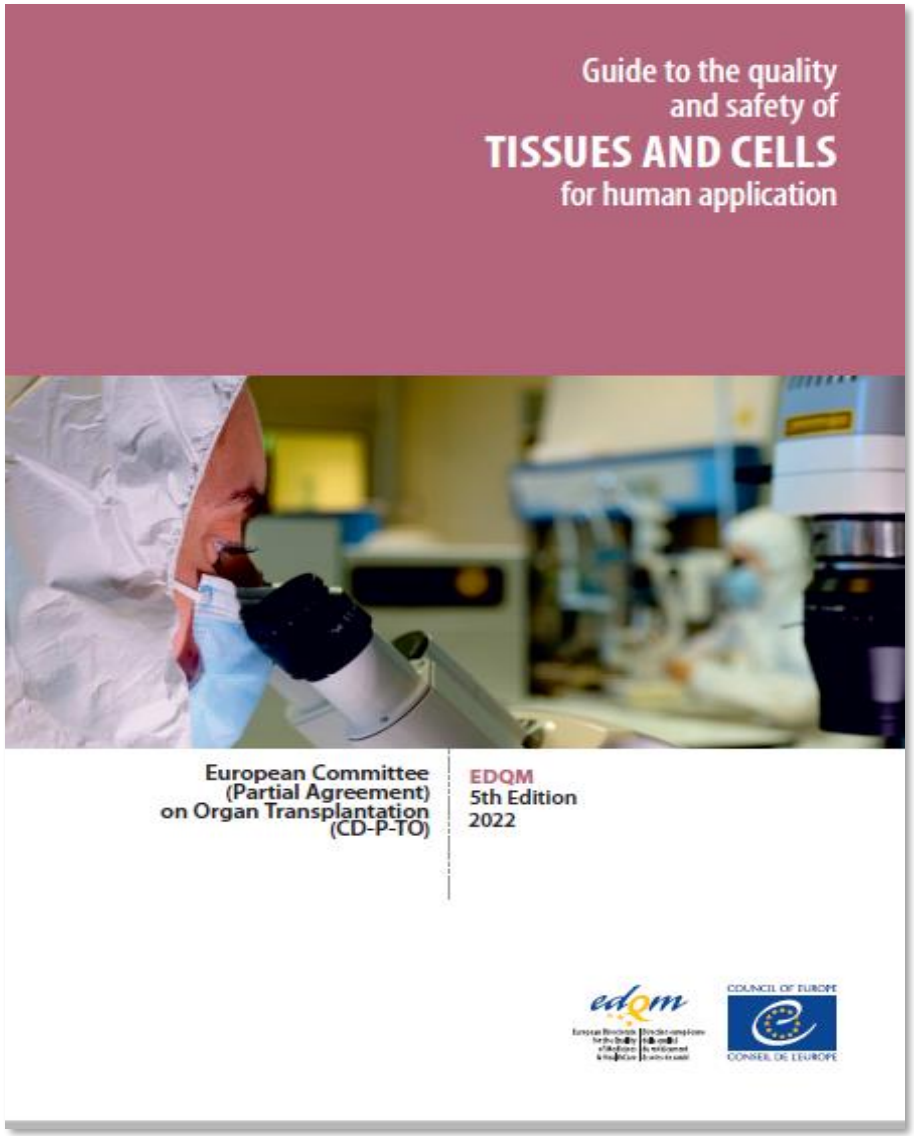
Guide to the Quality and Safety of Tissues and Cells for Human Application

2013 – 2023 (5 editions)

Collates updated **evidence-based information** to provide professionals with the **most recent advances** in the field, as well as technical guidance to ensure the **quality and safety** of tissues and cells for human application.

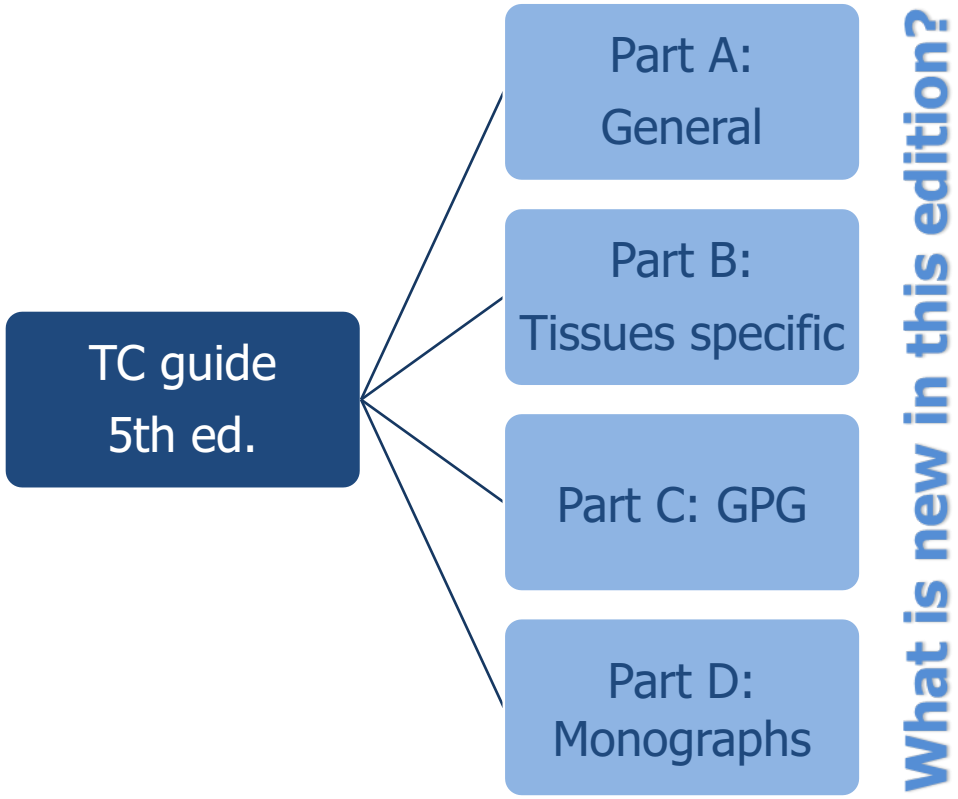


TC Guide: 5th Edition structure



- **Part A** (Chapters 1-18) => General requirements
- **Part B** (Chapters 19-34) => Specific guidelines and requirements for the various tissue and cell types
- **Part C** => Good Practice Guidelines (GPG) for tissue establishments
- **Part D** => Tissue and Cell Monographs
- **Tool** for Microbiological Risk of Contamination Assessment (MiRCA)

TC Guide: What's new in the 5th edition?



What is new in this edition?

Risk Assessment Tools (MiRCA; Euro GTP II)

Human milk

Intestinal microbiota

Tissues/cells as starting materials for ATMP

Completely reviewed and revised

43 monographs (23)

Funded by the European Union and the Council of Europe
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CONSEIL DE L'EUROPE
Implemented by the Council of Europe

5th Edition Updated Contents

Part A: General

Part B: Tissue specific

Part C: TC-GPG

Part D: Monographs

1. Introduction
2. Quality management and validation
3. Risk management
4. Recruitment of potential donors, identification and consent
5. Donor evaluation
6. Donor testing- markers for infectious diseases
7. Procurement
8. Premises
9. Processing
10. Storage
11. Principles of microbiological testing
12. Release, distribution and import/export
13. Interaction between tissue establishments and organisations responsible for human application
14. Computerised systems
15. Coding, packaging and labelling
16. Traceability
17. Biovigilance
18. Introduction of novel processes and clinical applications

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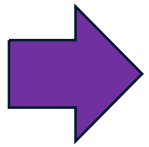
Biovigilance in the TC Guide

- Chapter 17 – Biovigilance
- Appendix 27 – Serious adverse reaction or event: impact assessment form
- Appendix 28 – Example of serious adverse reaction (SAR) for non-reproductive tissues and cells
- Appendix 29 – Example of serious adverse reaction (SAR) for reproductive tissues and cells
- Appendix 30 – Example of serious adverse event (SAE) for non-reproductive tissues and cells
- Appendix 31 – Example of serious adverse event (SAE) for reproductive tissues and cells
- Appendix 32 – Serious adverse reaction: notification form for ocular tissues (Agence de la Biomédecine, France)
- Appendix 33 – Serious adverse reaction or event: notification form for ocular tissues (NHS, UK)

Chapter 17. Biovigilance

- 1 – Introduction, biovigilance phases
- 2 – Definitions => adverse events, adverse reactions
- 3 – Management and quality of vigilance => vigilance, surveillance, surveillance for new risks
- 4 – Adverse reactions => detection, reporting, investigation and assessment
- 5 – Adverse events => detection, reporting, investigation and assessment
- 6 – Vigilance co-ordination, rapid alerts
- 7 – Vigilance communication, education and training => no blame culture, experience and feedback sharing, training and workshops
- 8 - References



Completed by practical examples in the appendixes

Where to find EDQM publications?

https://freepub.edqm.eu/publications

Strengthening biovigilance programmes for organs, tissues and cells project

Project objectives

- Increasing the **safety and quality** profiles of **organs, tissues and cells** for clinical application in Council of Europe member states and beyond, and ultimately **improving the health of European citizens**;

- Disseminating **best practices** in **biovigilance in the fields of organs and tissues and cells**;

- Project overseen by the **CD-P-TO**, co-ordinated by the **EDQM** and **co-funded** by **the EDQM/CoE** and the **European Commission** (Contribution Agreement SANTE/2022/SI2.879517).

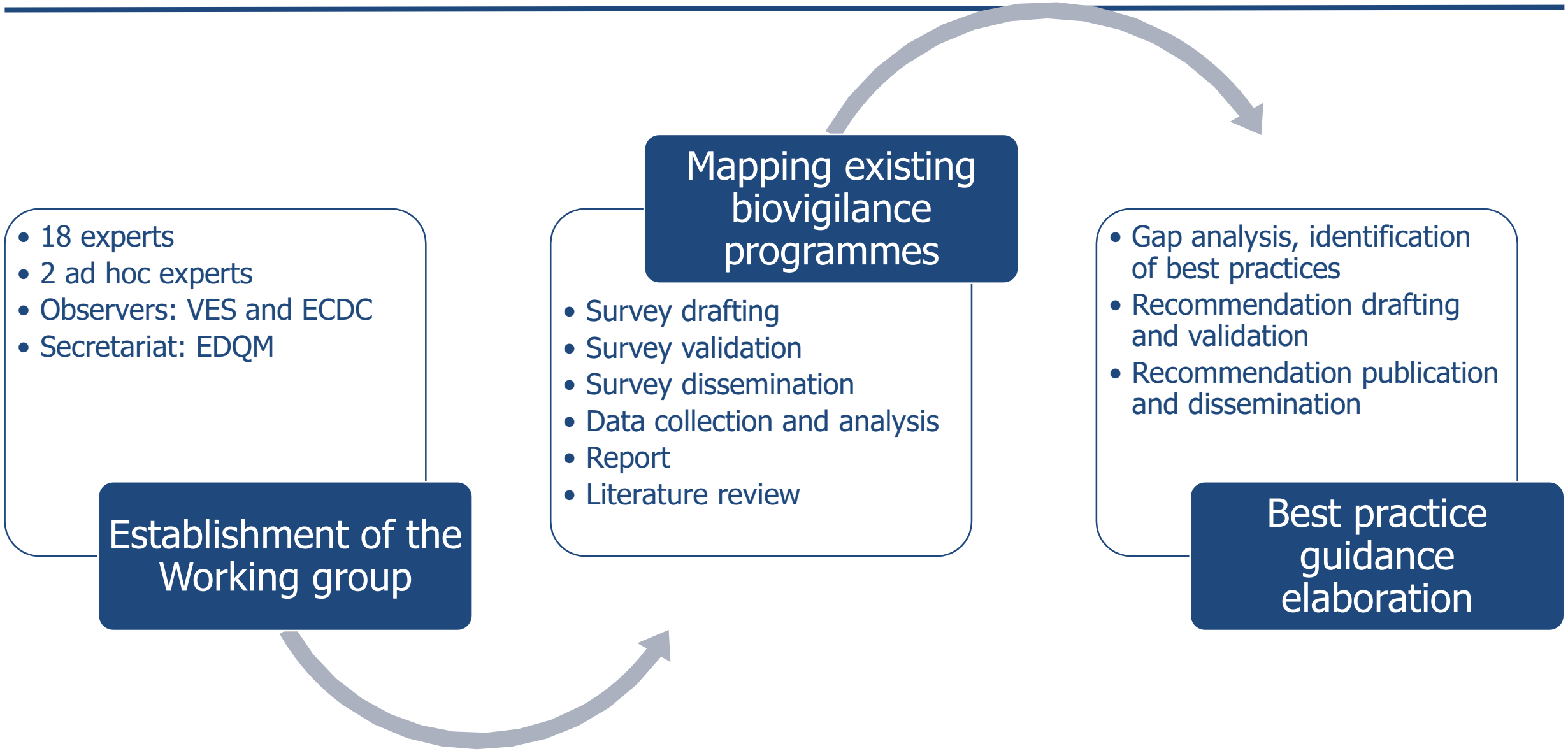
Project phases

- Evaluate the **state-of-play of biovigilance programmes** currently in place in Europe;

- Identify **best biovigilance practices**, in particular in terms of serious adverse reactions and events (SAREs) management *(e.g. detection, investigation/ root cause analysis, alerts and resolution, corrective and preventive actions)*;

- Provide **practical guidance to professionals** for the management of effective and efficient biovigilance programmes.

Tasks and deliverables



Gathering information - Surveys (1/2)

- **Aims and objectives**
  - Map the state-of-play of **biovigilance programmes** implemented in different countries
  - Identify **gaps**, **best practices** and **opportunities for improvement**
  - Map the **disparities between countries**
  - Identify needs for establishing **best practice guidance**
  - Identify needs for future biovigilance **trainings for professionals**

- **Two surveys**
  - One for **competent authorities**
    - Understand how the biovigilance system is set up in each country
  - One for **professionals in the field**
    - Understand the biovigilance programmes implemented locally and the challenges faced

Gathering information - Surveys (2/2)

- **Dissemination of the surveys**
  - December 2023 and January 2024
  - CD-P-TO, Competent authority network, TE Compendium…
  - Deadline for answering => 4 February 2024

- **Belgium**
  - **Competent authority survey**
    - Filled in by AFMPS
  - **Professional survey** (as of 25 January)
    - 9 respondents => 3 tissue establishments, 4 MAR clinics, 3 hospitals (one hospital being also a MAR clinic)

- **Next steps => Data analysis => Mapping => Best practice guidance**

Serious Adverse Reactions/Events reporting

SARE Exercise

Objectives:

- Introduction to SARE exercise
- Summary of SARE 2023 (2022 Data)
- Belgium - SARE Reporting
- Facts and Challenges
- Good Practices

Second TB Outbreak Caused by Bone Allografts Containing Live Cells - US, 2023

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 72 / No. 52-53
January 5, 2024

Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023

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Abstract

During July 7–11, 2023, CDC received reports of two patients in different states with a tuberculosis (TB) diagnosis following spinal surgical procedures that used bone allografts containing live cells from the same deceased donor. An outbreak associated with a similar product manufactured by the same tissue establishment (i.e., manufacturer) occurred in 2021. Because of concern that these cases represented a second outbreak, CDC and the Food and Drug Administration worked with the tissue establishment to determine that this product was obtained from a donor different from the one implicated in the 2021 outbreak and learned that the bone allograft product was distributed to 13 health care facilities in seven states. Notifications to all seven states occurred on July 12. As of December 20, 2023, five of 36 surgical bone allograft recipients received laboratory-confirmed TB disease diagnoses; two patients died of TB. Whole-genome sequencing demonstrated close genetic relatedness between positive *Mycobacterium tuberculosis* cultures from surgical recipients and unused product. Although the bone product had tested negative by nucleic acid amplification testing before distribution, *M. tuberculosis* culture of unused product was not performed until after the outbreak was recognized. The public health response prevented up to 53 additional surgical procedures using allografts from that donor; additional measures to protect patients from tissue-transmitted *M. tuberculosis* are urgently needed.

Introduction

On July 7, 2023, a state health department notified CDC that an otherwise healthy adult experienced symptoms of meningitis 5 weeks after spinal fusion surgery that incorporated a bone allograft product containing live cells; *Mycobacterium tuberculosis* was identified in the cerebrospinal fluid. On July 11, a different state health department notified CDC of a patient with a persistent surgical site infection after a laminectomy that appeared to have used a similar product; drainage from the surgical site tested positive for acid-fast bacilli, and a nucleic acid amplification test confirmed the presence of *M. tuberculosis*. When reporting these cases to their respective public health authorities, the clinicians caring for these two patients independently noted similarities to the 2021 outbreak (*1*–*4*) and asked that CDC investigate.

https://www.cdc.gov/mmwr/volumes/72/wr/pdfs/mm725253-H.pdf

Important Information for Human Cell, Tissue and Cellular and Tissue-based Product (HCT/P) Establishments Regarding Tuberculosis Outbreaks Linked to a Bone Matrix Product

September 6, 2023

FDA is working closely with the Centers for Disease Control and Prevention (CDC) to investigate recent reports of a tuberculosis (TB) outbreak caused by *Mycobacterium tuberculosis* (Mtb) that appears to be linked to a bone matrix product. We are issuing this communication to increase your awareness regarding the risk of transmission of Mtb through use of HCT/Ps in the United States.

Decades ago, Mtb transmission from transplantation of human bone, heart valves, and a dura mater allograft were reported in other countries. In 2021, a multi-state outbreak of Mtb in the United States was linked to transplantation of a bone allograft product and resulted in significant morbidity and mortality. A new, similar outbreak is currently under investigation.

Routine screening measures are in place for evaluating clinical evidence of infection in HCT/P donors. FDA has provided recommendations in guidance to reduce the risk of transmission of infections, including due to sepsis (which may be caused by Mtb); however, the following risk mitigation strategies concerning Mtb are important for public health safety.

Risk Mitigation Strategies

Responsible person

The HCT/P establishment's responsible person (21 CFR 1271.3(t)) must determine and document the eligibility of a cell or tissue donor (21 CFR 1271.50). The responsible person(s) who is(are) authorized to perform designated functions related to the donor eligibility determination, should have appropriate medical training and be qualified to review clinical evidence consistent with risks for sepsis and TB infection. In addition, a responsible person must verify and document that, on the basis of record review, release criteria have been met and they have determined that an HCT/P is available for distribution (21 CFR 1271.265(c)(1)).

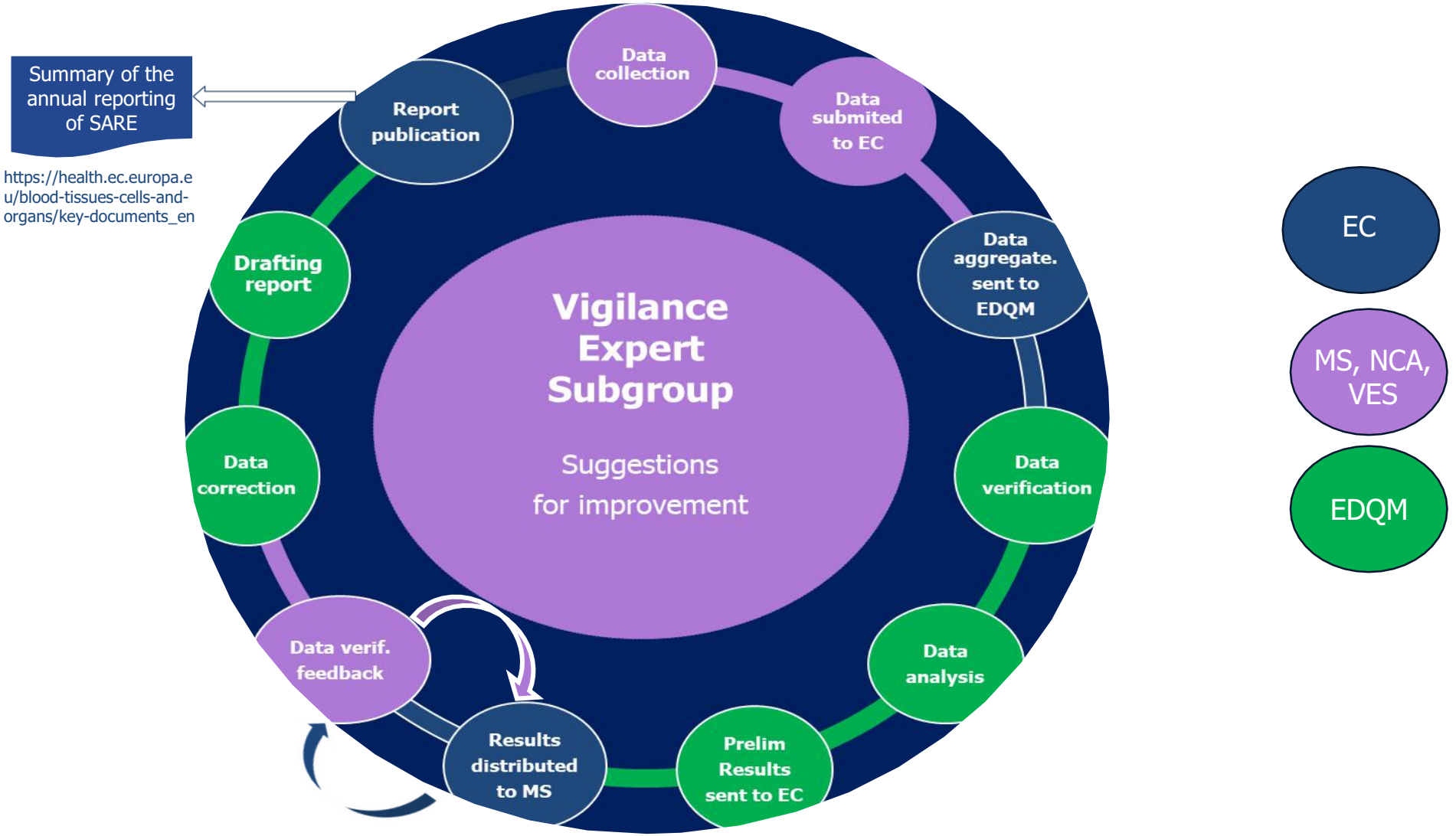
Maintaining knowledge and awareness of these outbreaks and seeking additional training and/or re-training will help enable responsible persons to identify risk factors, conditions, clinical evidence, and physical evidence that can be associated with an increased risk for TB (including active TB and LTBI) and/or an increased risk of sepsis.

Donor screening

TB may be underdiagnosed due to the lack of clinical suspicion, inherent diagnostic difficulty, and/or attribution of a group of symptoms to alternate causes. Although a donor with LTBI may be asymptomatic, a person with TB disease may have a number of symptoms or signs that can mimic or overlap with other medical conditions.

https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-information-human-cell-tissue-and-cellular-and-tissue-based-product-hctp-establishments-1

SARE Process



Summary of SARE 2023 (2022 Data)

DATA COLLECTED from 30 Countries (26 Member States + 4 Non-Member States):

AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IS, IE, IT, LV, LI, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, SE and UK (Northern Ireland)

- 2021 SARE exercise: 28 reporting countries
- 2022 SARE exercise: 29 reporting countries
- 2023 SARE exercise: 30 reporting countries (same as in 2022 + CY)

Data Summary - Tissues and Cells

Parameter	2020 (data 2019)		2021 (data 2020)		2022 (data 2021)		2023 (data 2022)	
	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	**Countries reporting**	**Number**
T&C Units Processed	26	2,922,117	24	2,646,079	25	3,159,362	**27**	**2,892,459**
T&C Units Distributed	27	1,360,315	26	1,116,519	28	1,192,203	**29**	**957,775**
Transplant Recipients	22	298,897	19	245,058	24	318,467	**26**	**327,961**
SAR	18	306	18	350	19	326	**17**	**347**
Fatalities in Recipients	-	-	7	16	6	20	**3**	**12**
SAE	20	949	22	910	23	694	**22**	**1,133**
SAR in donors	17	903	19	846	17	795	**19**	**777**
Fatalities in donors	-	-	-	-	-	-	**3**	**4**

SARE Analysis

General

- Number of Reporting Countries by Sub-category of T&C
- Incidence of each of the three categories of T&C – replacement, HSC and reproductive T&C (distributed & recipients pmp*)

Analysis of Denominators

- For each of the three categories of T&C:
  - Number of Distributed T&C by Sub-Category
  - Number of distributed T&C by type in the sub-category
- SAR denominators (TC distributed, recipients) and total number of SAR per year
- SAR denominators by country
- Number of TC processed by country and category of T&C

Analysis of SAR in Recipients

- For each of the three categories of T&C:
  - Number of SAR by Sub-category of T&C
  - Distribution of SAR by Type of Reaction

Analysis of Imputability Reporting

Analysis of Fatalities in Recipients and Offspring

Analysis of SAE in Recipients

- Total SAE - Distribution by Specification and by Year
- Distribution of SAE by Specification
- For each of the three categories of T&C:
  - Distribution of SAE by Specification
  - Distribution of SAE by Activity Step
  - Distribution of SAE by Activity Step and SAE Type

Analysis of SAR in Donors

- SAR in donor by reporting countries and year
- SAR in donor by reporting countries and year and by category of T&C
- SAR in Donors by Type of T&C and Type of Reaction

Analysis of Fatalities in Donors

Conclusions

Incidence of SAR and Fatalities

T&C Category	Number of Recipients 2022	Total SAR 2022	SAR incidence (per 100 000 units transfused) 2022	Fatalities (%) among SAR 2-3 2022	Fatalities incidence (per 100 000 recipients) 2022
Replacement T&C	149,823	34	22.7	-	0.67
HSC	21,487	60	279.2	1.7%	23
Reproductive T&C	156,651	253	161.5	0.4%	3.8
Total	327,961	347	105.8	0.6%	3.66

SARE Reporting by Belgium

General remarks	• National Vigilance Program
	• Commitment to Biovigilance
	  ○ Constant participation in SARE exercise
	  ○ VES Member
	  ○ Other?

T&C Units Processed	• Not reported • Collected?
T&C Units Distributed	• Reported for most types of T&C
Transplant Recipients	• Not reported • Collected?
SAR	• SAR submitted for all three categories of T&C in the scope of SARE exercise • Good and very good quality of information provided: - Clear and complete description - Impacted T&C specified - Impact on patient explained - Corrections, results of investigations, and CA/PA, where applicable, reported
Fatalities in Recipients	• 1 reported in 2021; adequate information provided
SAE	• Substantial number of SAE submitted for all three categories of T&C in the scope of SARE exercise • Good and very good quality of information provided: - Clear and complete description - Impacted T&C specified - Impact on patient explained - Corrections, results of investigations, and CA/PA, where applicable, reported - SAE specification seems adequate
SAR in donors	• Very good quality of information provided: - time of symptoms onset specified - symptoms and diagnosis specified - course of action described (medicines, surgical intervention in hospital, monitoring as outpatient)

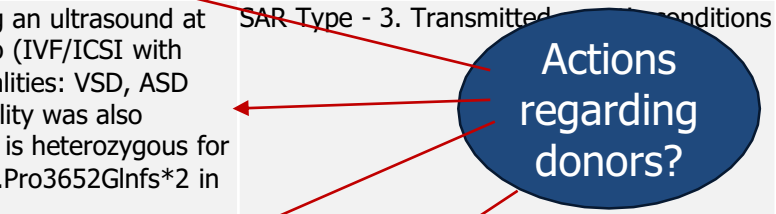
Tissue Type	SAR Description / Comments	SAR Type	SAR Subtype	IL
Ocular Tissues (Cornea - Sclera - Other Ocular Tissues)	Herpes infection in left cornea: Both the storage and transport medium and the residual corneal material were examined. Both the storage and transport medium tested positive for herpes simplex. No contamination seen on slit lamp examination. The other cornea tested negative.	SAR Type 1: Transmitted Infections	Viral : Other	-
	Slow clearance of corneal oedema. Small tear 0.2mm in the Descemet membrane transplant lamella at the hinge occurred during preparation. Upon receipt, the courier dropped the package on the floor; outer and inner packa intact, donor cornea was still suspended from floating device. Upon inspection perioperatively, the entire Descer membrane graft lamella appears to be loose in transport medium rather than attached to the hinge envelope. Su continue to perform empty artis. Postoperatively graft not abutted and re bubbling performed.		SAR: Reactions than those listed	-

Imputability not reported in 2021, but reported the next year for ALL SARs

Tissue Type	SAR Description / Comments	SAR Type	SAR Subtype	IL
Skeletal tissues	A left medial meniscus which was obtained by the tissue bank's examination team. The tissue bank 's prelevation team was still in training and under the supervision of professional. It is difficult to determine whether the tissue bank's employee responsible for the documents and the labelling of the jars has pasted an incorrect label, or whether an intern/someone of the tissue bank employees/professional has incorrectly named the graft. In the meantime, the tissue bank prelevators have been declared competent to independently pre-deliver and have been well trained, which means that the prelevations are now much smoother. On inquiry it appears that the patient was already under anaesthesia, and that the incision had already been made. Graft was not transplanted but destroyed in the hospital. It is the fact of anesthetizing a patient and making an incision with the associated risks which, from our point of view, constitutes the SAR and the origin is the impossibility of making the graft with the available material.	SAR Type - 4. Other SAR	Other SAR: Graft failure/delayed engraftment	3
	It concerns a left extensor that was delivered on 29/07/2017, it would expire in May 2022, TE+ Surgeon were aware of this. The graft was packed in 1 EVA bag and 2 regular kidney bags, which were only tied closed. The last bag was left unfolded and glued shut. Presumably, this was still allowed in 2017. However, in the meantime the packaging rules have become stricter and there is also stricter supervision to ensure that this is carried out correctly. Large bone pieces and autologous skull hatches are still packed in 3 sterile bags, but the bow tie is now folded inwards, and it is again glued with a sterile tape. However, the patient was already under anaesthesia and the incision was already made when it was determined that the graft had not been packaged in accordance. There is narcosis of the patient and incision for no reason since the material could not be grafted because of the suspicion of non-sterility. It is the fact of anesthetizing a patient and making an incision with the associated risks which, from our point of view, constitutes the SAR and the origin is the impossibility of making the graft with the available material.	SAR Type - 4. Other SAR	Other SAR: Graft failure/delayed engraftment	3

Tissue Type	SAR Description / Comments	SAR Type	SAR Subtype	IL
EMBRYO (IVF)	Autism spectrum disorder	SAR Type 3: Transmitted genetic conditions		-
EMBRYO (IVF)	Child with bilateral hearing impairment/deafness. The donor is a carrier of the GJB2 gene	SAR Type 3: Transmitted genetic conditions		-
EMBRYO (IVF)	Child with obvious hypotonia, with also more lax joints and the motor development is delayed	SAR Type 3: Transmitted genetic conditions		-
SPERM (IUI)	Child carrying a c.985A>G mutation of the ACADM gene in the homozygous state.	SAR Type 3: Other disease transmission		-
SPERM (IUI)	Child with Alpha-1 Anti-trypsin deficiency	SAR Type 3: Other disease transmission		-
SPERM (IUI)	Spina bifida	SAR Type 3: Other disease transmission		-
SPERM (IUI)	X – linked hypophosphatemia with vitamine D resistant rickets. Mutations PHEX gene on Xp22.1	SAR Type 3: Other disease transmission		-

Tissue Type	SAR Description / Comments	SAR Type	SAR Subtype	IL
Embryo (IVF)	Child with HPA (hyperphenylalaninemia) --> the child and the sperm donor were genetically screened, the pathogenic mutation confirmed in both	SAR Type - 3. Transmitted genetic conditions		2
Embryo (IVF)	termination of pregnancy due to serious heart defects in a foetus, determined during an ultrasound at 23 weeks of pregnancy. This pregnancy occurred after the transfer of a cryo-embryo (IVF/ICSI with donor semen). An internal scan of the foetus revealed the following cardiac abnormalities: VSD, ASD type II, right ventricular hypoplasia, tricuspid valve atresia. A genitourinary abnormality was also discovered (left renal agenesis).--> donor is a carrier of polycystic kidney disease. It is heterozygous for the pathogenic variant named NM_138694.4:c.10955delC leading to NP_619639.3:p.Pro3652Glnfs*2 in the PKHD1 gene.	SAR Type - 3. Transmitted [illegible]onditions		1
Sperm (IUI)	Baby born with hearing loss --> homozygous pathogenic mutation (c.35delG) in the GJB2 gene (Connexin 26) located on chromosome 13q11. Mutations in this gene are responsible for 10 to 20% of all cases of hereditary hearing loss and for more than half of the recessively inherited prelingual sensorineural forms of deafness. With an average carrier frequency of about 1 in 34 in the European population the mutation c.35delG is the most frequent GJB2 mutation in the European population.	SAR Type - 3. Other disease transmissions	Transmitted genetic disease	2
Sperm (IUI)	Baby born with suspected genetic disease -->After the heel prick, it turned out that the child had the following disease: VLCADD (autosomal recessive).	SAR Type - 3. Other disease transmissions	Transmitted genetic disease	1
Sperm (IUI)	Baby born with suspected genetic disease -->Donor has been tested and carries a variant in USH2A (c.1606T>C p.(Cys536Arg)). Usher Syndrome type 2 is inherited in a recessive manner, which means that both genetic parents most likely are carriers of the condition. A carrier is healthy and will not have any symptoms.	SAR Type - 3. Other disease transmissions	Transmitted genetic disease	2



Critical supplier control

Critical supplier control

Tissue Type	SAE D ption Comments	SAE Specification
Cardiovascular Tissues	Bad encoding by the laboratory of the tissues of the same donor, no i tification on the type of tis (FA Or AD,....) ==> when obtaining the results, impossible to match the tissue with the samples, the laboratory threw way the samples and destru n of all the tissues	System failure - Inadequate process, SOP or documentation
Cardiovascular Tissues	external pocket unsealed, overview of the problem during the prepa ation of the shipment. Result: n-sterile internal bag	Materials
Cardiovascular Tissues	The courier responsible for the transport to the subcontractor for decellularization did not respect th time limit, the tissue is no longer usable and must be destroyed.	System failure - Training or education
Cardiovascular Tissues	The transporter in charge of bringing the dry shipper to the centre for implantation went to the wrong hospital, this one took the allograft without checking if it was correct or not, the allograft was taken out of the dry shipper and put in the freezer. The driver contacts the tissue bank to report that the allograft has been put in the freezer and the tissue bank then realizes that it is not the right hospital even though all the instructions had been given. The tissue was put back in the dry shipper for return but given the thermal shock, the tissue bank choose for the destruction of the tissue. The patient's transplantation in the center which was initially planned could not be postponed, the center had to find an emergency alternative.	System fail… Tr…
Skeletal tissues	Lyophilized diaphysis: Application of an expired graft: expiry date was 28/02/2021 and the graft was still used for surgery on 05/03/2021 (5 days later).	S… failure - …dequate process, SOP or documentation

Multiple issues; actions?

Tissue Type	SAE Description Comments	SAE Specification
Cardiovascular Tissues	On 07/13/2022, a vascular graft, stored at -80°C, was distributed and transplanted. This graft had expired since 06/19/2022. It was not until 07/14 that it was found that the expiry date had passed at the time of distribution/transplantation. From the above it appears to be a human error after one first human error: - The expiration date of the graft was not checked at the time of ordering/reserving the graft - The expiration date of the graft was not verified at the time of preparing the graft pack. Post-operative patient follow-up: - On 25/08, the patient was seen by the treating surgeon: A very good postoperative control was noted in the file. No problems were identified clinically.	System failure - Other failure of the QMS
Multiple tissues & cells	Temperature rise in the freezer at -80°C in which the released amniotic membranes and certain musculoskeletal grafts are kept. On 28/10/2022 at 08:30 this freezer was in audible alarm and the display indicated -51°C. There was no alarm from central monitoring (MACQ probe) since the central probe is at the top of the freezer and the amniotic membranes at the bottom being kept. There was a large difference between the temperature measured by the MACQ probe (top of the freezer) and the internal probe of the appliance (middle/bottom, above the 3rd shelf). The cause of the temperature increase is the loading of a large number of cooling elements at room temperature. Since the measurements of the internal probe are not readable, it is not possible to know what the maximum temperature of the grafts on shelves 3 and 4 was between 27/10/2022 4:30 p.m. (loading of the cooling elements) and on 10/28/2022 08:30. Initially, the transplants were quarantined. A review of the literature demonstrating that the storage of amniotic membranes at a temperature from -28°C had no adverse effects on the tissues for 7 to 12 months was carried out. The grafts (in the middle of the layers) were also kept close together in an isomo box so that they buffered each other. There were no other amniotic membranes available. Based on the above, the responsible person decided to release the amniotic membranes again, but to store them now in another freezer (where no cooling element is kept). Musculoskeletal grafts stored on lower shelves were discarded out of caution and destroyed.	

Critical equipment qualification

Is there a procedure in place to require inventory verification to prevent … verification?

SARE T&C Exercise

Critical supplier control

Investigation (One time error? Detectability?)

Tissue Type	S Description Comments	SAE Specification
Peripheral Blood Stem Cells (auto+allo)	Bacterio positive for E. coli: The patient presented a positive urine ture for the same germ; it is likely that he h discharge in the blood that day.	T/C Defect
Peripheral Blood Stem Cells (auto+allo)	Incorrect delivery of additional blood samples for identification. F eign donor hematopoietic stem cells were de ed while the donor's blood samples, used to identify the donor, were missing. The blood samples were de ered to the wrong place and never made it to e tissue bank. Since verification for donor identification (ABO determination) was not possible on the dono blood samples, urgent HLA typing was perfor ed on a sample of the cryopreserved stem cells. The HLA typing appeared to correspond with the HLA data of the donor after whom the transplant could roceed. The blood samples were delivered to the wrong place by the courier service, or the donor centre specified the wrong delivery location.	System failure - Inadequate process, procedure or documentation
Donor lymphocyte infusions	A 1st dose of donor lymphocyte infusion was delivered to the patient. The requested bag was checked (dono /patient ID, cell product number) by 2 tissue bank employees and delivered to haematology. After delivery, the cell product was noted to contain an erroneous dose of CD3+/kg (70.10e6 CD3+/kg instead of 5.10e6 CD3+/kg). The application form does not indicate whether the cell product must be processed (thawed) before delivery. The cell product was recalled and the correct dose, after thawing, was delivered and administered.	System failure - Inadequate process, procedure or documentation

Tissue Type	SAE Description / Comments	Activity Step	SAE Specification
Peripheral Blood Stem Cells (auto+allo)	The donor/patient was called according to standard MDPB follow-up, and the patient informed us that she has breast cancer 10 years after the donation for allogenic use She is being treated for this by an oncologist in a hospital other than the hospital where the tissue establishment is located. Further information about the type of tumor is not known and the donor does not wish to comment further. No information is known about the status of the donor. A cancer diagnosis in this case breast cancer is always accompanied by serious consequences, even if the patient does not want to give further information about this Tissue establishment don't believe whether the donation is related to growth factors needed for stem cell transplantation, but since it happens within 10 years and we don't know the tumor type, it could possibly affect the acceptor. Tissue establishment just want to report this because tissue establishment have a fixed schedule of follow-up from the MDPD registry for transplantation	Donor selection	T/C defect
Peripheral Blood Stem Cells (auto+allo)	Concerns an allogeneic bag: The temperature of the transport box on arrival was 15°C instead of being in the 2-8°C range. Consequently, the viability of the fresh cells was measured at 84.3% => Criteria for inclusion of a fresh bag defined within the stem cell bank: the viability must be greater than 85% => Out of criteria/release specification for this bag due to the rise in temperature. the tissue bank concerned nevertheless froze the cells and transplanted a patient with this product. There was contact with the transport company to report the problem because the tissue bank concerned has an agreement with this transporter. Its terms were not respected.	Transport	T/C defect

Exceptional release?

Critical supplier control

Facts and Challenges

The scope of SARE exercise does not include all activities in the transplant cycle: import & export of SoHO, human application, and clinical outcome of donors and recipients

Reporting of SARE in donors is not mandatory

Current denominators are not optimal

- SAR incidence is calculated in relation to number of tissues distributed or number of recipients (if data is reported)
- SAE rates are calculated in relation to number of SoHO processed, irrespective of where the events were identified/occurred.
- For a meaningful analysis of SAE, denominators should be defined for each stage of the transplantation chain, to allow reporting of events in the right context and the calculation of rates of events relative to the units specific for the activity or task where events were identified

Reporting on denominators requires improvement

There is variability among countries in terms of data provided (denominator and data completeness)

SoHO Regulations

VES Improvements 2024

NL: TRIP REPORT 2021 BIOVIGILANCE

2.1 Recommendations

Recommendations	Who?
1 Give shape to biovigilance within the healthcare institution so that there is clarity about the use of human body material, and adverse events and reactions are reported through the appropriate channels; all this with the aim of improving the safety and quality of the application of human body material.	Boards and professionals involved in the application of human tissues and cells in hospitals and clinics.
2 In consultation with supervisory authorities and tissue establishments, work towards clear, simple and usable measures for activities within tissue establishments or transplant centres, and thus towards denominators for adverse events and reactions in the tissue and cell transplantation chain.	TRIP in consultation with the regulatory authorities and tissue establishments
3 Draft guidelines for reporting adverse events and reactions associated with new therapies that are not yet covered by current legislation, so that vigilance is covered from donation up to and including application.	TRIP in consultation with regulatory authorities and relevant institutions
4 Ensure more timely reporting of adverse events and reactions so that complete and adequate analysis of the cause and circumstances is possible.	Biovigilance staff and officers

2.2 Follow-up to previous recommendations

1 Tissue establishments, organ banks and transplant centres should improve the completeness and accuracy of their annual reports. TRIP should support this process by clarifying definitions, providing training courses and adapting and optimizing annual report forms. (Recommendation in the 2020 TRIP Biovigilance Report)
Development: In consultation with VWS and IGJ, TRIP further elaborated the definitions of distribution and processing in 2021 (see Section 1.2) and adapted the annual report forms. As a result of the collection of annual data in 2021, it became clear that more attention should be given to further elaborating and explaining the definitions and quality criteria the annual reports should meet.

2 For users of new products and medicines prepared from human tissue such as ATMPs, TRIP should, in consultation with IGJ, Lareb and VWS, draw up unambiguous and clear instructions for the criteria and routes for reporting adverse events and reactions. (Recommendation in the 2020 TRIP Biovigilance Report)
Development: Discussions with IGJ, Lareb and VWS started in early 2022.

https://www.tripnet.nl/wp-content/uploads/2023/08/TRIPJaarrapportBio2021EN-Final.pdf

France: Rapport annuel 2022 sur le dispositif de biovigilance Organes, Tissus, Cellules et Lait maternel à usage thérapeutique

VI. Perspectives pour les années 2023 et 2024

Pour les années 2023 et 2024 les perspectives du Pôle Sécurité-Qualité dans le domaine de la biovigilance sont notamment les suivantes :

[1] Développer et mettre à disposition des professionnels un dispositif de surveillance en temps quasi réel des effets indésirables considérés comme attendus et critiques au regard des référentiels de risque notamment par la surveillance des données du SNDS ; [2] Initier une surveillance du SNDS pour les organes sur les principales complications attendues

[3] Poursuivre le développement de la formation sur la biovigilance : ateliers thématiques en groupes plus restreints ;

[4] Etendre l'infoservice aux agences partenaires ou à d'autres groupes préalablement identifiés ;

[5] Finaliser l'élaboration de la cartographie de diffusion des alertes sanitaires et des recommandations à destination des professionnels sur l'ensemble des domaines de l'Agence ;

[6] Poursuivre la diffusion des bulletins d'informations BIO'VIGILANCES avec une fréquence idéale de deux numéros dans l'année ; [7] Poursuivre l'élaboration de la nouvelle application de télédéclaration des événements de vigilance (AMP vigilance et biovigilance) [8] Développer le concept de surveillance des effets indésirables attendus au sein des Etats membres de la communauté européenne et participer à la révision de la Directive européenne 2004/23/CE ;

[9] Poursuivre la participation aux travaux européens sur la vigilance, les tissus, cellules et les organes ;

[10]Poursuivre la réflexion sur un modèle de RMM adaptée à la biovigilance ;

[11]Poursuivre la réflexion sur l'automatisation du suivi des pertes de greffons ;

[12]Initier la création d'un groupe de travail pour la révision du guide sur les contaminations bactériologiques et fongiques lors des prélèvements d'organes et initier une réflexion sur l'amélioration/harmonisation de la prise charge prophylactique et thérapeutique des receveurs

https://www.agence-biomedecine.fr/IMG/pdf/rapport_biovigilance_2022.pdf

Key SHOT messages

- **Safe staffing:** Clinical and laboratory teams can function optimally only if adequately staffed and well-resourced. Staffing challenges in both clinical and laboratory areas are commonly cited as contributory in transfusion incidents and must be addressed urgently. Adequate numbers of appropriately trained staff must be available to ensure safe transfusions; there should be contingency planning for staffing levels below a minimum level and for times of high workload
- **Well-resourced systems:** Healthcare leaders and management must ensure that staff have access to the correct IT equipment which is fit for purpose. Adequate financial resources are a must for safe and effective functioning of teams
- **Addressing knowledge gaps, cognitive biases, and holistic training:** Transfusion training with a thorough and relevant knowledge base in transfusion to all clinical and laboratory staff along with training in patient safety principles, understanding human factors and quality improvement approaches are essential. It is important that staff understand how cognitive biases contribute to poor decision-making so that these can be mitigated appropriately
- **Patient safety culture:** Fostering a strong and effective safety culture that is 'just and learning' is vital to ensure a reduction in transfusion incidents and errors, thus directly improving patient safety
- **Learning from near misses:** Reporting and investigating near misses helps identify and control risks before actual harm occurs, providing valuable opportunities to improve transfusion safety
- **Shared care:** Clear, timely and comprehensive communication between all teams and hospitals involved in patient care is vital in ensuring patient safety. Robust and transparent processes must be in place for safe and effective transfer of information at all points in the patient-care pathway

SHOT Serious Hazards of Transfusion

2022 Annual SHOT Report – Supplementary information

Chapter 5: Acknowledging Continuing Excellence in Transfusion (ACE)

Additional case studies not included in the main 2022 Annual SHOT Report.

ACE case studies

Case 5.3: Service improvements expedited by introduction of 'Improvement and Development Lead' role

A lead BMS was employed as an 'Improvement and Development Lead' by a large foundation Trust to drive transformation and innovation. Service change was traditionally led by the transfusion managers who have many conflicting priorities and improvements, or developments were sometimes side-tracked for more immediate issues. The role was created to give the freedom from the routine roles of a transfusion manager to concentrate on change and expedited many of the service improvements and transformational needs of the service. In this Trust, change is now planned in line with best practice and managed to a high level. The Trust has written an article on the role for 'The Biomedical Scientist' magazine to share successes and learning with others.

Case 5.4: Good practice by laboratory staff triggers lifesaving treatment of baby

A BMS identified a mixed field result within a group and screen sample for a pregnant patient. This prompted the BMS to contact the clinical area to request an additional sample and highlight the risk of large fetomaternal haemorrhage. The patient was brought back into hospital for cardiotocography, the results of which were suspicious and resulted in early delivery of the baby. The baby was very anaemic and required red cell transfusion. If this had not been noted by the BMS and escalated, the mother may not have been reassessed and the baby not successfully delivered. A 'Greatix' report was raised within the organisation to acknowledge the prompt action of the BMS who has also received acknowledgment throughout the pathology network.

2022 Annual SHOT Report – Supplementary information

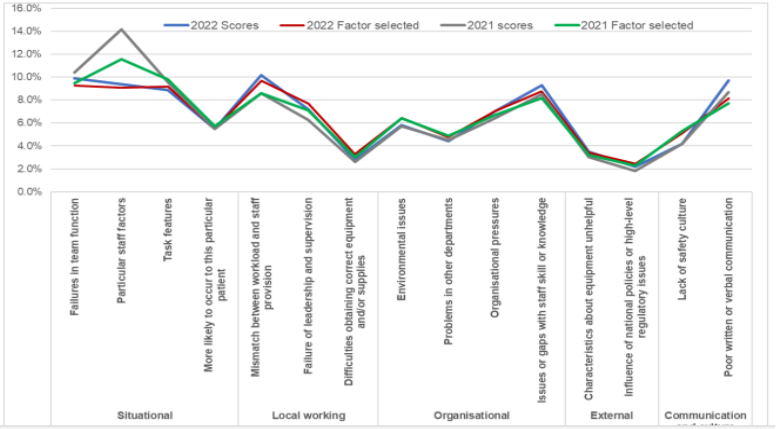
Chapter 7: Human Factors and Ergonomics in SHOT Error Incidents

Additional analysis not included in the main 2022 Annual SHOT Report.

Human factors scoring

Figure 7.4 compares percentage scores assigned to each factor in 2022 (blue) and 2021 (grey) plus percentages of each factor being assigned at all in 2022 (red) and 2021 (green). This demonstrates that irrespective of scoring, the percentages of each factor are almost identical, particularly in 2022. This justifies the decision taken by SHOT to remove the need for scoring factors in HFIT since January 2023. The only variance seen in Figure 7.4 is at a question related to 'particular staff factors' under the situational section, which in 2021 was 14.2% of the scores given compared to 11.6% of that factor being selected at all. Having identified that anomaly last year, the question was changed to suggest system-level staff factors, not individual issues. This has had a demonstrable effect on the responses to that question this year with the comparable percentages being 9.4% of scores given and 9.1% of that factor being selected, hence showing both a flattening of the curve at that data point and a much closer match of the respective percentages.

Figure 7.4: 2022 and 2021 comparison of scores assigned to each contributory factor and if factor identified at all



Accreditation Canada - ORGAN AND TISSUE TRANSPLANT STANDARDS

Safety

! 21.7 Timely investigations and notifications are conducted following patient safety incidents and adverse reactions.

Guidelines

If the patient safety incident or adverse reaction relates to the donated organs or tissues, the donor identification code is identified and communicated to the donation centre so that the donation centre can quarantine other implicated organs and tissues and notify the donation team.

Safety

! 21.8 Patient safety incidents and adverse reactions related to donated organs or tissues are investigated and reported to the donation program or tissue supplier as soon as they occur.

Guidelines

All patient safety incidents and adverse reactions related to donated organs and tissues are investigated.

This criterion reflects Health Canada's Regulations for the Safety of Human Cells, Tissues and Organs for Transplantation.

The team delivering transplant services is responsible for implementing the organization's monitoring and reporting processes. In addition, information about patient safety incidents and adverse reactions related to transplant is tracked and reported in a manner that is consistent with others across the organization so that the information may be summarized at the organization level.

Safety

! 21.9 Patient safety incidents are analyzed to help prevent recurrence and make improvements, with input from clients and families.

Guidelines

Analyzing patient safety incidents includes determining the contributing factors, taking action to prevent the same situation from recurring, and monitoring the effectiveness of those actions. Organizations use this information when developing strategies to proactively anticipate and address risks to client and team safety.

The Canadian Patient Safety Institute offers a framework for incident management. It provides an in-depth description of the process of analyzing and managing patient safety incidents. An online Incident Analysis Learning Program series is available to assist organizations to apply the principles of incident analysis at www.patientsafetyinstitute.ca/.

22.0 Indicator data is collected and used to guide quality improvement activities.

22.1 Information and feedback is collected about the quality of services to guide quality improvement initiatives, with input from clients and families, team members, and partners.

Guidelines

Information and feedback is collected in a consistent manner from key stakeholders about the quality of services. Feedback can take the form of client and family satisfaction or experience data, complaints, indicators, outcomes, scorecards, incident analysis information, and financial reports. It may be gathered by a variety of methods, including surveys, focus groups, interviews, meetings, or records of complaints.

22.2 As part of the quality improvement program, every transplant case is reviewed to identify opportunities for improvement.

Guidelines

Reviewing every transplant case may include reviewing the transplant process or surgical report.

22.9 There is a process to regularly collect indicator data and track progress.

Guidelines

How indicator data will be collected and how often is determined. Regularly collecting data allows the team to track its progress and understand the normal variation of values.

22.10 Indicator data is regularly analyzed to determine the effectiveness of the quality improvement activities.

Guidelines

The team compares the intended and actual effects of its quality improvement activities, and, if the objective has not been achieved, adjusts its actions accordingly to meet the objective.

Analyzing data helps identify trends and may reveal areas that could be considered for future quality improvement initiatives. Indicator data can be displayed in a run chart or control chart, both of which are valid means of data analysis.

Safer Healthcare Now! offers Patient Safety Metrics, a web-based tool where organizations can submit data on various interventions, analyze results, and generate reports.

https://physicians.nshealth.ca/sites/default/files/2022-09/Organ%20and%20Tissue%20Transplant%20Standards%20v.14.pdf

Thank you for your attention

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