# VIGILANCE: LESSONS LEARNED FROM THE TISSUE AND CELL EXPERIENCE IN THE EUROPEAN UNION. PART 1: REPORTING AND COMMUNICATION

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**Summary** - SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) was a project co-funded by the European Union Public Health Programme. The project ran from March 2010 to February 2013. Its scope included tissues and cells for transplantation and gametes and embryos for assisted reproduction. The broad aim of the project was to support European Union Member States in the establishment of effective vigilance and surveillance (V&S) systems for tissues and cells used for human applications, including transplantation and assisted reproduction, ensuring the adoption of a common approach that would allow sharing of data and didactic information for the improvement of safety and quality. To achieve this broad objective, a number of key activities were carried out, including the development of guidance to EU Competent Authorities on the investigation and management of severe adverse reactions and events associated with tissues and cells for transplantation and for assisted reproduction. Equivalent guidance was developed for professionals in European Union hospitals and clinics who apply human tissues and cells to their patients. The latter guidance addressed the roles and responsibilities of clinical users in relation to supporting traceability and vigilance of tissues and cells for transplantation and assisted reproduction. This article, and its sister article (due to in March 2014), describe the key issues that arose and the conclusions reached in the development of these two guidance documents. This article describes the key points of guidance developed on reporting and communication of serious adverse events and reactions.

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## Introduction

Since the adoption of Directive 2004/23/EC (1), with its requirement for the implementation of national systems of vigilance for tissues and cells, much has been achieved and much has been learned at the European Union (EU) level. The generic requirements in place in that Directive, and the more detailed requirements specified in the technical Directive 2006/86/EC (2) adopted two years later, owe a great deal to the previous experience of vigilance of blood and blood products. The projects funded by the European Commission (EC) to support Member States (MS) in the implementation of the Directives have also drawn on the 20 year history of haemovigilance internationally and their outputs may be of benefit for the future development of organ vigilance at national and EU level, following the adoption of Directive 2010/53/EU (3) in 2010.

When the tissue and cell directives were first adopted, few EU MS had well developed vigilance systems in place. The most important exception at that time was France which had a well developed system with vigilance contact persons in hospitals, tasked with encouraging and co-ordinating reporting and with supporting investigations. The early development of vigilance systems at a national level was demonstrated by a survey conducted in the EUSTITE project (European Union Standards and Training in the Inspection of Tissue Establishments) (4) and the rapid rate of change was shown by a subsequent update survey carried out in a project entitled Vigilance and Surveillance of Substances of Human Origin project (SOHO V&S). These two projects, supported by co-funding from the Public Health Programme of the European Community, have provided important opportunities for EU MS to work together to agree common definitions and common approaches to reporting criteria and to the evaluation of adverse events and reactions reported at national level. EUSTITE developed and piloted tools for severity, imputability and impact assessment, as well as criteria for the reporting of serious adverse events (SAE) where no donor or patient has been harmed (5) and the SOHO V&S project focused entirely on specific vigilance topics that had been identified as requiring a common EU approach.

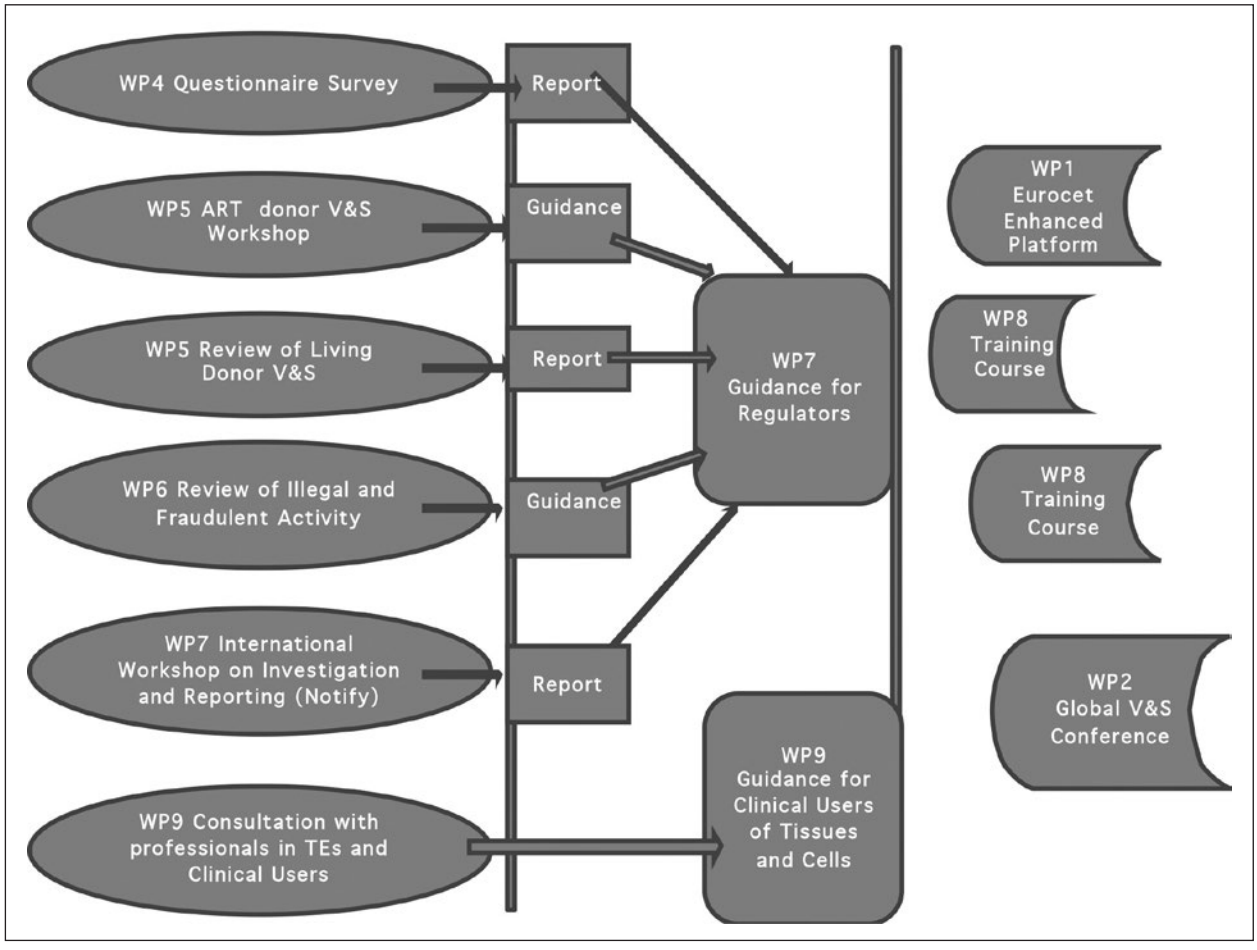


FIGURE 1 - Project activity outline structure.

The SOHO V&S project ran from March 2010 to February 2013. The scope addressed tissues and cells for transplantation and gametes and embryos for assisted reproduction. The broad aim of the project was to support EU MS in the establishment of effective vigilance and surveillance (V&S) systems for tissues and cells used for human applications, including transplantation and assisted reproduction, ensuring the adoption of a common approach that would allow sharing of data and didactic information for the improvement of safety and quality. Within the broad objective of the project, a number of key objectives were identified including the provision of guidance to EU Competent Authorities (CAs) on the investigation and management of severe adverse reactions and events (SARE) associated with tissues and cells for transplantation and for assisted reproduction; equivalent guidance was developed for professionals in EU hospitals and clinics who apply human tissues and cells to their patients. The latter guidance addressed the roles and responsibilities of clinical users in relation to supporting traceability and vigilance of tissues and cells for transplantation and assisted reproduction. This paper, and its sister paper, describe the key issues that arose and the conclusions reached in the development of these two guidance documents.

The project also addressed training of vigilance officers, providing successful e-learning and residential training for officers from across the EU, and developed a report and guidance for EU Competent Authorities on the detection and investigation of illegal and fraudulent activity (IFA) in the field of tissues and cells. Outcomes of these activities are not described in this paper as they have been or will be reported elsewhere. An outline structure of the full project activities is shown in Figure 1.

## Development of vigilance guidelines - methodology

The SOHO V&S project applied a number of different methods to identify key principles of good vigilance practice for inclusion in the guidelines. One important method was the use of international interactive workshops, where expert professionals in the fields under consideration met with regulators from many countries to explore a specific vigilance-related subject. One of these focused on assisted reproduction technology (ART) specialist topics and facilitated the development of a number of consensus principles which the drafting group then took forward to develop guidance. Another addressed approaches to vigilance investigation and communication. In this case, the participation of WHO in the working group facilitated a collaborative effort with a broad group of experts from within and outside the EU and the organisation of a three-day global conference where vigilance information and data from around the world were shared and analysed (the Notify Bologna meeting). The latter initiative was published as a report (6) and resulted in the construction of a public global database to support communication of didactic vigilance information, with the participation of over 100 experts in transplantation and assisted reproduction together with regulators of those fields (7). The report and database provided critical input for the SOHO V&S drafting groups that were developing guidance for EU CAs and for health professionals in hospitals and clinics that apply these health products of an exceptional nature.

Consultation on drafts with experts and regulators was widely used as a methodology for improving draft guidance texts. Guidance document drafts were distributed to all tissue and cell CAs, and to collaborating experts across the EU and beyond it, who were asked to provide structured comments with proposals for improvements to texts. The communication and investigation guidance was also the subject of focus group consultations in Germany, Spain and the UK where key invited experts and vigilance officers considered key questions identified by the drafting group to help improve and validate the guidance. Targeted consultations with substance-specific professional societies were used to enrich the draft texts for the guidance of clinical users.

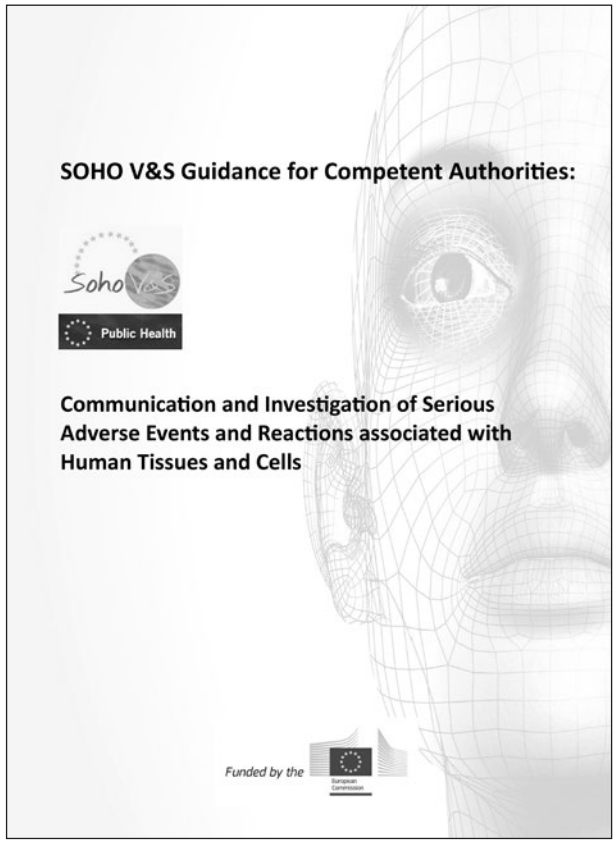


FIGURE 2 - Vigilance communication and investigation guidance for competent authorities.

## SOHO V&S vigilance guidance documents

The guidance for vigilance in the field of ART is the first of its kind, exploring adverse incidents in this field and providing recommendations on reporting and evaluation of these incidents in the EU. The communication and investigation guidance has been printed as a booklet, incorporating the ART guidance, and provided to all MS CAs (Figure 2).

This text provides support to competent authority vigilance officers in knowing what to require when they review an investigation of a suspected disease transmission or an operational error that had an important negative impact that can be prevented in future if the root cause is well established.

The SOHO V&S guidance for clinical units that apply these medical products of an exceptional nature (Figure 3) has been developed with the help of professionals from those organisations liaising directly with clinical users. It has been provided in electronic format to EU competent authorities so that they can translate, adapt and distribute them in their MS, promoting vigilance at this critical level.

The following summarises some of the key concepts incorporated in the guidance documents developed to support tissue and cell vigilance in the EU, with particular emphasis on SARE detection and communication.

## SARE detection

The key to successful vigilance is the engagement of clinicians who should always be suspicious that an unexpected and undesired response in a recipient might have some connection with the tissues or cells they have applied to their patient. Clinicians need to be aware that the implications of an adverse reaction in their recipient may be far-reaching if it was caused, for example, by an error in testing, contamination during processing or if it originated from a donor that provided tissues, or organs, to many recipients. Raising the awareness of clinical users is an important and challenging task given that, particularly for tissues, they do not form a homogenous professional group but include a very wide range of specialities from orthopaedic surgeons and dentists to cardiac and plastic surgeons.

In contrast to the field of tissue transplantation, the field of haematopoietic stem cell transplantation has been very successful in engaging clinical users via their international

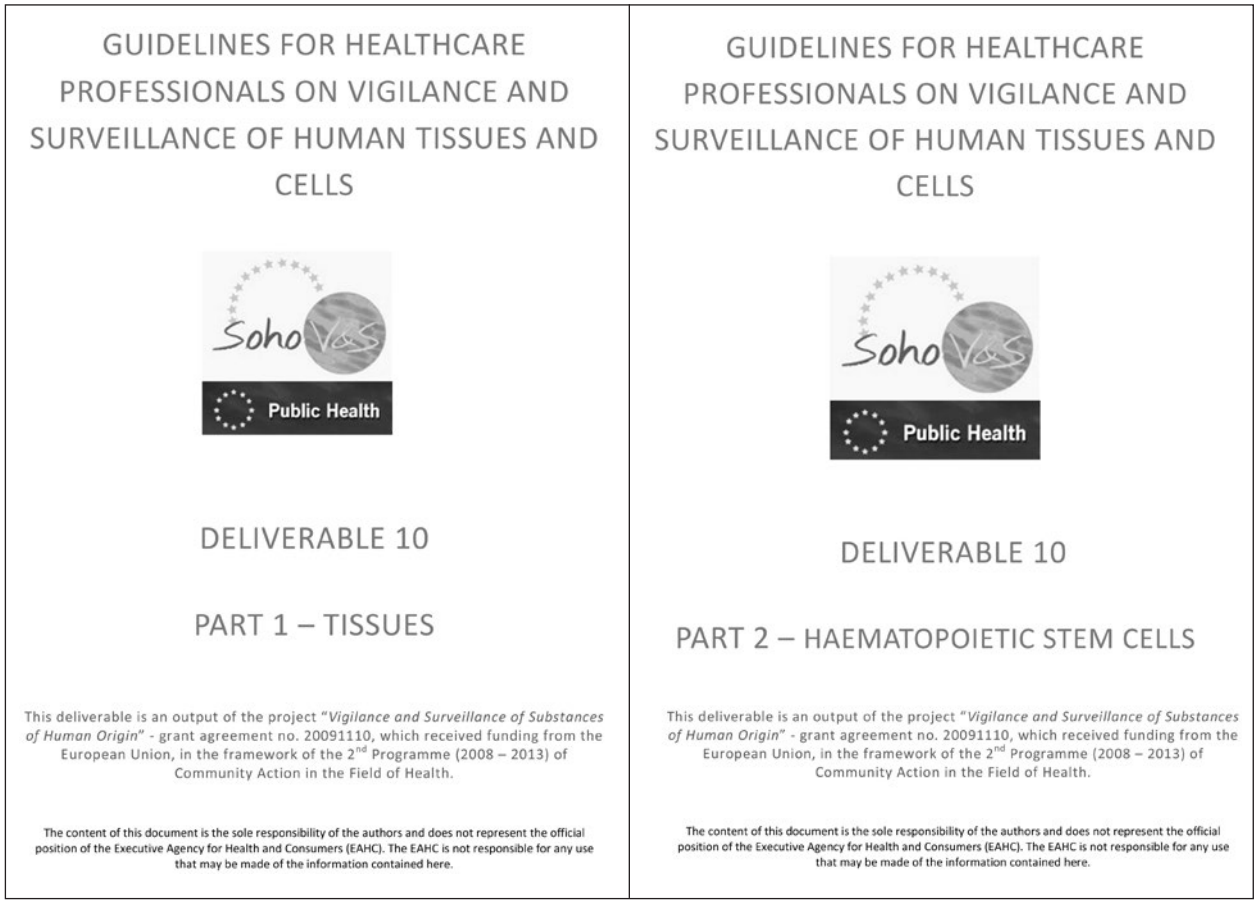


FIGURE 3 - Guidelines for healthcare professionals on vigilance and surveillance of human tissues and cells.

vigilance reporting system S(P)EAR (8) managed by the World Marrow Donors Association. It is an excellent example of how international collaboration within a specific field of cell transplantation can achieve the benefits of analysing accumulated data for the purposes of safety monitoring and improvement. The Eye Bank Association of America is another example where professionals have been supporting the detection, reporting and sharing of vigilance information for many years. Their database is a unique resource for estimating the risks associated with cornea transplantation (9).

For clinicians to participate in active detection and reporting, they need to see the benefits of their efforts. In particular they should see two key outcomes of their notifications: firstly, there should be a thorough and complete investigation led by the tissue establishment (TE) that provided the tissues or cells so that the real cause of the problem is identified and, secondly, there should be regular feedback of consolidated vigilance reporting data that will help them to learn from adverse outcomes elsewhere. The SOHO V&S project and the Notify Library have both provided practical tools for improving vigilance investigation and communication. Good investigations and easily accessible didactic information from vigilance should become increasingly evident to clinicians, providing motivation for their active participation in adverse outcome detection and reporting.

Tissue establishments play a key role in promoting SARE detection and notification among their clinical users. Indeed, Directive 2006/86/EC (2) specifies their responsibilities for informing clinical users on how to report adverse outcomes. In many ways, TEs are the key to promoting detection and reporting among clinical users as they have direct communication lines with the heterogeneous and widely dispersed group of clinicians who are using so many different kinds of tissue and cell products.

The SOHO V&S guidelines for healthcare professionals are divided into two parts, one for tissues and one for haematopoietic stem cells. The documents go beyond guidance that is strictly related to vigilance reporting, addressing many other safety and quality responsibilities of clinical users or their organisations, including ordering tissues or cells from appropriately authorised TEs, handling and storage of received substances according to the instructions provided by TEs and maintenance of the traceability chain to the patient. The group that developed the texts drew on previous work carried out for hospitals transplanting tissues in the United States (10).

## Reporting - to competent authorities

### The EUSTITE tools

According to the EU tissue and cell directives, only those adverse reactions linked to the quality or safety of the tissues or cells applied, or to the donation process should be reported nationally and only if they are serious in nature. The EUSTITE tools provided a common approach to evaluation of severity and imputability (5) and they are

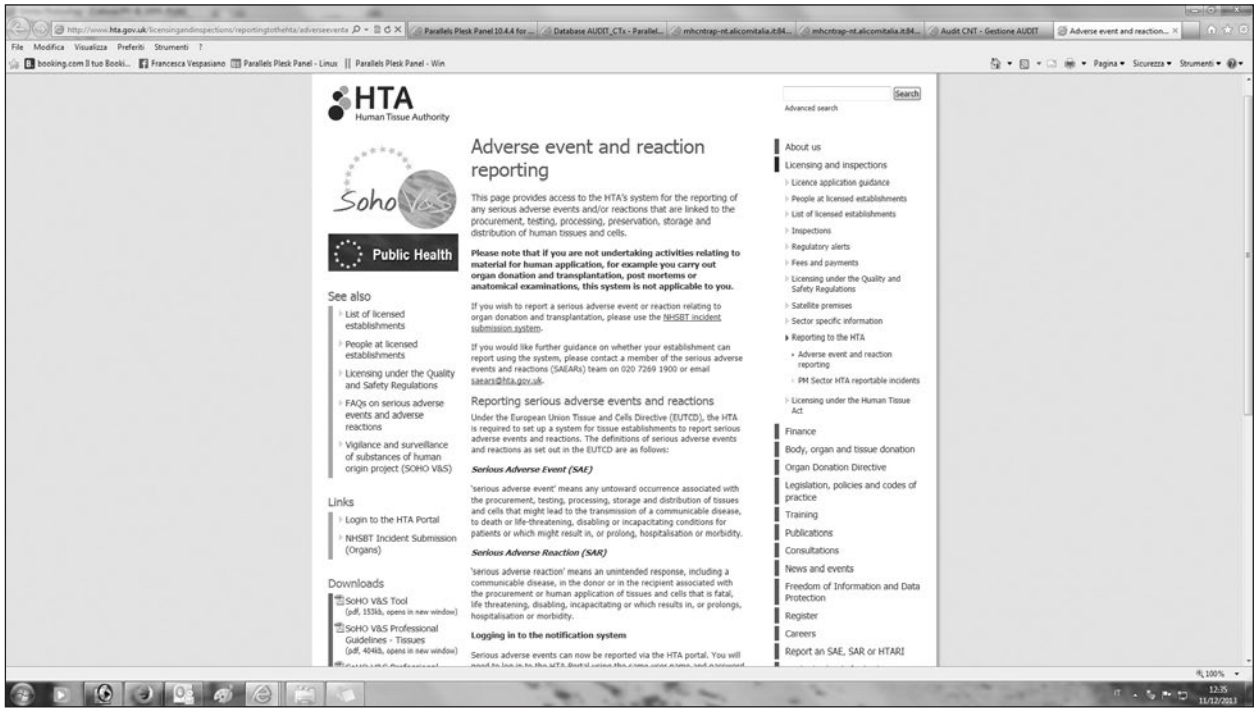


FIGURE 4 - Example of a competent authority that disseminates the vigilance tools.

now incorporated in the EC guidance to CAs and they are reiterated in the SOHO V&S guidance documents. They have been widely adopted by individual MS who provide them to their tissue establishments to promote common approaches to reporting (as an example, see Figure 4).

They were not, however, easily applicable to the field of ART. To address this, a working group co-ordinated by the Agence de la Biomédicine in France and including both professionals from the European Society for Human Reproduction and Embryology (ESHRE) and a number of CA representatives focused specifically on this field, adapting the EUSTITE tools and developing other ART-specific vigilance principles (11).

### Living donors

The SOHO V&S project dedicated a specific effort to reviewing the area of living donor vigilance and making recommendations. Programmes of allogeneic tissue and cell transplantation rely entirely on the good will of donors and donor families; without them, there would be no transplantation. Living donor care and protection is of fundamental importance both from an ethical perspective and to ensure the continued willingness of society to donate for the benefit of others. Allogeneic living donors should be well informed of the risks they take when agreeing to donate and the collation of donor reactions provides concrete information on which this risk evaluation can be based. As the numbers of reactions are relatively low, the data are more valuable when consolidated from a wide geographic area.

Currently, the EU Directives require the reporting of serious adverse reactions in donors only when the quality or safety of the tissues or cells donated has been compromised. Considerable benefit can be accrued from gathering data on adverse donor reactions on a national or EU-wide basis, even where the safety or quality of the tissue or cells was not compromised by the adverse reaction, so that potential donors can be better informed and systems can be improved.

As evident from the NOTIFY exercise, the group of allogeneic living donors, non-ART, exposed to the greatest risk is the HPC donor group, both bone marrow and peripheral blood stem cells. It is noted that the World Marrow Donors Association (WMDA) already collects, records and publishes all cases of serious adverse reactions in allogeneic, unrelated donors reported by its members; indeed almost all of the cases included in the NOTIFY collection were provided by this registry (Serious Events and Adverse Reactions, SEAR). Worldwide, unrelated bone marrow donor registries must participate in this vigilance programme, sending quarterly reports, to maintain their accreditation. The results are made publicly available.

In the light of this well-developed programme, the added value of reporting donor reactions to CAs in the EU, where they do not impact on the safety or quality of the donated cells, in unrelated HPC donors, might be questioned. The benefits of reporting these reactions to CAs would be to include also the related allogeneic donors (although this extension is already planned by WMDA) and the autologous donor reactions. It is clear that the latter cases, none of which were included in the NOTIFY collection, do not impact on willingness to donate but they could provide important information for safety improvements in allogeneic programmes.

Donors of tissues removed for therapeutic purposes, such as living femoral head donors, are not normally exposed to additional risk by agreeing to donate. In some countries these tissues are referred to as "surgical residue". No cases of harm to such donors were recorded in the NOTIFY process. Some reactions associated with tissue removal for autologous transplantation were recorded. As these tissues are not normally donated by living donors in the allogeneic setting (apart from the different circumstance of surgical residue), reactions in this setting do not impact on the willingness of donors to donate and they do not provide information for improving allogeneic donor safety. For these reasons, reactions associated with autologous tissue removal should be reported and managed within the hospital patient safety system and not necessarily reported to the tissue and cell vigilance system.

In the allogeneic donor setting (related or unrelated) donor reactions should be reported, collated and the information made available publicly, either by the vigilance registries or by the authorities, regardless of the impact on the quality and safety of the donated cells. According to the global organisation World Bone Marrow Transplantation (WBMT), donors of bone marrow and peripheral blood stem cells should be followed up for at least 10 years, with follow-up at 1, 5 and 10 years, to ensure that long-term reactions such as haematologic and non-haematologic malignancy or autoimmune disease are detected and survival monitored. In general, duplicate reporting should be avoided. Thus, where a competent authority requests that these cases be reported, consideration should be given to CAs requesting a copy of the S(P)EAR report rather than asking for a duplicate report in a different format.

It is recommended that in any future revisions of the EU tissues and cells Directives, consideration should aim to make the reporting of all donor reactions mandatory as already required in some MS, regardless of any impact on the quality or safety of the donation. Where a donor reaction is caused by a medical device or a drug, for example, for stimulating the release of stem cells to the peripheral blood, it should be reported through a relevant vigilance system; in any case, the vigilance systems should communicate with each other to ensure that an overview of such reactions is maintained.

## Vigilance communication

Effective vigilance is important for three reasons. Firstly, it allows immediate corrective and preventive actions to be taken to ensure that no further harm is caused by the specific incident and, secondly, it allows lessons to be learned by the broad professional field with resulting improvements in safety and quality generally. Thirdly, vigilance is an important element of public transparency, without which public trust in human tissues and cell donation programmes cannot be maintained. These objectives can only be achieved if there is effective communication, for rapid action where necessary, for learning and system improvement among professionals and for greater public transparency.

### Vigilance communication for rapid action

There are situations where information should be reported and communicated rapidly in order to protect donors or recipients. The types of threats that should be communicated rapidly include:

- quality and safety defects of specific tissues/cells that have been distributed for human application;
- detection of illegal and fraudulent activities in the field of tissues and cells intended for human application;
- development of rapid/significant epidemiological situations (e.g. disease outbreaks) which may have cross-border implications in the field of tissues and cells intended for human application;
- notifications (recalls, preventive measures, advice, etc.) from other related healthcare sectors (e.g. medical devices, blood and blood products, medicinal products, organs) with potential consequences on the quality and safety of tissues and cells intended for human application.

The EU Rapid Alert Tissues Cells (RATC) system ensures the secure transmission of information between CAs of the EU and the European Economic Area and the EC when urgent remedial or precautionary action is needed due to a serious public health threat. The procedure is supported by an electronic communication tool hosted within the secure area of the EC's internet platform. The system has been live since February 2013. All EU CAs have nominated individuals who have access to this platform where they can launch a Rapid Alert, respond to a Rapid Alert launched by another MS, notify further MS of a Rapid Alert if they consider it necessary and contribute to the final reports of individual Rapid Alerts as appropriate. This rapid exchange of information allows all the MS to verify immediately whether they are affected by a problem initially raised by a MS or the EC, and for which a precautionary/corrective measure should be implemented. The system has proven an effective tool and is likely to be replicated for rapid communication regarding other human substances in the EU.

### Vigilance communication for learning

Tissue establishments and clinical users who have detected and investigated a specific SARE are encouraged to publish the results of their investigations in clinical and scientific journals where there are useful lessons that could prevent recurrence. Publication of adverse outcomes, even when they resulted from avoidable error, increases transparency and facilitates improvements in practice on a wide scale. The publication of sentinel events, such as the transmission of HIV to organ and tissue recipients by a donor in the seroconversion window period (12) or the transmission of *Clostridium* infection to multiple tendon recipients by tissues for which the sterilisation process had not been properly validated (13), has provided invaluable evidence for the need for practice improvements to increase safety.

CAs should summarise the reports they receive and make this information available to the TE and clinical user community, for example on their website. The European consolidated annual reports received from the EC should be shared with the TEs. These reports provide an opportunity to monitor trends so that evidence of increasing risk or improving practice can be highlighted. The process of collecting this information annually has been challenging, particularly in relation to the definition of tissue and cell unit definitions, important to provide denominators and because of differences in the interpretation of reporting criteria. Experts from the SOHO V&S project supported the European Commission in the development of the Annual SARE reporting process and in 2013 the first report was published for SARE notified at a national level in 2011 and reported to the European in 2012 (14). As this process becomes better defined and more complete, the reports will become a valuable source of information for high level trending of adverse incidents in the field in the 28 Member States of the EU.

The Notify Library (www.notifylibrary.org) is hosted by the Italian National Transplant Centre on behalf of WHO and it contains over 1,800 bibliographic references related to adverse outcomes in organ, tissue and cell applications, together with guidance notes on alerting symptoms and methods of confirmation, by type of reaction. New cases are reviewed by experts for inclusion in the searchable database. This communication instrument is the result of a large international collaboration in which the SOHO V&S project participated. It aims to improve the sharing of lessons learned from vigilance, on a global scale (7).

### Vigilance communication for transparency

The general public is entitled to be informed about the risks associated with donation, transplantation and assisted reproduction and the quality of the services provided should be open to scrutiny. Ultimately, public confidence is key to ensuring the continued success of tissue and cell

donation and transplantation programmes. Consolidated vigilance reports provide a valuable parameter for allowing potential donors and recipients to evaluate risk and should be communicated in a comprehensible and easily accessible manner. The SOHO V&S project worked with the Eurocet team (www.eurocet.org) to develop a new area of their publicly accessible website where vigilance related information could be made available to any member of the public who is interested in following this topic.

Although openness and transparency are key elements of effective vigilance, CAs and professionals in the field should manage communication with the media attentively, so that rare negative outcomes are not presented in a sensational manner. Negative outcomes should always be communicated in the context of the numbers of procedures carried out and the numbers of tissues or cells transplanted with positive results. This balance is essential to ensuring the continued support of the public for donation of tissues and cells.

## Discussion

It is hoped that the developing organ vigilance systems at a European level will be able to benefit from the experience of the tissue and cell field. Certainly, this field has learned a great deal from the experience of haemovigilance. The history of haemovigilance has recently been summarised and published by pioneers in that field (15). The authors highlighted some of the key results of the programmes that have been put in place to monitor adverse events and reactions in blood transfusion. They noted that haemovigilance, while highlighting undesirable errors and disease transmissions, has also shown that blood transfusion is relatively safe compared with the use of medicinal drugs and that, at least in Europe, blood components have reached a high safety standard. Nonetheless, some adverse reactions are not avoidable and have to be considered an inherent risk of blood transfusion. The authors note that it is known that most adverse reactions in blood transfusion today occur in the hospital and are preventable incidents caused by clerical errors. The very important contribution of international collaboration was highlighted by the authors who also pointed out that individuals given roles in haemovigilance systems often take on other roles aimed at improving the quality and safety of blood transfusion, such as the promotion of appropriate use. They suggested that haemovigilance systems will also be of benefit for vigilance and surveillance of other human products such as cells, tissues and organs. Many of the key principles that these authors highlight for haemovigilance are echoed already in the early experience of implementing vigilance for tissues and cells in the EU.

The EU projects that have worked on tissue and cell vigilance have built strong links with developing tissue and cell vigilance in other parts of the world, particularly the USA where a number of recent initiatives aim to improve the potential for learning and for increasing the safety of tissue and cell donation and transplantation through vigilance (16).

In conclusion, a number of key conclusions can be drawn from the EU experience to date.

**Definitions**: all of the initiatives on this topic in the EU, whether within EU-funded projects or managed directly by the European Commission, have focused effort on agreeing key definitions and terms. This is fundamental to effective sharing of information and data and to achieving the full potential benefits of vigilance, in terms of systems improvement. The definitions developed within the EU, particularly those for SAR and SAE have been widely adopted, including by the Notify Library, in a global context. The EUSTITE vigilance tools have been widely used and adapted in the EU and provide a basis for common evaluation of SARE with respect to severity, imputability and impact.

**Engagement of clinical users**: without the active participation of clinical users there can be no effective vigilance. This is more challenging for tissues than it is for organs, haematopoietic stem cells or blood, where the clinical user communities are more clearly defined and more homogenous. Raising the awareness of tissue users regarding their critical role in vigilance detection and reporting is a huge challenge that will take time and effort. At the same time, they should appreciate the important role of the hospital in maintaining the quality and traceability chain, particularly important in the light of the evidence in haemovigilance that the most significant risks appear at the user hospital.

**"No blame" culture**: reporting adverse reactions or events should not be associated with punishment. However, hiding errors or transmissions should be a cause for disciplinary action. Achieving a "no blame" culture will result in greater participation by all those involved and more effective vigilance systems.

**Thorough investigation**: if adverse events and reactions are not followed by good and thorough investigations, important opportunities for prevention of recurrence can be lost. Time and effort should be dedicated to working in multi-skilled teams to establish the real causes of adverse outcomes. SOHO V&S Guidance on vigilance investigation will be described in a sister article in the next issue.

**Reliable denominators**: using vigilance to demonstrate the level of safety and risk requires reliable denominators of activity. This has proved challenging in the EU where the approach to gathering and describing activity data has varied from country to country. The EC annual reporting activity has contributed to harmonizing the description of activity levels and cumulative vigilance information is now beginning to emerge.

**Vigilance communication for increasing safety**: reporting of SARE, with rapid communication of information when necessary, can bring overall improvements to systems, allowing preventive and corrective actions to be taken and increasing the safety of tissues and cells for other patients.
**Vigilance communication for learning**: information sharing globally, and across medical products of human origin, will optimize the degree to which lessons learned through vigilance can result in improvements in safety and quality. The Notify Library, where vigilance incidents across the spectrum from organs to tissues, cells and gametes and embryos are described, is an example that demonstrates the high degree to which risk, investigation methodology and communication principles are common in these different clinical fields.

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**Disclaimer**

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## References

1. Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF
2. Directive 2006/86/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, available at http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf
3. Directive 2010/53/EC on standards of quality and safety of human organs intended for transplantation, available at http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_directive_en.pdf
4. Alvarez M., Garrido G., Fehily D., Delvecchio C., Nanni Costa A., Matesanz R.: Tissue and cell inspection systems in Europe: a EUSTITE survey. *Organs, Tissues & Cells*, 2008; **2**:87-89.
5. Fehily D., Sullivan S., Noel L., Harkin D. *et al*.: Improving vigilance and surveillance for tissues and cells in the European Union: EUSTITE, SOHO V&S and Project NOTIFY. *Organs, Tissues & Cells*, 2012; **15**(2):85-95.
6. NOTIFY. Exploring vigilance notification for organs, tissues and cells. *Organs Tissues & Cells*, 2011; **14**(3):Suppl.
7. Fehily D., Strong D.M., Minutoli D., Chatzixiros E., Araya H., Noel L., Nanni Costa A.: Sharing vigilance experience and knowledge globally: a preliminary overview of the Notify Library. *Organs, Tissues & Cells*, 2013; **16**(2):117-125.
8. SEAR/SPEAR vigilance system of the WMDA http://www.worldmarrow.org/index.php?id=525&type=1
9. Aldave A.J., DeMatteo J., Glasser D.B., Tu E.Y., Iliakis B., Nordlund M.L., Misko J., Verdier D.D., Yu F.: Report of the Eye Bank Association of America medical advisory board subcommittee on fungal infection after corneal transplantation. *Cornea*, 2013; **32**(2):149-154.
10. *Hospital tissue management: a practitioner's handbook*. 1st edition - published jointly by AABB, the American Association of Tissue Banks (AATB), and the Eye Bank Association of America (EBAA), 2008.
11. SOHO V&S Guidance on Vigilance in ART http://registry.eurocet.org/soho/index.php?option=com_phocadownload&view=file&id=50:deliverable-5-wp5-art-vigilance&Itemid=94
12. Simonds R.J., Holmberg S.D., Hurwitz R.L., Coleman T.R., Bottenfield S., Conley L.J. *et al*.: Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. *N Engl J Med*, 1992; **326**(11):726-732.
13. Kainer M.A., Linden J.V., Whaley D.N., Holmes H.T., Jarvis W.R., Jernigan D.B. *et al*.: Clostridium infections associated with musculoskeletal-tissue allografts. *N Engl J Med*, 2004; **350**(25):2564-2571.
14. European Commission Health and Consumers Directorate General: Summary of the 2011 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2010 to 31/12/2010) http://ec.europa.eu/health/blood_tissues_organs/key_documents/index_en.htm#anchor6
15. de Vries R.R., Faber J.C., Strengers P.F., Board of the International Haemovigilance Network: Haemovigilance: an effective tool for improving transfusion practice. *Vox Sang*, 2011; **100**(1):60-67.
16. Brubaker S.A., Fehily D.: Development of vigilance and surveillance systems. In: *Tissue and cell clinical use: an essential guide*. Eds. Warwick R.M., Brubaker S.A., Wiley-Blackwell, 2012.