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RECOMMENDATIONS ON THE VIGILANCE OF HUMAN ORGANS INTENDED FOR TRANSPLANTATION

Deliverable 10
(Part II)

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Deliverable 10 (Part II)

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I. INTRODUCTION

The development of a vigilance system (V-System) applied to organ donation and transplantation is a requirement of *Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation*, in force since the 26th of August, 2010¹. European Union (EU) Member States (MS) should transpose the provisions of this Directive into their national legislations within two years following such date.

Organ transplantation has become a consolidated therapy, which saves the life and improves the quality of life of about 100,000 patients yearly worldwide.² Consolidation of this therapy is the consequence of the excellent results achieved with all types of transplanted organs, both in terms of survival and quality of life. Nevertheless, the probability of occurrence of a harmful endpoint (risk) is present due to a potential deviation in the sophisticated chain which extends from donation to transplantation or due to the simple transfer of biologic material from one individual to another, as this implies a risk of disease transmission. This risk has to be seen under the perspective of a relatively low reported complication rate confronted with the great benefits provided by organ transplants and the universal challenge of organ shortage. Because of the scarcity of organs patients deteriorate or even die while waiting to be transplanted. It has been estimated that 12 EU patients die each day while on the waiting list for an organ transplant³. This almost unique feature of organ transplantation along with the time constraints of the organ donation and transplantation process, make it necessary in case of every organ offer that the clinician (and the patient) have to balance the risk of accepting an organ offer with a potential risk of diseases transmission against the risk derived from not proceeding with the transplantation (and thus the risk of clinical deterioration or even death of the recipient on the waiting list).

¹ Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation. European Union website. Available at url: http://europa.eu/legislation_summaries/public_health/threats_to_health. Last access: February 2011.

² 2010 Report of the Global Observatory on Donation and Transplantation. Global Observatory on Donation and Transplantation website. Available at: <http://www.transplant-observatory.org/Data%20Reports/2010%20Report%20final.pdf>. Last access: February 2011.

³ International figures on organ donation and transplantation-2009. Newsletter Transplant 2010;15. Organizacion Nacional de Trasplantes website. Available at url: <http://www.ont.es>. Last access: February 2011.

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Due to the need to allocate each organ to the most appropriate recipient within a territory, every time a donation occurs, each organ travels to a recipient, more or less far away from the donor and from other recipients transplanted with organs from the same donor. This also applies to tissues and cells obtained from that donor. This form of organization, specific to the donation and transplantation system, makes the involved community become a network in which every team (recovering, allocating or transplanting organs) is a node. One peculiarity of this network is that the teams involved in one donation share a group of factors (known or unknown) that might influence the results of transplantation and the appearance of Serious Adverse Events and/or Reactions (see below), regardless of the distance or the different health care system. In other words, patients far off from each other may be submitted to equal or similar risks as their transplanted organs come from the same donor. Team working is crucial: communicating to the other stakeholder/partners involved a health problem detected in one recipient would improve the diagnostic and therapeutic capacity of the teams treating the other recipients from the same donor. Therefore, establishing a system for systematic reporting and managing this information (including alerting other centers concerned), as well as connecting it with the system in place for tissues and cells, is absolutely necessary in this community.

In order to allow this communication to occur effectively and find the recipients wherever they are, it is essential to keep **traceability** of organs at all phases from donor to recipient (or disposal) and *vice versa*. Traceability is understood as the ability to locate all organs (as well as tissues and cells) along all phases from donation to transplantation (where they are and where they have been). This information must be securely stored in case a patient needs to be diagnosed, treated or followed-up. Ensuring traceability is also a requirement of *Directive 2010/53/EU*. The main objective of a Vigilance system is **PREVENTION (primary, secondary and tertiary)**. The immediate preventive action is on affected or potentially affected patients. However, there is an additional prevention strategy based on the concept of surveillance: the analysis of pooled data may provide indicators and information on stratification of the risks that might be very useful for future risk management and interpretation of the cases reported. In the field of organ donation and transplantation, pooled data analyses could ideally integrate **the systematic follow-up of recipients transplanted with organs from non-standard risk donors**, a safety management tool specifically recommended by EFRETOS as part of its registry of registries. This approach would broaden the possibilities in prevention. Another way to protect patients can derive from the interaction between national networks. Rapid transmission of European Public Health alerts, affecting organ safety, may allow local centers to consider low prevalence diseases when making a risk analysis.

Classically, **SURVEILLANCE IN PUBLIC HEALTH** is defined as the systematic and continuous collection, analysis, interpretation, and dissemination of health data, seeking to reduce morbidity and mortality and to

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improve the health of the population. Surveillance is based on a careful **VIGILANCE**.⁴ The system is based on several steps: **detection, reporting, assessment and management** of the case under study, **including alerting without delay** (Figure 1).

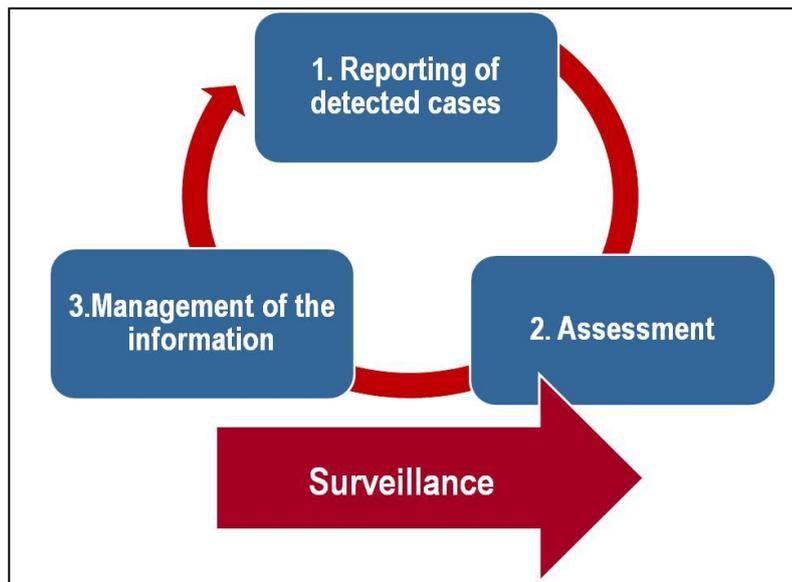


Figure 1: Steps of a Vigilance and Surveillance system.

A V-System of human organs intended for transplantation should aim at the **PREVENTION OF SERIOUS ADVERSE EVENTS AND/OR REACTIONS (see below) THEREBY PROTECTING THE HEALTH OF ALL ORGAN RECIPIENTS AND THE LIVING ORGAN DONORS**. As a V-System operates in a given administrative framework, it is necessary that its design fits such framework and the peculiarities in which its activities are to be developed. However, independent of the administrative and operational organization in place, an effective support from regulatory agencies taking action in certain situations in which risks may arise is of great importance, as well as the strong commitment of all participants.

The present document intends to **provide a minimum set of recommendations for the development of a V-System applied to organ donation and transplantation in the European setting**. MS could broaden the scope of the V-System beyond this minimum, but these recommendations may serve as a common basis for

⁴ Buehler JW: Surveillance. In Rothman KJ, Greenland S (eds): Modern Epidemiology, 2nd Ed. Philadelphia, Penn: Lippincott-Raven Publishers; 1998, p 435.

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the transposition and overall for the subsequent implementation of provisions related to organ vigilance, as reflected in *Directive 2010/53/EU*, to be applied at a MS level and in those situations where organs are to be exchanged between MS. Recommendations provided by EFRETOS are based on the limited experience on organ V-Systems currently in place in Europe and in the United States, as described in Deliverable 3. These recommendations are also based on expert opinions and on the interpretations of the relevant provisions within the *Directive*, as discussed and agreed upon during the corresponding meetings held by the EFRETOS consortium. A **pilot experience** to validate these recommendations is therefore essential and a matter of further work. Also, the impact assessment of implementing these recommendations from the point of view of human and material resources and the resulting financial implications needs to be subsequently performed.

II. OBJECTIVE OF A VIGILANCE SYSTEM OF HUMAN ORGANS INTENDED FOR TRANSPLANTATION

To prevent the avoidable occurrence of a health problem to organ transplant recipient(s), associated with the donor or to the different procedural steps extending from donation to transplantation and to prevent the avoidable occurrence of a health problem to living organ donors, associated with donation, testing, characterization or procurement.

III. THE ORGAN DONATION AND TRANSPLANTATION PROCESS

Although the reality of donation and transplantation is often complex and the limits of their processes are many times grey areas, for the purpose of the design of a V-System, the phases extending between donation and transplantation (or disposal) have to be clear regarding their limits and meaning.

The process to be covered by the V-System applied to organ donation and transplantation is already defined in *Directive 2010/53/EU*. It includes the following phases: donation, testing, characterization, procurement, preservation, transport, transplantation and disposal. For the purpose of this project, in line with the *Directive*, EFRETOS proposes the following definitions and suggested limits for each of these phases:

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- **DONATION:** Donating organs for transplantation (*Source: Directive 2010/53/EU*). The non-specific definition provided by the Directive makes it difficult to establish limits for this phase. For practical purposes, and taking into account that donor testing and characterization are considered separately, it is suggested that other critical steps of the donation process in which deviations might affect the quality and safety of the organs to be transplanted are included under this term.
- **TESTING:** Carrying out the corresponding complementary tests (i.e. laboratory, radiology, pathology studies) relevant for donor and organ characterization, according to established standards.
- **CHARACTERISATION:**

Donor characterization: The collection of relevant information on the characteristics of the donor to evaluate his/her suitability for organ donation, in order to undertake a proper risk assessment and minimize the risks for the recipient, and optimize organ allocation. (*Source: Directive 2010/53/EU*)

Organ characterization: The collection of the relevant information on the characteristics of the organ needed to evaluate its suitability, in order to undertake a proper risk assessment and minimize the risks for the recipient, and optimize organ allocation. (*Source: Directive 2010/53/EU*)

The exchange of information on donor and organ characterization within and between centers and other bodies involved is to be included in this phase.
- **PROCUREMENT:** The process by which the donated organs become available. (*Source: modified from Directive 2010/53/EU*).
- **PRESERVATION:** The use of chemical agents, alterations in environmental conditions or other means to prevent or retard biological or physical deterioration of organs from procurement to transplantation. (*Source: Directive 2010/53/EU*)
- **TRANSPORT:** The transfer of an organ from the operating theater where procurement takes place to the operating theater where transplantation is to take place.
- **TRANSPLANTATION:** A process intended to restore certain functions of the human body by transferring an organ from a donor to a recipient. (*Source: Directive 2010/53/EU*). The inclusion

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of patients into the waiting list and the follow-up of the transplanted recipients are both included under this phase.

- **DISPOSAL:** The final placement of an organ where it is not used for transplantation (*Source: Directive 2010/53/EU*).

Another critical step in the process is the **ALLOCATION** of human organs, consisting of the assignment of the donated organs to the corresponding transplant candidates, based on a set of rules (definition modified from *WHO glossary*). A deviation in the procedures of allocation might lead to health risks to patients if there is an incorrect matching. This might concern both the patients (incorrectly) receiving an organ and the patients skipped in the allocation process and thereby not receiving an organ).

For establishing a comprehensive V-System addressing all the phases of the process that might potentially imply a health risk to patients, EFRETOS recommends that MS consider the inclusion of all the relevant steps in the process in this regard, as depicted in Figure 2. Note that these phases **are not necessarily ordered in time sequence**, as they may run parallel or in different order.

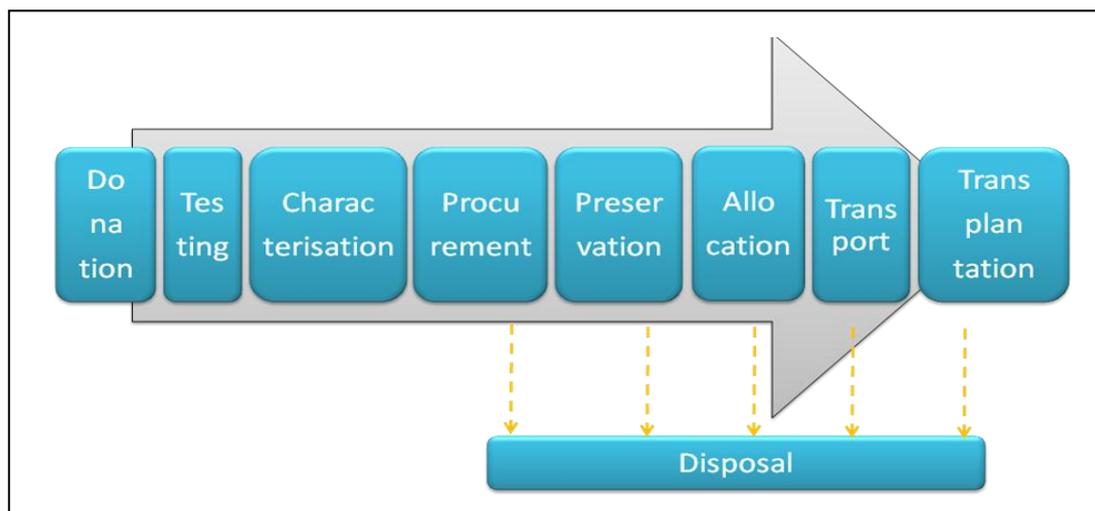


Figure 2: Process extending from donation to transplantation (or disposal) of human organs.

MS can go into more level of detail in the description of the process, but for the purpose of homogeneity across the EU, the organization of the phases should avoid overlapping of concepts, keeping the same boundaries for the mentioned stages or phases.

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IV. DESIGN AND ELEMENTS OF A VIGILANCE SYSTEM OF HUMAN ORGANS INTENDED FOR TRANSPLANTATION

1. POPULATION

The population to be protected by this V-System is composed by those individuals who have been allocated an organ or those ones who donate organs during lifetime and may have a health problem as a result of any steps of the chain from donation to transplantation.

2. CASE

A case in a V-System of human organs intended for transplantation would be a Serious Adverse Event (SAE) or a Serious Adverse Reaction (SAR), according to the definitions⁵ established in the *Directive 2010/53/EU (article 3)*.

‘serious adverse event’ means any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life- threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity.

‘serious adverse reaction’ means an unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity.

⁵ The practical interpretation given by the Consortium to the concepts included in the definitions can be found in section VI. Reporting.

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3. NETWORK

It is essential that the proposed V-System respects both the administrative and the health care organization within each country. Notwithstanding the necessary respect for the internal organization of each MS, some common basic items regarding structure and functions need to be considered.

3.1. Structure

The network is constituted by the following **bodies** (references from *Directive 2010/53/EC*):

- **Procurement Organization (PO):** *'A health care establishment, a team or a unit of a hospital, a person, or any other body which undertakes or coordinates the procurement of organs, and is authorized to do so by the competent authority under the regulatory framework in the Member State concerned'* (article 3).
- **Transplantation centre (TC):** *'A health care establishment, a team or a unit of a hospital or any other body which undertakes the transplantation of organs and is authorized to do so by the competent authority under the regulatory framework in the Member State concerned'*(article 3).
- **Competent Authority (CA):** *'An authority, body, organization and/or institution responsible for implementing the requirements of this Directive'* (article 3). With regards to an organ V-System, the CA shall *'put in place a reporting system and management procedure for SAE and SAR'* (article 17).
- **Delegated Body (DB):** *'A body deemed suitable under national provisions in whom the CA delegates part or all the tasks assigned to it under the Directive or which assists the CA to carry out its functions'* (modified from article 17). Hence, the task related to the V-System could be delegated totally or partially to a DB. According to the terms of such delegation, DB would be a node within the network.
- **European Organ Exchange Organizations (EOEO):** *'A non-profit organization, whether public or private, dedicated to national and cross-border organ exchange, in which the majority of its member countries are MS'* (article 3). Some CA might totally or partially delegate the task of organ vigilance to an EOEO, hence the EOEO would be acting as a DB. Independent of that, when cases suspected to fulfill criteria occur in countries members of an EOEO, these should also be reported in any case to the EOEO and the EOEO should participate in the management of the cases.
- **European Commission (EC).**



3.2. Functions

Regardless of the above, main tasks in a V-System are organized in different levels. As a minimum, the **level of the centre** and that of the **vigilance coordination** have to be recognized (Figure 3).

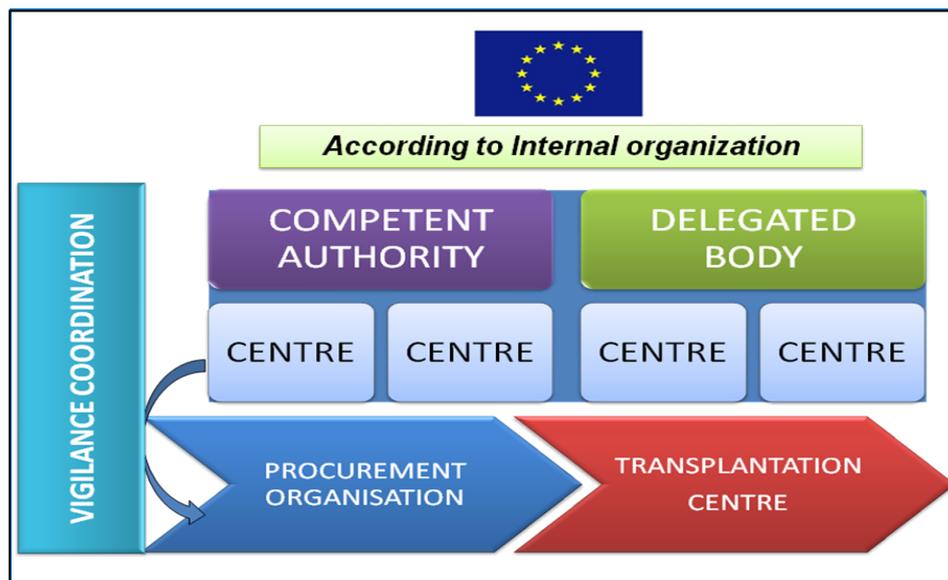


Figure 3: Minimum levels of the Organ V-System. The arrow specifies that the centre level is composed of POs and TCs.

a) **Centre level** (composed of PO and TC) involves at least the following functions:

- Reporting identified cases.
- Assessment and management of cases at local level in full cooperation with the level of the vigilance coordination (see below), including the alert to other centers concerned.

b) **Vigilance coordination level**, with at least the following tasks:

- Reception of reported cases.

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- Coordination of the assessment and management of cases in cooperation with the center level and other relevant bodies when applicable, including the alert to other centers concerned.
- Pooled analysis of reported cases and relevant information from other sources.
- Establishment of the procedures for the correct functioning of the V-System.

To properly develop the functions of the vigilance coordination, the assigned body is recommended to have deep knowledge of the organ transplantation system as well as of the related safety matters, the ability of tracing organs, donors and recipients, the capability of contacting the V-System for tissues and cells, and the availability 24 hours / 7 days / 365 days.

This coordination level can be assigned to any of the bodies of the network as described above or even be shared between several bodies, always according to the decision and internal organization of each MS.

The participation of the EC regarding organs exchanged between MS will be defined through the ongoing implementing procedures foreseen in *Directive 2010/53/EU*. Additional participation of the EC is to be agreed upon with the network of Competent Authorities.

A summary of the functions of each of the levels of the vigilance network is provided in **Annex 1**.

V. RESOURCES

1. STAFF

Each node of the network should have appropriate staff, in number and qualification:

- Center level:** On the basis of the most experienced organ V-systems (see Deliverable 3), it is **recommended** the figure of a **'Go to' person**, so professionals identifying cases of SAE and SAR can share this information with a specific figure familiar with the procedures to follow.
- Vigilance coordination level:** The assigned body (or bodies) should have specific and **qualified** professionals for **the development** of the aforementioned tasks.

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Personnel participating in the network of organ donation and transplantation in a MS would act as the Vigilance network. When **the reporting** activity increases, the need of staff might need to be recalculated.

2. EQUIPMENT

Although a **transmission platform, with high security standards is the ideal**, for setting up the system, the following resources are desirable, as a minimum:

- Telephone (multiconnection and mobile)
- Computer (with database, electronic mail and Word processor)
- Printer
- Fax
- Photocopier

3. OPERATING PROCEDURES

Operating procedures, defined as *'written instructions describing the steps in a specific process, including the material and methods to be used and the expected end outcome'* (Source Directive 2010/53/EU, article 3), as foreseen in this Directive, *'shall be adopted and implemented'* (article 4) for:

- *'The accurate rapid and verifiable reporting of SAE and SAR'*
- *'The management of SAE and SAR'*

Both procedures should be components of the 'Framework for Quality and Safety' that MS (through CA and/or DB) shall establish. Moreover, *'these procedures shall specify, inter alia, the responsibilities of PO, EOEO and TC'*.

4. ADVISORY ROLE

Support from a wide range of professional expertise is desirable for an organ V-System: haematology, infectious diseases, intensive care, oncology, radiology, laboratory or epidemiology.

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At a centre level, professionals at reach might be easily consulted. At the level of the Vigilance coordination, it is recommended that this expertise is also available, if feasible, in the form of an advisory committee. This could also support another type of decisions (i.e. regulatory) taken at a coordination level.

5. INFORMATION SERVICE

Information is essential for an effective a V-System. Access to up-to-date publications and results of series published is crucial for assessing cases reported. On the other hand, providing information to others in the form of final reports, periodical reports or alerts is a good element to stimulate reporting.

Sharing SAE/SAR evaluations would also be strongly advisable, on the basis of the principle that all donation and transplant network “nodes” can take advantage from the knowledge and the experience of others, which might help them to prevent similar SAE/SAR. Using secure web based platforms for the appropriate dissemination of this information would also be desirable.

VI. REPORTING

1. REPORTING CRITERIA (WHAT TO REPORT?)

Directive 2010/53/EU sets down the obligation of reporting SAE and SAR as previously defined. Through this document, the EFRETOS consortium sets down a number of situations fulfilling the mentioned definitions, and which would represent **a minimum set of cases to be reported to the organ V-System in each MS**. In addition, the consortium has also reviewed situations considered out of this minimum, but which could be included under the scope of the V-system in those MS willing to do so. Both relations of situations are the result of the available experience in running organ V-systems, as well as expert opinions within the group, in accordance with a number of criteria:

- Seriousness understood in the context of the common critical health status of patients in need of an organ transplant or already transplanted, since severe complications in these patients are common.
- Frequent assumption of risks in organ transplantation when balanced with the risk of not proceeding with the transplant procedure. Although evidence needs to be built in this area,

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through a dedicated follow up registry (see part I of Deliverable 10), reporting these situations to the V-system would imply an unnecessary overburden on transplant professionals.

- Need to rapidly provide information on newly identified and shared risks for an appropriate management of the transplanted patients.
- Deviations in the procedures applied to the process extending from donation to transplantation are considered to be locally assessed and eventually corrected through a quality control system, foreseen to be developed within the Framework for Quality and Safety, as provided for in the *Directive 2010/53/EU*. As an exception, those deviations with a direct or potentially high impact on the health of the transplanted recipient have been included in the minimum set of cases to be reported to the organ V-System, unless covered by the local Quality control system.

1.1 SERIOUS ADVERSE EVENTS

Directive 2010/53/EU only establishes the obligation of reporting a SAE if this might potentially imply the risk of a SAR in the recipient or if it in fact leads to a SAR. In the EU setting, an Adverse Event is defined as an 'undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation'. Below is described the minimum set of cases to be reported to the V-System as SAE:

- a) **Deviations from operating procedures or other Adverse Event during the chain from donation to transplantation that might lead to a SAR, when at least one patient has been transplanted or subjected to anesthesia for the purpose of transplantation (even if the organ has not been transplanted in the end).**

Examples of SAE related to:

- **Testing:** Test not performed in accordance with standard criteria; inappropriate interpretation of a test.
 - **Characterization:** Inappropriate transmission of the information on the donor/organ characterization (HBs-Ag, Anti-HCV, Anti-HIV, HLA, blood group), characterization not performed in accordance with *Directive 2010/53/EU*.
 - **Preservation:** Fungal contamination of preservation solution.
- b) **Deviations in operating procedures or steps during the chain from donation to transplantation, with a potential high impact on the health of the patient and easy to be prevented, even if the patient was not subjected to anesthesia for the purpose of transplantation, unless covered by the local Quality control system.**

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The Consortium recognizes the need of further work to identify those critical operating procedures or steps. As a minimum, the Consortium agreed on one situation meeting the mentioned criteria: **the inappropriate transmission of the information on the donor characterization with regard to ABO group, Anti-HIV, HBsAg, and Anti-HCV.**

- c) Infection or positive serological status discovered in an organ donor (deceased or living) when at least one organ has been transplanted after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 of Directive 2010/53/EU).

Reporting to the system should be limited to those conditions that would have prevented the transplantation of the organ (contraindication) or modified allocation (restricted allocation) should have these been known in advance*.

Example: p24Ag positive in an anti-HIV negative donor identified after the transplantation of at least one organ.

**It is not infrequent that results of cultures or serologies of a donor are known after transplantation. The corresponding information should be communicated from the PO to the TC, directly or through the CA/DB/EOEO as foreseen in the corresponding MS. This is essential for good practice as this information might lead to preventive measures in the recipient. However, this does not imply that all positive cultures/serologies which are received after transplantation (i.e. positive anti-CMV, positive Anti-EBV, positive urine, blood or other types of cultures) should lead to the reporting of the case to the organ V-system, since overburden could occur. As a cutoff point and because they could definitely lead to a SAR, only those conditions that would have prevented the transplantation of the organ or those that could have modified the allocation are considered the ones to be reported to the system.*

- d) Malignant tumor discovered in an organ donor (deceased or living) when at least one organ has been transplanted, after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 of Directive 2010/53/EU).

Example: Necropsy reveals a glioblastoma multiforme in a donor whose cause of death was a spontaneous intracranial bleeding.

- e) Discovery of any other potentially transmissible disease in an organ donor (deceased or living) when at least one organ has been transplanted, after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 Directive 2010/53/EU).

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Example: Metabolopathy in the donor undiagnosed at the moment of organ transplantation.

f) **Other.**

1.2 SERIOUS ADVERSE REACTIONS IN TRANSPLANT RECIPIENTS

Below is described the minimum set of cases to be reported to the V-System as SAR in the recipient:

a) **Unexpected and serious immunological reactions that are outside of the inherent known risk of the transplantation procedure.**

Example: Death of a transplant recipient due to non-intended ABO mismatch, because of inappropriate characterization of donor.

b) **Abandoned transplantation procedure due to a deviation in an operating procedure in the process or to other AE involving unnecessary exposure to risk.**

Example: Deviation in an operating procedure in the chain from donation to transplantation or other type of AE that leads to discarding the organ, when the potential recipient has already been subjected to anesthesia.

c) **Unexpected infection or unexpected serological conversion in an organ transplant recipient that might be donor-derived or derived from the donation to transplantation process.**

d) **Malignant tumor in an organ transplant recipient** that might be donor-transmitted.

e) **Other unexpected disease in an organ transplant recipient** that might be donor-derived (i.e. a metabolopathy transmitted through liver transplantation).

f) **Death of recipient that might be the consequence of a SAR.**

g) **Other.**

1.3 SERIOUS ADVERSE REACTIONS IN LIVING DONORS

A SAR in the living donor refers to those serious unintended responses in the living donor as a consequence of donation. The importance of the appropriate follow up of living donors is reflected in international standards, including *Directive 2010/53/EU*. Moreover, the *Directive* establishes the obligation for MS to develop a dedicated follow-up registry of the living donor to which serious complications derived from the

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donation process could be systematically reported. Whether (some of) the information provided to this registry is to be complemented with the simultaneous notification of these SAR to the V-system has not been fully agreed by the consortium.

Should SAR in the living donors be decided to be included under the organ V-System by MS, the following minimum situations are recommended to be notified:

- a) **Death of a living donor as a consequence of donation.**
- b) **Serious surgical and non surgical complications in a living donor related to donation.**
- c) **Loss of a graft from a living donor before transplantation is performed.**

1.4 SITUATIONS NOT INCLUDED IN THE MINIMUM SET OF CASES TO BE REPORTED

The consortium considers the following situations not to be included in the minimum set of cases to be reported mentioned above (1.1 – 1.3). However, individual MS might broaden the scope of their organ V-system and foresee their reporting, as previously explained:

- a) **Losses of donors and organs along the process extending from donation to transplantation, if there is not direct exposure to a health risk.**
Losses of donors and organs along this process imply indirect health risks to potential recipients due to the lost opportunities for transplantation. However, these losses may fall under the scope of a quality system. Although MS might decide that these problems are to be consistently communicated to their V-system, the consortium has considered these situations to be out of the minimum recommendations.
- b) **Deviations from operating procedures applied to the process from donation to transplantation, except if exposure to a direct health risk is implied or if significant avoidable potential impact could result (see 1.1.a and 1.1.b).**
- c) **Situations where certain risk is known and taken by the clinicians (and the patient) before transplantation is performed. If a health problem associated with this risk occurs in the recipient, reporting should be limited to those situations which are unexpected or expected to occur infrequently.**
Assuming risks is a common practice in organ donation and transplantation, as there are situations in which the clinician weighs up a risk derived from the donor or the process with the risk derived of not proceeding with the transplantation. Reporting such cases to a V-system would generate a remarkable load of work. However, systematically collecting information on the follow-up of recipients from non standard risk donors in a dedicated registry (and in the

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registry of registries) is recommended as part of a safety management system in transplantation (see part I of deliverable 10).

Finally, cases that are to be reported to **other** V-Systems **should be excluded**, in order to avoid duplication of work and inconsistencies due to the necessary differences between systems, i.e.:

- Drug related adverse events or reactions.
- Devices related adverse events or reactions.
- Working accidents, unless the diagnosis was unknown.

2. REPORTING STAFF (WHO REPORTS AND TO WHOM)

2.1 REPORTING BY WHOM

Effective systems for organ Vigilance are primarily dependent on the notification of SAE or SAR by the corresponding professionals at the PO and the TC (centre level). Hence **the culture of notifying** cases should be fostered by all the bodies within the vigilance network.

As previously stated, the appointment of a **'go to' person** at a centre level would be recommended, so professionals identifying SAE and SAR could share the corresponding information and gain knowledge on the procedures to follow. This 'go to' person could be then the final responsible for reporting the case.

2.2 REPORTING TO WHOM

If a SAE or SAR is identified in a PO or TC, the PO and TC detecting the case should report it **to the vigilance coordinating level**, whatever the body within the network is assuming this role.

When the case involves organs exchanged between MS or with a third country, 'MS shall ensure the reporting of SAE and SAR in conformity with the procedures established by the Commission (...)' (article 11.4 of *Directive 2010/53/EU*).

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When a case is identified, the immediate actions are ITS PRELIMINARY ASSESSMENT AT A LOCAL LEVEL AND ALERTING OTHER CENTERS POTENTIALLY INVOLVED (both PO and / or TCs). Alerting other centers and patients at risk is hence part of the management of the case. This is referred to in the corresponding section; however a warning message on this key action is kept in this section, so staff in charge is reminded on the importance of the alert.

3. PROCEDURES FOR REPORTING (HOW AND WHEN TO REPORT?)

3.1 TRANSMISSION OF INFORMATION

Reporting should be simple and inexpensive. Fax and/or e-mail are good options when an electronic secure alert system is not available. Where fax or e-mails are used, receipt should be checked by phone, especially if there may be other patients at risk. If there is no other option, a phone call might alert the system until the case report arrives.

When it is necessary to establish communication with other MS, EFRETOS recommends using English for the exchange of information, unless a different language is of common use and/or agreed between those involved.

3.2 MINIMUM DATA TO BE REPORTED

The **minimum information to be reported** on identified cases would consist of:

- **Regarding the REPORTER:** Identification of the reporter (including contact details), identification of the reporting center, identification of coordinator/go to person (including contact details). (This information is considered confidential and to be used only for completion, verification and follow-up of the case).
- **ORGAN(s) or other substances CONCERNED:** Type of organ (s), its (their) right / left location(s) if applicable, tissue(s) and cells, if applicable.
- **Regarding the DONOR and the RECIPIENT:** Necessary information for their identification (identifiers).
- **Regarding the SAR:** Start date, detection date, description (nature, severity, characteristics), results of diagnostic tests or other investigations, measures taken* (description, information to centers involved), course and outcome.

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- **Regarding the SAE:** Start date (or suspected or confirmed start stage), detection date, description (nature, severity, characteristics), related phase of the process (if appropriate), results of diagnostic tests or other investigations, measures taken* (description, information to centers involved), course and outcome.
- **Regarding DISPOSALS (IF ANY):** Number and type of organs disposed due to an event) during any stage(s) of the process from donation to transplantation (if it is disposed in the transplantation operating theatre) should be reported. Reason for the disposal.

* *Directive 2010/53/EU* establishes that 'MS shall ensure that operating procedures are in place for the notification, in due time of, [...] *'the management measures with regard to SAE and SAR to the Competent Authority'*

3.3 REPORTING PERIOD

Directive 2010/53/EU establishes that '*MS shall ensure that operating procedures are in place for the notification in due time, of SAE and SAR (...)*' (article 11.3.a).

It is advisable that SAE and/or SAR are reported to the coordinating level **IN DUE TIME after its detection. Please note that the concept 'in due time' can imply WITHOUT ANY DELAY in certain situations when time is of paramount importance in the prevention of the health problem** (i.e. alerting/ reporting is crucial when a new finding has been identified in the donor which requires reassessing the risk and the benefit when the organs are about to be transplanted).

In order to make the final conclusion of the case (see investigation and management section), a **FINAL INVESTIGATION REPORT is expected to be released by the vigilance coordination level.**

3.4 RECEPTION OF REPORTING

Whenever a report is received at the coordinating level, prompt and careful evaluation is necessary to decide where actions are required and if these need to be immediate or can be delayed. It is necessary to ascertain whether the centers concerned have been warned or not.

In any case, an **acknowledgement of receipt** is to be sent to the reporter.

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VII. ASSESSMENT AND MANAGEMENT

This section summarizes the steps to be taken in the assessment and management of the identified and reported cases. These steps are not necessarily sequential but developed in parallel. Both assessment and management need to be developed in close cooperation between the centre level (all centres involved) and the vigilance coordination level.

1. ALERTING OTHER CENTRES CONCERNED

Once a case has been raised, the corresponding mechanisms to alert other centres concerned should be activated. Alerting other centers is essential for the development of therapeutic or preventive measures on potentially affected recipients if appropriate. Moreover, the collective investigation starting as a result of the alert is required for the final assessment of the case (i.e. several recipients of organs from the same donor developed the same condition).

Traceability plays a key role as tracing is the step previous to alerting other teams concerned in the corresponding case. According to *Directive 2010/53/EU*, traceability means *'the ability to locate and identify the organ at each stage in the chain from donation to transplantation or disposal (...)'*. Tracing should also include tissues and cells, which implies that a link between different systems should be ensured. In any case, the **capability of tracing should be guaranteed at the level of coordination.**

Notifications and alerts should be delivered in due time, (without delay in specific circumstances – see above) as prompt decisions on the management of the patients might need to be taken. However, the collection of information and the final assessment and report may take longer.

2. ASSESSMENT OF CASES REPORTED

The first assessment should take place at the level centre, when the case is identified and decided to be reported. The centre reporting the case should ascertain the information relevant in order to make a first assessment of the case and the circumstances in which it occurred.

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When receiving a report, the vigilance coordinating level will assess the report with the aim of its confirmation. For that purpose, the following items need to be covered:

- **Verify case report and check the quality of the notification.**
- **Complete the necessary information with the reporting center:** For the appropriate interpretation of the case, the centre might be asked to provide additional information, including clinical data or results of additional complementary tests.
- **Verify that the centers concerned have been alerted and compile from them all relevant information.**
- **Complete the necessary information with other sources:** Information relevant to the assessment of the case might be available in published literature, ongoing transplant and living donor follow-up registries (national and international registries) and ad-hoc registries (i.e. Deliverable 3 mentions specific registries / data collection performed in some MS with regards to non standard risk donors).
- **Assess SAR cases reported with regards to their ATTRIBUTABILITY to the organ donation and transplantation process or to the donor.** The compiled information should be analyzed objectively and systematically in this regard. If necessary, the case may be assessed by a group of experts with different perspectives.

3. OTHER PREVENTIVE AND CORRECTIVE MEASURES

Along with the results of the investigation and assessment of the case, centres should be taking the necessary measures to protect the health of the patients concerned, when appropriate. Such actions, preventive and corrective, should be communicated to the vigilance coordination level. Actions to be taken locally could also be guided by the coordination level, based on the investigation of the case, pooled analysis and evidence gained through the system itself.

In order to raise a conclusion, the case should be followed up and the responses to the centres or other stakeholders registered by the coordination level.

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4. FINAL REPORT

A final report containing a brief description of the case/s, the assessment and investigation made and its final conclusions, as well as the actions taken should be prepared by the vigilance coordination level and delivered.

5. OTHER RESPONSES FROM CA /DB

▪ OTHER TYPES OF COMMUNICATION TO THE NETWORK:

- **Regulatory notifications** might be appropriate in certain situations in which a change in a procedure is recommended.
- **Rapid Alerts:** A quick notification of a new threat potentially leading to a SAE or SAR coming from other V-Systems should be notified to the network (i.e. West Nile Virus). Those types of notifications are not expected to be transmitted within the organ vigilance network if they are under surveillance by other bodies (i.e. Public Health), however warnings coming from such bodies that might affect the quality and safety of the organs should be notified top-down to the centers for practical reasons.
- **COMMUNICATION TO OTHER STAKEHOLDERS:** In some specific cases, actions might require intervention with particular stakeholders (i.e. the media, or other Health Authorities). In these circumstances, it should be the CA/DB the one to react.
- **PERIODICAL REPORTING:** Periodical analyses of pooled data of cases reported and might lead to conclusions or recommendations which might be useful to the network. This report should be made at least on a yearly basis by the vigilance coordinating level.

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VIII. SPECIAL ISSUES

1. RECORDING OF CASES AND RECORD KEEPING

All cases reported should be **ASSIGNED A NUMBER** by the vigilance coordinating level.

All records should be kept in appropriate format for **at least 30 years**, both at the center and at the coordinating level, ideally.

Initially, case reports might be managed manually. This will contribute with no doubt to the familiarization with the reporting system and the assessment and management of the cases. However, when the number of notifications increases, it is essential to have a registry available for the cases, allowing an easier management and analysis of the compiled information. For registering the information, internationally recognized and used codification systems are advised to be used (i.e. ICD-9 or ICD-10). This will facilitate further international comparisons.

2. EDUCATION/ TRAINING

Staff at each of the nodes of the network should be appropriately trained. Besides, each of these nodes should foster the culture of safety in general and reporting in particular, among professionals. This education activity together with appropriate assistance and feedback to the centers represents the best way of preventing underreporting.

3. EVALUATION OF THE SYSTEM

As any other V-system, that applied to organ donation and transplantation **should be evaluated on a periodical basis**, with the aim of improving its effectiveness.

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IX. ETHICAL PRINCIPLES APPLICABLE TO THE ORGAN V-SYSTEM

The following are core ethical principles that should guide the Vigilance of organs in the EU setting:

CONFIDENTIALITY

The organ V-System should manage and process personal data and medical information in a confidential and secure way in accordance with *Directive 95/46/EC* (protection of personal data)⁶.

COMPROMISE

As any other system of this nature, the organ V-System relies on the collaboration between the different nodes of the network. Participation, which needs to be encouraged at all levels, relies on trust and knowledge of the usefulness of the system. Rigor in the application of procedures and the scientific methodology applied, as well as giving feedback to any input to the system will contribute to the necessary participation. An excellent incentive to foster cooperation is by providing statistics and developing indicators.

NO PUNIBILITY

The system should never be punitive for raising an alert and communicating a case of SAE or SAR. The spurious use of the V-systems with punitive purposes will only lead to loss of confidence in the system, with the subsequent underreporting and waste of resources.

BALANCE BETWEEN NEEDS AND FEASIBILITY

Epidemiologic investigation requires a careful balance between information needs and the feasibility of the tasks. In the world of donation and transplantation, where activity is often determined by urgency and risk assumption, the lack of this balance will lead to a loss of the usefulness of the system.

⁶ Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. European Union website. Available at url: http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf. Last access: February 2011.

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**X. ANNEX 1: FUNCTIONS BY LEVEL IN AN ORGAN V-SYSTEM**

	FUNCTIONS IN ORGAN VIGILANCE
CENTRE LEVEL	<ul style="list-style-type: none"> ▪ Reporting identified cases. ▪ Management of cases at local level in full cooperation with the coordination level: <ul style="list-style-type: none"> ▪ Investigation and first assessment of the case. ▪ Implementation of any corrective or preventive actions. ▪ Record of reported and managed cases. Record keeping (30 years). ▪ Training and education to foster locally the culture of safety. ▪ 'Go to person' designated and necessary equipment provided. ▪ Development of operating procedures.
COORDINATION LEVEL	<ul style="list-style-type: none"> ▪ Responses to queries on cases to be reported by the centers. ▪ Reception of reported cases. ▪ Coordination of the assessment and management of cases in cooperation with the centre level and other bodies, when applicable: <ul style="list-style-type: none"> ▪ Verification of the case report and revision of the notification, completing the necessary information with the reporting center. ▪ Tracing, alerting the centers concerned, unless direct alerting between the centres is foreseen by the MS, and compiling from them all relevant information. ▪ Searching for the necessary information from other sources and pooled analysis of previous cases. ▪ Assessment of the case reported, and if appropriate, its attributability to the process or to the donor. ▪ Proposal of possible corrective and preventive actions for each case. ▪ Delivery of a final report. ▪ Other communications to the network or other stakeholders. ▪ Periodical reporting. ▪ Record of reported and managed cases. Record keeping (30 years). ▪ Training and education to foster the culture of reporting. ▪ Specific professionals appointed and provided with the necessary resources. ▪ Development of operating procedures. ▪ Control of the functioning of the V-System.
EUROPEAN COMMISSION	<ul style="list-style-type: none"> ▪ Set up procedures for vigilance applied to organs exchanged between MS.

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XI. ANNEX 2: ASSESSMENT OF ATTRIBUTABILITY

Over recent years, some tools have been developed to try to establish to what extent the occurrence of a SAR can be attributed to a donor or a deviation in a procedure. The tools developed so far (by the EU funded project EUSTITE⁷, and by the DTAC⁸ in the United States) do not result fully satisfactory as either has been developed not taking into account the idiosyncrasy of solid organ transplantation, or is not adapted to the requirements of the EU regulatory setting (See Deliverable 3, State of the Art):

- DTAC tool is specifically prepared to study donor derived diseases. This means that Adverse Reactions derived from the donation-transplantation process (i.e. infectious disease in recipient because of contamination of preservation fluid) are not specifically studied and hence graded, this being a requirement of *Directive 2010/53/EU*.
- The attributability tool applied to blood (per *Directive 2005/61/EC*) and cells and tissues (EUSTITE recommendations) is too open to interpretation and not easily adapted to organs. In contrast, specifications provided by DTAC seem to be more objective.

For the common understanding on the management of risk and SARs in organ recipients and organ living donors, EFRETOS recognizes the need of a tool developed ad hoc for these situations in the EU setting, based on objective criteria and applicable to those situations in which the SAR is attributed to a donor transmitted disease and to those attributed to a deviation in the operating procedures applied. Some of the partners are developing their own tools, but this work is ongoing and needs further validation before it can be recommended.

⁷ EUSTITE website. Available at url: <https://www.eustite.org>.

⁸ Ison MG, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, DiMaio JM, Hasz R, Kuehnert MJ, Ortiz-Rios E, Teperman L and Nalesnik M. Donor-derived disease transmission events in the United States: Data derived by the OPTN/UNOS Disease Transmission Advisory Committee. *Am J Transplant* 2009; 9: 1929-1935.

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XII. ANNEX 3: SUMMARY OF EFRETOS RECOMMENDATIONS ON ORGAN VIGILANCE FOR THE EU SETTING

Recommendation 1:	Developing an effective V-System in the long term needs vision, dedication, and institutional support.
Recommendation 2:	The objective of an organ V-System is to prevent the avoidable occurrence of a health problem to organ transplant recipient(s), associated with the donor or with the different procedural steps extending from donation to transplantation and to prevent the avoidable occurrence of a health problem to living organ donors, associated with donation, testing, characterization or procurement.
Recommendation 3:	As for any other system, the main tasks to be carried out in organ vigilance are: <ul style="list-style-type: none">▪ Reporting of identified cases (SAE and / or SAR).▪ Assessment of the information reported (including tracing).▪ Management of the case.
Recommendation 4:	For establishing a comprehensive and homogeneous organ V-System in the EU context, EFRETOS recommends a common basic structure and definitions for the phases extending from donation to transplantation / disposal (Section III). If MS wish to develop further detail in the description of the process, it would be advisable that they avoid overlapping of concepts, keeping the same boundaries for all countries.
Recommendation 5:	It is essential that the proposed organ V-System respects both the administrative and the health care organization within each country. Notwithstanding the necessary respect for the internal organization of each MS, some common basic items regarding structure and functions need to be considered. <ul style="list-style-type: none">▪ Two roles should be clearly differentiated: that of the centre level (composed of PO and TC) and that of the vigilance coordination level.▪ To properly develop the functions of the vigilance coordination, the

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	<p>assigned body is recommended to have deep knowledge of the organ transplantation system as well as of the related safety matters, the ability of tracing organs, donors and recipients, the capability of contacting the V-System for tissues and cells, and the availability 24 hours / 7 days / 365 days.</p> <ul style="list-style-type: none"> ▪ This coordination level can be assigned to any of the bodies of the network or even be shared between several bodies, always according to the decision and internal organization of each MS.
<p>Recommendation 6:</p>	<p>Personnel participating in the network of organ donation and transplantation in a MS could act as the Vigilance network. When the reporting activity increases, the need of staff might need to be recalculated.</p> <p>At a centre level, on the basis of the most experienced organ V-systems, it is recommended the figure of a 'Go to' person, so professionals identifying cases of SAE and SAR can share this information with a specific figure familiar with the procedures to follow.</p> <p>At the Vigilance coordination level, the assigned body (or bodies) should have specific and qualified professionals for the effective development of the corresponding tasks.</p>
<p>Recommendation 7:</p>	<p>Although a V-System can be set up with a limited number of material resources, a platform for the transmission and management of the information, with high security standards, would be the ideal.</p>
<p>Recommendation 8:</p>	<p>Support from a wide range of professional expertise is desirable for an organ V-System. At a centre level, professionals at reach might be easily consulted. At the level of the Vigilance coordination, it is advisable that this expertise is also available, if feasible, in the form of an advisory committee.</p>
<p>Recommendation 9:</p>	<p>The EFRETOS consortium has agreed a number of situations fulfilling the definitions of SAE and SAR, as defined in <i>Directive 2010/53/EU</i> (Section VI.1). These situations are the result of the available experience in running organ V-systems, as well as expert opinions within the group, in accordance with a number of criteria, namely:</p> <ul style="list-style-type: none"> ▪ Seriousness understood in the context of the common critical health

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	<p>status of patients in need of an organ transplant or already transplanted, since severe complications in these patients are common.</p> <ul style="list-style-type: none">▪ Frequent assumption of risks in organ transplantation when balanced with the risk of not proceeding with the transplant procedure.▪ Need to rapidly provide information on newly identified and shared risks.▪ Inclusion of specific deviations in the procedures applied to the process extending from donation to transplantation when they imply a direct or a potentially high impact on the health of the transplanted recipient, unless covered by the local Quality control system. <p>EFRETOS recommends that all MS report to their organ V-system at least this minimum set of cases, for the purpose of homogeneity and common understanding in the EU setting, even though MS might broaden the scope of their local V-System.</p>
Recommendation 10:	Bearing in mind that the <i>Directive</i> establishes the obligation for MS to develop a dedicated follow-up registry of the living donor to which SAR derived from the donation process could be systematically reported, the consortium has not reached a unified interpretation on whether (some of) the information provided to this follow-up registry is needed to be complemented with the simultaneous notification of these SAR to the V-system. A clarification on such issue should be provided at European level.
Recommendation 11:	When it is necessary to establish communication between MS or with third countries, it is recommended using English for the exchange of information , unless a different language is of common use and/or agreed between those involved.
Recommendation 12:	It is advisable that SAE and/or SAR are reported to the coordinating level IN DUE TIME after its detection. Please note that the concept 'in due time' can imply WITHOUT ANY DELAY in certain situations when time is of paramount importance in the prevention of the health problem.

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Recommendation 13:	Alerting other centers is essential for the development of therapeutic or preventive measures on potentially affected recipients if appropriate. Moreover, the collective investigation starting as a result of the alert is required for the final assessment of the case.
Recommendation 14:	A final investigation report containing a brief description of each case, the assessment made and its final conclusions, as well as the actions taken, is recommended to be released by the vigilance coordination level.
Recommendation 15:	Staff at each of the nodes of the network should be appropriately trained and motivated regularly. Hence, each of the levels within the Vigilance network should foster the culture of safety in general and reporting in particular, among professionals. This education activity together with appropriate assistance and feedback to the centers represents the best way of preventing underreporting.
Recommendation 16:	Ethical principles guiding an organ vigilance system should include, at a minimum, confidentiality, compromise of all stakeholders involved, no punibility, and feasibility (unnecessary overburden of the network should be avoided).
Recommendation 17:	A common tool for assessing attributability of SAR in organ recipients and / or organ living donors is necessary in the EU setting. This tool should be based on objective criteria and be applicable to those situations in which the SAR is attributed to a donor transmitted disease and to those attributed to a deviation in the operating procedures applied. Some of the partners are developing their own tools, but this work is ongoing and needs further validation before it can be recommended.
Recommendation 18:	All recommendations above are based on the limited experience on organ Vigilance and on expert opinions. Hence, a pilot experience to validate these recommendations is essential and a matter of further work.