ORIGINAL ARTICLE

Critical pathway for deceased tissue donation: a novel adaptative European systematic approach

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ABSTRACT

A 'Critical pathway for deceased tissue donation' was developed by the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO) with the aim of providing a common systematic approach to the deceased tissue donation process. Definitions of tissue donors according to the donation stage have been developed so that they can be adapted to different local scenarios. This critical pathway can be used retrospectively to evaluate the potential of tissue donation, assess performance in the tissue donation process and identify areas for improvement. It sets the basis to build indicators to compare organizations, regions and countries. The critical pathway can also be used prospectively to promote good practices in tissue donation programmes aimed at covering the tissue transplantation needs of patients.

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Introduction

Medical use of human tissues and cells obtained from both deceased and living donors is a rapidly expanding field of medicine that offers great opportunities for the treatment of otherwise incurable diseases and for improvements in quality of life in a variety of illnesses, disorders and injuries. Human tissues and cells have also allowed the promising development of advanced therapy medicinal products (ATMPs) – either as somatic-cell therapy or tissue-engineered medicines – thanks to significant advances in biotechnology [1].

Some tissues (e.g. bone marrow and gametes for *in vitro* fertilization) can be donated by living donors. However, replacement tissues are mainly donated after death. In contrast to organs, these tissues and cells may be stored for years in 'tissue establishments', where they can be processed or transformed and then distributed for clinical use [2]. The process, requirements and key elements of tissue and cell donation have been broadly described in the recently updated Council of Europe *Guide to the quality and safety of tissues and cells for human application* (2019, 4th Edition) [3].

The process by which tissues are procured and made available for medical use is highly complex. It requires the participation of many different stakeholders, including donor coordinators, procurement organizations and tissue establishments. Tissue donation activities vary widely across countries and even within jurisdictions. Lack of uniformity hampers efforts to compare tissue donation performance between countries and within regions, to set standards to allow 'the highest possible level of protection to safeguard public health regarding safety and quality of tissues and cells' [4] and to identify areas for improvement (benchmarking). This pitfall, which is critical for improving performance, is further worsened by the lack of a detailed, fully harmonized and globally recognized terminology across the tissue and cell donation pathway. This may lead to a given term being used in different scenarios to define donors at different stages of the donation process. Lack of homogeneity also hampers uniform data collection. Initiatives to harmonize the terminology in the field of organ, cell and tissue donation and transplantation, such as the 'Global Glossary of Terms and Definitions on Donation and Transplantation' promoted by the World Health Organization (WHO) together with The Transplantation Society (TTS) and the Organización Nacional de Trasplantes (ONT) [5] in Spain, and the glossary elaborated by the European Registry for Organs, Cells and Tissues (EUROCET) [6] have not addressed donor definitions at different stages of the tissue donation process.

These challenges are shared with organ donation, for which a common (universal) systematic approach to the deceased donation process (a 'Critical pathway'), applicable to every country (region or hospital), was developed in 2010 in the context of the *Third WHO Global Consultation on Organ Donation and Transplantation: Striving to Achieve Self-Sufficiency* held in Madrid, Spain [7]. This tool was aimed at creating uniformity when assessing the potential of deceased donation, describing the process, evaluating performance and identifying areas for improvement. This 'Critical pathway' was also intended to be used as a prospective tool, supporting early identification and referral of possible deceased organ donors. The pathway was incorporated into the latest edition of the *Guide to the quality and safety of organs for transplantation* issued by the Council of Europe (2018, 7th Edition) [8].

Pursuing the same objectives as the critical pathway for deceased organ donation, that is describing a common systematic approach adaptable to different scenarios and reaching an agreement on definitions across the donation process to enable comparisons, a 'Critical pathway for deceased tissue donation' has been developed under the auspices of the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO) (see Appendix 1).

To develop the 'Critical pathway for deceased tissue donation', the CD-P-TO established an ad hoc multidisciplinary working group composed of CD-P-TO and external experts in tissue donation from European hospitals and procurement organizations, regulators, representatives of health authorities responsible for tissue activity and tissue bankers. They brought together different clinical backgrounds and expertise from a range of institutions involved in organ and tissue donation with a variety of donation models within the European context. This multidisciplinary expert group was led by the main European scientific associations in the field – the European Eye Bank Association (EEBA) and the European Association of Tissue and Cell Banks (EATCB) – both members of the CD-P-TO. An initial proposal for the critical pathway was first prepared and discussed by the working group, who agreed upon concepts and the most suitable nomenclature and definitions. The previously published Critical Pathway in

Organ Donation was taken as a reference, with its original nomenclature preserved and transposed to the tissue field. The draft was progressively advanced following a systematic description of the pathway as conceived and performed in different European settings and countries. An iterative deliberative approach allowed experts of the working group to reach an agreement. This proposal was further discussed with members of the CD-P-TO at three separate meetings of the Steering Group, with its final approval and formal adoption at the meeting held in October 2020.

The critical pathway presented here is consistent with the current scientific knowledge and European and local regulations on this issue. It is focused on deceased tissue donation for medical purposes (replacement), leaving aside the procurement of tissue for other purposes such as research or as starting material for ATMPs.

The critical pathway for deceased tissue donation

Figure 1 shows the 'Critical pathway for deceased tissue donation' from the identification of a 'possible tissue donor', wherever this takes place, until the tissue is released for medical use. The tool includes the definition of tissue donors according to the different stages of the tissue donation pathway – from possible to potential, eligible, actual and utilized tissue donor. It also describes the causes of tissue donor loss. These have been classified as 'non-modifiable' (i.e. those related to medical unsuitability or non-viability) and 'modifiable' (i.e. potential targets for improvement). All these aspects are described hereunder. Non-modifiable causes of tissue donation loss are included as part of the definition and are therefore described together. Modifiable causes of tissue donation loss are described separately, as these largely depend on local conditions. Generic measures to minimize the latter type of tissue donation loss are proposed.

Definitions

A **possible tissue donor** is defined as a person who has died (with determination of death based on neurological or circulatory criteria) or whose death is imminent. Possible donors are typically identified in hospitals (intensive care units, emergency rooms, wards), although they may also be identified in medical examiners' offices, mortuaries, coroners' offices, forensic institutes, funeral homes and nursing or retirement homes [3]. The commitment of the staff at these facilities, their proper training, the availability of protocols and a close relationship with tissue banks or procurement organizations are essential to ensure deceased tissue procurement following a systematic identification and referral of possible tissue donors [3]. The above-mentioned Council of Europe guide recommends that 'all deaths (typically in-hospital, but also community deaths) should be routinely referred to a donor coordinator, procurement organization or tissue establishment, regardless of the age of the individual, the cause of death or the known wishes of the donor to become a tissue donor' and that 'any possible donor considered for organ donation should also be referred for potential tissue donation'. [3]

A **potential tissue donor** is defined as a deceased possible donor with no apparent absolute contraindication for tissue donation and whose body has been preserved according to the requirements for tissue procurement. Generic contraindications for deceased tissue donation are summarized in Figure 1. For more information about contraindications, readers are referred to the Council of Europe *Guide to the quality and safety of tissues and cells for human application* (2019, 4th Edition) [3]. Information about contraindications to tissue donation may be found in the patient's medical records. Regulations that exclude donors presenting certain risks may differ between countries and regions, with these being based on local disease prevalence and risk assessments. Regular updates are therefore recommended [3]. Although an unknown cause of death is a contraindication for tissue donation, some local regulations allow the cause of death to be determined later in the donation process owing to the relatively longer time limit between tissue procurement and donation in comparison with that for organs. Age and weight limits for tissue donation also vary across local regulations.

Proper preservation of the body requires that the preservation system is guaranteed according to the standards governing tissue procurement. These are described in detail for each type of tissue in the Council of Europe guide [3].

Referral to the donor coordinator or the relevant procurement organization should occur at this time point, if it has not occurred at the stage of possible tissue donation. In the event that a health facility does not have the means to manage a potential tissue donor or is not licensed/authorized for tissue procurement by the relevant health authority, arrangements could be made, where possible and with specific authorization by legal representatives, to transfer the

CRITICAL PATHWAY FOR DECEASED TISSUE DONATION

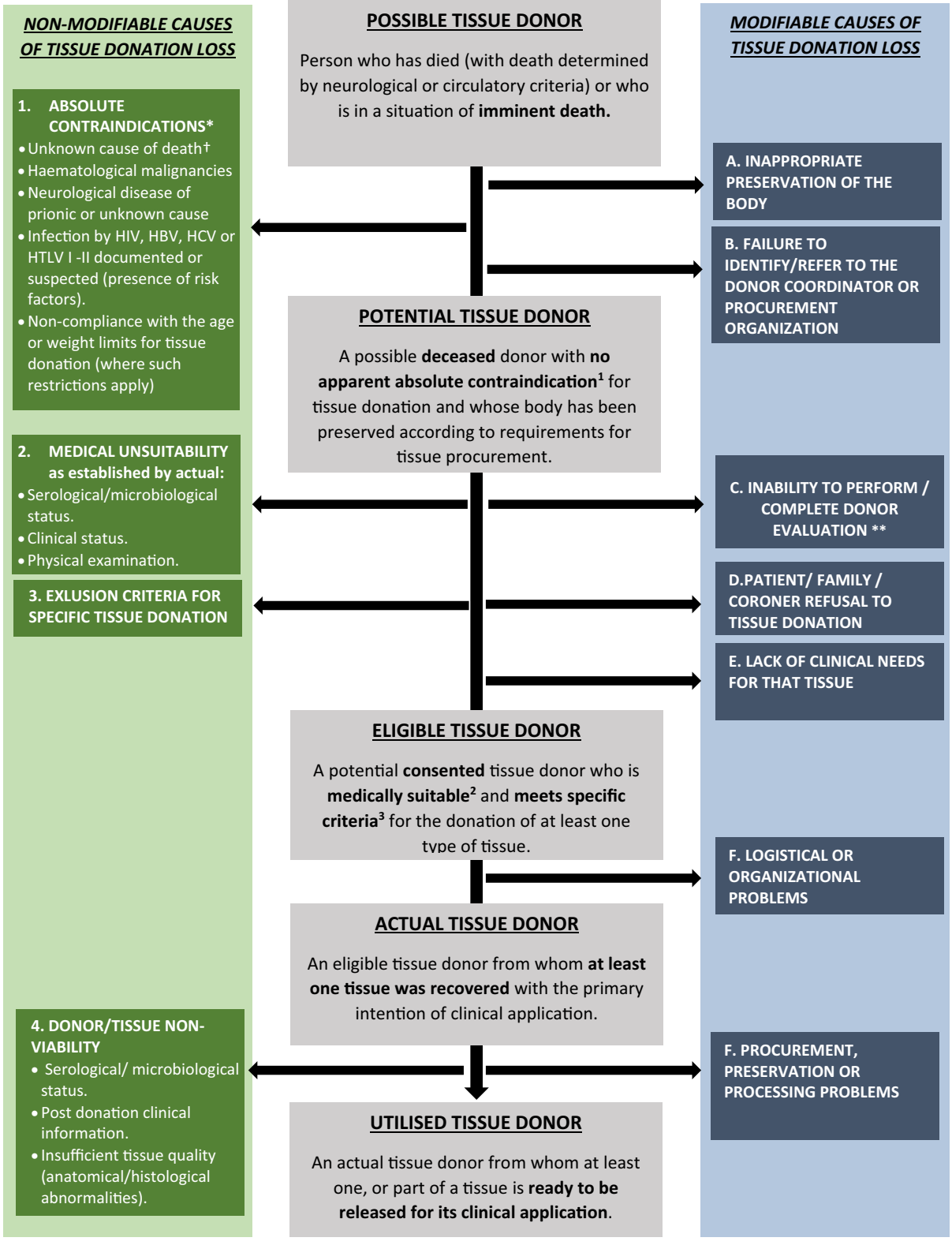

Figure 1 Critical pathway for deceased tissue donation. * See European Guidelines. † Unless an autopsy is performed to clarify the cause of death after tissue procurement. **Including feasibility to perform validated serological/microbiological blood testing. See corresponding non-modifiable causes of tissue loss.

potential donor to a suitable hospital or procurement centre [3].

An **eligible tissue donor** is defined as a consented (whether under an opt-in or opt-out policy) potential tissue donor who is medically suitable and meets specific criteria for the donation of at least one type of tissue. Evaluation of medical suitability requires an investigation into the medical history of the potential donor, their clinical status before death, autopsy findings, physical examination and tests for infectious diseases. The serological and microbiological assessment of the potential tissue donor might not be possible until after tissue retrieval, which does not preclude continuing to advance the donation pathway (see utilized tissue donor). Other information, including the donor's risk factors, may be gathered from interviews with medical staff (attending clinician and nurse, general practitioners, healthcare providers), relatives, close friends or legal representatives [3]. The potential donor's medical suitability to become an eligible donor is assessed in accordance with tissue-specific selection criteria and after an evaluation of risk factors such as sexual behaviour, travel and exposure to sources of infection [3]. Tissue-specific selection criteria are specified in the Council of Europe guide and may vary according to local regulations, as noted above [3].

Consent to donation must be obtained and recorded before procurement of any tissues from a deceased person. Tissue donation is usually not subject to the same time constraints as organ donation. Consequently, evaluation of suitability for tissue donation can be completed after consent has been obtained in those cases when only tissues are going to be procured. This is also relevant given the amount of resources necessary to evaluate the medical suitability of the tissue donor. When the potential donor has not expressed their wishes regarding tissue (and organ) donation during their lifetime, authorization for tissue recovery must be provided by their legal representatives, who presumably know the position of the deceased towards donation and whether it would be consistent with their wishes and values [3].

An **actual tissue donor** is defined as an eligible tissue donor from whom at least one tissue type has been recovered with the primary intention of use for medical application (i.e. not for research). If it has not been done at a previous stage, it is recommended that every actual tissue donor is consistently reported to the appropriate authorities following local legislation. Information about the number and type of tissues recovered should also be reported at this time.

A **utilized tissue donor** is defined as an actual tissue donor from whom at least one tissue, or part of it, is ready to be released for clinical application (tissue replacement). This last step in the tissue donation process may be hampered due to the medical unsuitability of the donor, based either on serological/microbiological status – in cases where this information was not available earlier in the process (see potential tissue donor) – or on post-retrieval medical information. Inadequate tissue quality (i.e. anatomical or histological abnormalities) found during or after the processing of the tissue is an exclusion criterion for its clinical use.

Modifiable causes of tissue donor loss

Modifiable causes of losses of tissue donors may vary between countries based on their legal and/or technical provisions or day-to-day practices. Most modifiable reasons for potential tissue losses are inherent to the tissue procurement or evaluation system in place. Generic measures to overcome these barriers are proposed below. Their applicability is subject to specific tissue donation scenarios or regulations.

- Failure to identify and refer possible tissue donors to the donor coordinator of the relevant procurement organization is the first modifiable cause of donation loss that should be addressed. Initiatives to improve tissue donation at this step should focus on creating awareness of the importance of a timely referral of the possible donor, professional training and provision of tools to facilitate donation (i.e. protocols, checklists). Training activities should target all professionals who may eventually identify possible tissue donors. Protocols must be built by consensus with all stakeholders involved and be complemented by tools that facilitate the identification of circumstances of death consistent with tissue donation and the activation of the tissue donation pathway. These are already basic recognized measures in the field of organ donation [9]. Practices in donor referral should always be aligned with the local regulatory framework. For example, the referral of possible donors in a situation of imminent death – before death has been declared – is not allowed in certain jurisdictions, while it is a common standard in others. Evaluation of the medical suitability for tissue donation should not be made by the referring professional but by the donor coordinator or procurement organization. This avoids inappropriate losses of tissue donors based on the presence of perceived medical contraindications [10]. Age and weight limits for tissue donation are

also variable. Timely referral (i.e. within the first 6 hours after death) allows proper tissue preservation.

- For potential donors, the inability to perform complete donor evaluations (including the feasibility of performing validated serological/microbiological blood testing) is a modifiable cause precluding their transition to eligible donors. Access to standardized evaluations should be promoted and facilitated at all sites where potential tissue donors are available. In those areas or countries where regulations allow for on-demand tissue procurement, initiatives should be promoted to enhance the allocation and distribution of the remaining tissues to sites where these may be needed.
- Explicitly refusing organ or tissue donation while alive or refusal by the family of the potential deceased donor is another modifiable cause of tissue donation loss. Increasing public awareness about the benefits of the medical applications for different tissues and cells is needed to foster donations of deceased organs, tissues and cells by appealing to altruism, solidarity and social engagement [2]. Given that altruistic donation largely depends on providing adequate information to the public – resulting in people who express their wish to donate their tissues after passing away – or to relatives of a deceased person, or even people that do not consciously express their refusal to donate their tissues after passing away, an effort should be made to train donor coordinators and the staff of procurement organizations on how to provide this information, conduct the interviews and approach grieving families, as noted above. Coroners and judges should also be made aware for cases in which disposition of the remains of the deceased are subject to legal proceedings.
- Logistical or organizational problems affecting tissue procurement facilities or personnel are currently important causes of tissue donor loss. Protocols, procedures and circuits should be established in hospitals in accordance with human and logistical resources to ensure the process runs smoothly. In the event that a health facility does not have the means to manage a potential tissue donor or is not licensed/authorized for tissue recovery by the relevant health authority, arrangements could be made, where possible and with specific authorization by the legal representatives, to transfer the potential donor to a suitable hospital or retrieval centre [3]. As an alternative, the establishment of mobile tissue recovery teams could be considered.
- Inadequate tissue quality, which is the main cause of tissue donation loss from actual tissue donors, may be due to problems in procurement, preservation or processing. As per logistical or organizational issues, these types of losses should also be properly addressed. Benchmarking is undoubtedly useful for making improvements.

Conclusions

By providing for the first time definitions of donors according to the donation stage, this critical pathway provides a common systematic approach that can be adapted to different scenarios. By agreeing on these definitions and being flexible enough to adapt them to local scenarios, the 'Critical pathway for deceased tissue donation' can be used retrospectively to assess the potential for tissue donation and evaluate performance in the tissue donation pathway. It enables the establishment of indicators to compare performance in the tissue donation process across organizations (including tissue establishments) regions and countries. The pathway can also be used prospectively, to promote best practices in tissue donation that may help increase the availability of tissues to better satisfy the clinical needs of patients. Nevertheless, the potential validity of this critical pathway in tissue donation requires institutional support and commitment on the side of centres, tissue establishments and authorities to provide, share and compile the required data. The pathway represents a great step in the progress towards transparency of practices and sufficiency in the availability of tissues for clinical application.

Authorship

Alberto Sandiumenge, Teresa Pont and Esteve Trias contributed to the conception and design of the study. The first draft of the manuscript was written by Alberto Sandiumenge, with contributions from Beatriz Domínguez-Gil, Teresa Pont, Jacinto Sánchez Ibáñez and Esteve Trias. All authors reviewed and commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript. The document was formally adopted by the CD-P-TO on October 2020.

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Conflict of interest

The authors declare that they have no competing interests.

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APPENDIX 1

The European Committee on Organ Transplantation (CD-P-TO) is the steering committee in charge of organ, tissue and cell donation and transplantation activities at the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe. As of October 2020, the CD-P-TO is composed of 35 members (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Republic of Moldova, Turkey, Ukraine, United Kingdom) and 22observers (Armenia, Belarus, Canada, Georgia, Israel, Russian Federation, United States of America, Council of Europe Committee on Bioethics, DTI Foundation, European Association of Tissue and Cell Banks, European Eye Bank Association, European Society for Human Reproduction and Embryology, European Society for Organ Transplantation, European Commission, Eurotransplant, South Europe Alliance for Transplantation, Scandiatransplant, The Transplantation Society, United Network for Organ Sharing, World Health Organization and World Marrow Donor Association).