MINIMUM MEDICAL STANDARDS *

DONOR MEDICAL ASSESSMENT

PURPOSE

The purpose of these standards is to comment on the principles of donor selection, as laid down by the COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 describing the minimum information required for donor risk assessment and the sources of information that should be documented as part of the donor record.

INFORMATION REQUIRED FOR DONOR RISK ASSESSMENT

- donor's identity and age;
- cause, time and circumstances of death;
- past and recent medical history;
- behavioural activity that increases the risk of transmissible diseases.

SOURCES OF INFORMATION

- medical records;
- attending medical and nursing staff;
- family members or other relevant persons close to the deceased;
- family doctor;
- physical examination of the donor;
- post-mortem report if available and timely (when autopsy is performed).

MICROBIOLOGICAL TESTING OF DONORS

As a minimum sero-negativity for the following tests is required:

- HIV 1 and 2 antibody (The European Directive does not require PCR/NAT testing for HIV, and there is no scientific evidence to suggesting that PCR/NAT testing is beneficial).
- HBsAg;
- HBc antibody (When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use. For example, a positive anti-HBsAg, or negative HB PCR/NAT test should allow the donor tissue to be used for clinical use);
- HCV antibody;
- Syphilis (A specific syphilis positive reaction does not necessarily require discard and the tissue could be transplanted on the basis of a thorough risk assessment. A thorough risk assessment is defined as a re-evaluation of all donor sources of information, with particular focus on transmissible diseases).

HTLV-I antibody testing should be performed for donors living in, or originating from, high-incidence areas (Caribbean Basin, Central and Southern Africa, South Japan, Central and South America, as

---

Annual review of the Minimum Medical Standards undertaken by the Medical Special Interest Group on 31 January 2020 [P. Maier (Chair), D. Ponzin, E. Trias, J. Hjortdal, M. Hermel].

well as localized areas of Iran and Melanesia), or with sexual partners originating from those areas or where the donor's parents originate from those areas.

Blood samples must have been obtained just prior to death or, if not possible, the time of sampling must be as soon as possible after death and in any case within 24 hours after death, although it should be noted that there is no scientific evidence showing that blood samples obtained later than 24 hours after death turn out to be false negative.

If the donor has received transfusions or infusions within the last 48 hours, the volumes must be recorded and an algorithm applied to assess plasma dilution. Plasma dilution may not exceed 50% if the testing procedures have not been validated for such plasma. According to the EDQM "Guide for the quality and safety of tissues and cells for human application" [3rd Edition 2017, pages 86-88] the following formula can be used to calculate the respective plasma dilution:

Donor total plasma volume = 0.04 [l/kg] * donor body weight [kg]

Infused colloids within 48h pre mortem = $colloids_{48h}$ [l]

Infused crystalloids within 1h pre mortem = $cristalloids_{1h}$ [l]

Total relevant infused volume = $colloids_{48h}$ [l] + $crystalloids_{1h}$ [l]

Acceptable plasma dilution: Total relevant infused volume ≤ Donor total plasma volume

or

($colloids_{48h}$ + $crystalloids_{1h}$) [l] ≤ (0.04 [l/kg] * body weight [kg]).

Explanation: Donor body weight (kg) × 0.04 (l/kg) serves as an estimate of the donor total plasma volume. The infused volume of colloids (within 48 hours prior to death) and crystalloids (within 1 hour prior to death) is summarized. Their total volume must be less than the estimated donor plasma volume.

Eye banks may accept tissues from donors with plasma dilution of more than 50 % only if the testing procedures used are validated for such plasma or if a pre-transfusion sample is available.

The *ante mortem* blood sample should be taken before any transfusions or infusions, and up to 7 days before the donation.

As the treatment with immunosuppressive agents may invalidate serological antibody tests, a thorough risk assessment is recommended (re-evaluation of all donor sources of information, with particular focus on transmissible diseases). In case of uncertainty PCR/NAT testing for HIV, HBV and HCV might be helpful for a thorough risk assessment.

DONOR AGE AND *POST MORTEM* TIME

Provided that corneas are examined to exclude those with inadequate endothelium, no upper donor age limit needs to be set, but other age-related corneal changes must be taken into account. The lower age limit is less certain and will depend on surgical demand.

It is recommended that corneal preservation occurs as soon as possible after death. All time intervals for each donor (death to enucleation and preservation) shall be recorded.

CONTRAINDICATIONS TO THE USE OF DONOR OCULAR TISSUE FOR TRANSPLANTATION

The listed contraindications are an interpretation of the general criteria for exclusion, as given by Annex I, EC 17, 2006, with particular relevance to ocular tissues

- Cause of death unknown, unless autopsy provides information on the cause of death after procurement and none of the general criteria for exclusion set out in the present section applies;
- History of a disease of unknown aetiology;
- Donors with malignant diseases can be evaluated and considered for cornea donation (not for donation of vascularized ocular tissues),except for those with retinoblastoma, haematological neoplasm (such as leukaemia, lymphoma, myeloma), and malignant tumours of the anterior segment of the eye (i.e. primary tumours such as conjunctival intraepithelial neoplasia, squamous cell carcinoma or malignant melanoma as well as metastasis in the anterior ocular segment from other primary malignant tumours). In the case of donors with malignant diseases and a potential risk of metastasis formation in the anterior ocular segment, a thorough slit-lamp examination of the globe or the corneo-scleral disc focused on possible metastasis must be undertaken in the eye bank;
- Risk of transmission of diseases caused by prions. This risk applies, for example, to:
    a) people diagnosed with Creutzfeldt–Jakob disease, or variant Creutzfeldt-Jacob disease, or having a family history of non-iatrogenic Creutzfeldt-Jakob disease;
    b) people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin, such as Alzheimer's Disease, multiple sclerosis, amyotrophic lateral sclerosis;
    c) recipients of hormones derived from the human pituitary gland (such as growth hormones) and recipients of grafts of cornea, sclera and dura mater, and persons that have undergone undocumented neurosurgery (where dura mater may have been used).
- Systemic infection which is not controlled at the time of donation, including bacterial diseases, systemic viral (such as rabies), fungal or parasitic infections, or significant local infection in the tissues and cells to be donated. Donors with bacterial septicaemia (except for encephalitis and meningitis) may be evaluated and considered for eye donation but only where the corneas are to be stored by organ culture to allow detection of any bacterial contamination of the tissue;
- History, clinical or laboratory evidence of HIV or AIDS, acute or chronic hepatitis B (except in the case of persons with a proven immune status), hepatitis C and HTLV I/II, transmission risk or evidence of risk factors for these infections;
- History of chronic, systemic autoimmune and/or inflammatory disease that could have a detrimental effect on the quality of the tissue to be retrieved;
- Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor social history (e.g. intravenous drug abuse, sexual promiscuity), travel and exposure history and local infectious disease prevalence; in this context according to the Standards to the surveillance and epidemic intelligence actions of the European Centre of Disease Control it is important to investigate travel in high-risk regions when checking social anamnesis with regards to new or emerging communicable diseases such as the Ebola virus, Zika-virus, new Corona virus (referred to as 2019-nCoV or Corona-Wuhan) etc. To look for a specific disease index for a country the UK Blood Services Geographical Disease Risk Index for example lists the current disease risks for specific countries (www.transfusionguidelines.org).
- Presence on the donor's body of physical signs implying a risk of transmissible disease(s), such as bruises, lacerations, scars, piercing, needle tracks not compatible with recent clinical history, fresh tattoos that may hide parenteral drug use, and signs of transmissible diseases such as Kaposi sarcoma, swollen lymph nodes, skin rashes, Jaundice of unknown aetiology, should be interpreted in the context of donor medical and social history;
- Ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that may affect the quality of the ocular tissue, or may be transmitted to recipients in a dose that could endanger their health;
- Recent history of vaccination with a live attenuated virus where a risk of transmission is considered to exist;
- Transplantation with xenografts;
- Additional exclusion criteria for deceased child donors;

- Any children born from mothers with HIV infection or that meet any of the exclusion criteria described above must be excluded as donors until the risk of transmission of infection can be definitely ruled out:
    a) Children aged less than 18 months born from mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests;.
    b) Children of mothers with HIV, hepatitis B, hepatitis C or HTLV infection, or at risk of such infection, and who have not been breastfed by their mothers during the previous 12 months and for whom analytical tests, physical examinations, and reviews of medical records do not provide evidence of HIV, hepatitis B, hepatitis C or HTLV infection, can be accepted as donors;
- Eye diseases and ocular surgery: congenital or acquired disorders of the eye (e.g. herpetic keratitis), or previous ocular surgery, that would prejudice graft outcome (e.g. corneas with previous refractive surgery, or stromal scars, may be acceptable for posterior lamellar keratoplasty).

USE OF PRESERVED SCLERAL AND LIMBAL TISSUES FOR KERATO-LIMBAL-ALLOGRAFTS

Donor medical assessment is the same as for corneas. Malignancies represent additional contraindications because the sclera and the limbus are vascularised.

LITERATURE

The following literature review is meant as a resource for eye banks and competent national authorities. It summarises papers on donor selection and screening, disease transmission and risk assessment.[†]

1. Allan B, Tuft S. Transmission of Creutzfeldt-Jakob disease in corneal grafts. *BMJ*. (1997); 315.7122: 1553-54.
2. Armitage WJ, Tullo AB, Ironside JW. Risk of Creutzfeldt-Jakob disease transmission by ocular surgery and tissue transplantation. *Eye* (2009); 23.10: 1926-30.
3. Armstrong SA et al. The prevalence of positive hepatitis B, hepatitis C, and HIV serology in cornea donors prescreened by medical and social history in Ontario, Canada. *Cornea*. (1997); 16.5: 512-16.
4. Baer GM et al. Human rabies transmitted by corneal transplant. *Arch.Neurol*. (1982); 39.2:103-07.
5. Basu S. Mycobacterium tuberculosis in donor cornea. *Br.J.Ophthalmol*. (2011); 95.5: 747.
6. Bialasiewicz AA, Naumann GO, Jahn GJ. Virologic considerations in donor selection for allogeneic keratoplasty. *Klin.Monbl.Augenheilkd*. (1988); 192.6:634-36.
7. Bloomfield SE, et al. Retrocorneal pigmentation secondary to iris stromal melanocytic proliferation. *Ophthalmology*. (1981); 88.12: 1274-80.
8. Borderie VM. Donor selection, retrieval and preparation of donor tissue. Donor selection. *Dev Ophthalmol*. (2009);43:22-30. Epub 2009 Jun 3. Review.
9. Bredehorn T et al. Incidence of potential transmitters of Creutzfeldt-Jakob disease. A study of a collective of potential cornea donors. *Ophthalmologe*. (2001); 98.3: 269-72.

[†] A useful collection of papers on adverse events and reactions for ocular tissues can also be found on the www.notifylibrary.org database (The Global Vigilance and Surveillance Database for Transplantation and Assisted Reproduction).

10. Campanelli M, Mistò R, Limongelli A, Valente MG, Cuttin MS, D'Amato Tóthová J. A donor cornea with metastatic cells from a cutaneous malignant melanoma. Cornea. (2013) Dec;32(12):1613-6.
11. Camposampiero D, Caramello G, Indemini P, Gerten G, Franch A, Birattari F, Donisi PM, Paolin A, Ferrari S, Ponzin D. Two red eyes and one asymptomatic donor. *Lancet*. (2009); 374.9703:1792.
12. Carneiro-Proietti AB et al. HTLV in the Americas: challenges and perspectives. *Rev.Panam.Salud Publica* (2006); 19.1: 44-53.
13. Caron MJ, Wilson R. Review of the risk of HIV infection through corneal transplantation in the United States. J *Am Optom Assoc*. (1994); 65.3:173-8. Review.
14. Catedral EJ et al. Detection of Mycobacterium tuberculosis in corneas from donors with active tuberculosis disease through polymerase chain reaction and culture. *Br.J.Ophthalmol*. (2010); 94.7:894-97.
15. Challine D et al. Serological viral testing of cadaveric cornea donors. *Transplantation*. (2006); 82.6: 788-93.
16. Cockerham GC, Bijwaard K, Sheng ZM, Hidayat AA, Font RL, McLean IW. Primary graft failure: a clinicopathologic and molecular analysis. *Ophthalmology*. (2000); 107.11:2083-90; discussion 2090-1.
17. DeVoe AG. Complications of keratoplasty. *Am J Ophthalmol*. (1975); 79.6:907-12.
18. Dixon WS. AIDS and donor eyes. *Can.J.Ophthalmol*. (1988); 23.1: 1-2.
19. Duffy P et al. "Letter: Possible person-to-person transmission of Creutzfeldt-Jakob disease. *N.Engl.J.Med*. (1974); 290.12:692-93.
20. Eastlund T. Infectious disease transmission through cell, tissue, and organ transplantation: reducing the risk through donor selection. *Cell Transplant*. (1995); 4.5:455-77. Review.
21. European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe. Guide to the quality and safety of tissues and cells for human application, 3rd Edition (2017)
22. Gandhi SS, Lamberts DW, Perry HD. Donor to host transmission of disease via corneal transplantation. *Surv Ophthalmol*. (1981); 25.5:306-11. Review.
23. Glasser DB. Serologic testing of cornea donors. *Cornea*. (1998); 17.2: 123-28.
24. Gode GR, Bhide NK. Two rabies deaths after corneal grafts from one donor. *Lancet*. (1988); 2.8614:791.
25. Goode SM, Hertzmark E, Steinert RF. Adequacy of the ELISA test for screening corneal transplant donors. *Am.J.Ophthalmol*. (1988); 106.4: 463-66.
26. Gonz´Alez-P´Erez MP, Munoz-Ju´Arez L, et al. Human T-cell leukemia virus type I infection in various recipients of transplants from the same donor. *Transplantation* (2003); 75 .7:1006-1011.
27. Gottesdiener KM. Transplanted infections: donor-to-host transmission with the allograft. *Ann Intern Med*. (1989); 110.12:1001-16.
28. Hammersmith KM et al. Creutzfeldt-Jakob disease following corneal transplantation. *Cornea*. (2004); 23.4: 406-08.
29. Hannah EL et al. Creutzfeldt-Jakob disease after receipt of a previously unimplicated brand of dura mater graft. *Neurology* (2001); 56.8: 1080-83.
30. Heck E et al. ELISA HIV testing and viral culture in the screening of corneal tissue for transplant from medical examiner cases. *Cornea.* (1989); 8.2: 77-80.
31. Herzberg L. Creutzfeld-Jakob disease and corneal grafts. Med.J.Aust. (1979); 1.6: 248.
32. Hoft RH, Pflugfelder SC, Forster RK, Ullman S, Polack FM, Schiff ER. Clinical evidence for hepatitis B transmission resulting from corneal transplantation. *Cornea*. (1997); 16: 132-7.

33. Hogan RN, Brown P, Heck E, Cavanagh HD. Risk of prion disease transmission from ocular donor tissue transplantation. *Cornea*. (1999); 18.1:2-11. Review.
34. Hogan RN, Cavanagh HD, Brown P. Qualifications to the report of a new case of Creutzfeldt-Jakob disease in the recipient of a corneal transplant. *Arch.Neurol*. (2003); 60.2: 293-94.
35. Hogan RN, Cavanagh HD. Transplantation of corneal tissue from donors with diseases of the central nervous system. *Cornea.* (1995); 14.6:547-53. Review.
36. Holland EJ et al. The risk of cytomegalovirus transmission by penetrating keratoplasty. *Am.J.Ophthalmol*. (1988); 105.4: 357-60.
37. Houff SA et al. Human-to-human transmission of rabies virus by corneal transplant. N Engl J Med. (1979); 300.11:603-4.
38. Javadi MA, Fayaz A, Mirdehghan SA, Ainollahi B. Transmission of rabies by corneal graft. *Cornea*. (1996); 154:431-3.
39. Keen GA et al. Corneal transplantation from an HIV seroconverting donor. *S.Afr.Med.J.* (1993); 83.2:132-33.
40. Krajden M, Bishai F, Quan C., et al. Multi-organ donor transmission of hepatitis C virus to five solid organ transplant recipients and lack of transmission to corneal transplant recipients. *Clin Diagn Virol* (1995);3:113-121.
41. Lang CJ, Heckmann JG, Neundörfer B. Creutzfeldt-Jakob disease via dural and corneal transplants. *JNeurol Sci*. (1998); 160(2):128-39. Review.
42. Lindquist TD, Miller TD, Elsen JL, Lignoski PJ; Policy and Position Research Subcommittee of the Medical Advisory Board of the Eye Bank Association of America. Minimizing the risk of disease transmission during corneal tissue processing. *Cornea*. (2009); 28.5: 481-4.
43. Lueck CJ, McIlwaine GG, Zeidler M. Creutzfeldt-Jakob disease and the eye. I. Background and patient management. *Eye.* (2000); 14 (Pt 3A):263-90.
44. Maddox RA et al. Creutzfeldt-Jakob disease in recipients of corneal transplants. *Cornea*. (2008); 27.7: 851-54.
45. Maguire MG. Cytomegalovirus transmission and corneal transplantation. *Arch.Ophthalmol*. (1988); 106.7: 877.
46. Manuelidis EE et al. Experimental creutzfeldt-jakob disease transmitted via the eye with infected cornea. N.Engl.J.Med. (1977); 296.23:1334-36.
47. Mitrova E et al. Experience with preventive genetic testing of corneal donors in Slovakia. *Cornea*. (2011); 30.9:987-90.
48. Mitrova E, Belay G. Creutzfeldt-Jakob disease risk in Slovak recipients of human pituitary growth hormone. *Bratisl.Lek.Listy*. (1999); 100.4: 187-91.
49. Moffatt SL, Pollock GA. Creutzfeldt-Jakob disease: perceptions and realities of risk. *Clin.Experiment.Ophthalmol*. (2006); 34.7: 635-36.
50. Najjar D. Informed consent for creutzfeldt-jakob disease after corneal transplantation. *Cornea*. (2005); 24.1:121-22.
51. No authors listed. Patient received cornea: rabies case linked to transplant. Am.Med.News 21.44 (1978): 3.
52. No authors listed. Second rabies death attributed to graft [news]. AORN J. 31.5 (1980): 818.
53. O'Day DM. Diseases potentially transmitted through corneal transplantation. *Ophthalmology.* (1989); 96(8):1133-7; discussion 1137-8. Review.
54. Oguido AP, Casella AM, Hofling-Lima AL, Pacheco SA, Bispo PJ, Marques F. Pseudomonas aeruginosa endophthalmitis after penetrating keratoplasty transmitted from the same donor to

two recipients confirmed by pulsed-field gel electrophoresis. *J Clin Microbiol*. (2011); 49.9:3346-7.

55. Pepose JS. The risk of cytomegalovirus transmission by penetrating keratoplasty. *Am.J.Ophthalmol*. (1988); 106.2: 238-40.
56. Pepose JS, MacRae S, Quinn TC, Ward JW. Serological markers after the transplantation of corneas from donors infected with human immunodeficiency virus. *Am J Ophthalmol* (1987); 103:798-801.
57. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. *JAMA 2020 Jan 30. doi: 10.1001/jama.2020.1097.*
58. Proietti FA et al. Global epidemiology of HTLV-I infection and associated diseases. *Oncogene*. (2005); 24.39: 6058-68.
59. Randolph ME. An experimental study of the possibility of transmitting syphilis by a corneal graft. *Am J Ophthalmol.* (1952); 35:352-7.
60. Remeijer L, Maertzdorf J, Doornenbal P, Verjans GM, Osterhaus AD. Herpes simplex virus 1 transmission through corneal transplantation. *Lancet*. (2001); 357.9254:442.
61. Robert PY, Adenis JP, Denis F, Ranger-Rogez S. Transmission of viruses through corneal transplantation. *Clin Lab*. (2005); 51(7-8):419-23. Review. Erratum in: *Clin Lab*. 2005;51(9-10):608.
62. Robertson I. Corneal transplants and rabies. *Med.J.Aust*. (1979); 2.13: 697.
63. Schotveld JH, Raijmakers AJ, Henry Y, Zaal MJ. Donor-to-host transmitted Candida endophthalmitis after penetrating keratoplasty. *Cornea*. (2005); 24.7:887-9.
64. Schwarz A, Hoffmann F, L age-Stehr J, Tegzess AM, Offermann G. Human immunodeficiency virus transmission by organ donation. *Transplantation* (1987); 44:21-4.
65. Sepsakos L1, Cheung AY, Nerad JA, Mogilishetty G, Holland EJ. Donor-derived conjunctival-limbal melanoma after a Keratolimbal Allograft. *Cornea. (2017); 36(11):1415-1418.*
66. Simani S et al. Six fatal cases of classical rabies virus without biting incidents, Iran 1990-2010. *J.Clin.Virol.* (2012).
67. Simonds RJ, Holmberg SD, Hurwitz RL, et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. *N Engl J Med* (1992);326:726-32.
68. Srinivasan M. Informed consent for Creutzfeldt-Jakob disease after corneal transplantation. *Cornea*. (2005);24.1: 121-22.
69. Sureau P et al. Prevention of inter-human rabies transmission after corneal graft. *C.R.Seances Acad.Sci.III*. (1981); 293.13: 689-92.
70. Thiel HJ et al. Manifestation of Creutzfeldt-Jakob disease 30 years after corneal transplantation. *Klin.Monbl.Augenheilkd*. (2000); 217.5: 303-07.
71. Tugwell BD, Priti R. Patel PR, et al. Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor. *Ann Intern Med*. (2005);143:648-654.
72. Tullo AB et al. Transplantation of ocular tissue from a donor with sporadic Creutzfeldt-Jakob disease. *Clin.Experiment.Ophthalmol*. (2006); 34.7:645-49.
73. Vetter JM et al. Survival after transplantation of corneas from a rabies-infected donor. *Cornea.* (2011); 30.2: 241-44.
74. Vrielink H, Reesink HW. HTLV-I/II prevalence in different geographic locations. *Transfus.Med.Rev*. (2004); 18.1: 46-57.
75. Yates P, Tedder R, Armitage J, Kaye S. Risk assessment for immunosuppression and corneal donation. *Joint UK BTS / HPA Professional Advisory Committee – Summary Sheet* (2011); JPAC 11-56

76. Zarranz Imirizaldu JJZ, Gomez Esteban JC, Rouco Axpe I, Perez Concha T et al. Post-transplantation HTLV-1 myelopathy in three recipients from a single donor. *Journal of Neurology, Neurosurgery and Psychiatry*. (2003); 74 (8);1080-1084