Hepatitis C Screening Guideline Development Group
Background to recommendation 19: Donors of substances of human origin

The purpose of this document is to provide the background information to the formulation of recommendations by the Guideline Development Group (GDG).

Not all evidence in this document is presented in the National Clinical Guideline.

The National Clinical Guideline is available from: http://health.gov.ie/national-patient-safetyoffice/ncec/national-clinical-guidelines/

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Contents

History of development of the recommendation

Date	Process	Outcome
02/06/2015	Recommendations from quality appraised national and international guidelines reviewed	Agreed to augment evidence from existing HCV guidelines guidelines on microbiological safety of SoHO
20/01/2017	GDG subgroup meeting to undertake considered judgement process	Formulation of recommendation
23/02/2017	Review of subgroup recommendation by GDG	Recommendation accepted
25/04/2017	Consultation feedback reviewed by GDG	Recommendation adjusted and accepted
June – July 2017	Editing	Recommendation reworded in final editing process

Considered judgement process

The considered judgment form completed by the GDG subgroup in formulating the recommendations is presented below. Please note the final wording of the recommendation may have changed after review of the GDG, after the consultation process, or during the editing process.

Date:19/01/2017
Attendees: LT, SD, ER, NOF, CDG, JC

Table 1: Considered judgement form

1. What is the question being addressed? Present PICO if relevant
What screening of blood, tissue or organ donations, or donors should be undertaken?
2. What evidence is being considered to address this question and why? (This section will explain the approach taken to address this question and what GDG members are being asked to consider)
Screening of SoHO and their donors for infectious diseases such as HCV is regulated under EU and national legislation, and the respective competent bodies are responsible for implementation. The GDG considered it appropriate to refer to legislative requirements on screening of SoHO. *Other guidance:* Further best practice guidelines for organs, tissues and cells are provided by the UK's Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) *Guidance on the microbiological safety of human organs, tissues and cells used in transplantation* (1). For blood and blood products the equivalent is *The Guidelines for the Blood Transfusion Services in the UK* (referred to as the 'Red Book') published by the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) (2).
3. What is the body of evidence? Source of evidence: (tick all that apply) Guidelines √ Primary literature □ Other √ ; specify: _Legisla□on_____
Blood and blood components Legislation Directive 2002/98/EC and S.I. No. 360/2005 requires that at a minimum Anti-HCV testing be performed on donors of whole blood and apheresis donations, including autologous predeposit donations, at each donation (3, 4). Other guidance JPAC mandate anti-HCV and HCV RNA testing of blood donations (2). **Donors of organs, tissues and cells (other than reproductive cells)** Legislation • COMMISSION DIRECTIVE 2006/17/EC and S.I. No. 158/2006 requires that at a minimum donors must be tested for Anti-HCV Ab. Testing must be carried out on donor's serum or

plasma (5, 6).

- In addition to biological testing, legislation requires the exclusion of donors (either living or deceased) where the medical or behavioural history, or physical examination show evidence of HCV, or evidence of risk factors for HCV.
- As per DIRECTIVE 2010/45/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 July 2010 on standards of quality and safety of human organs intended for transplantation all procured organs and donors thereof should be characterised before transplantation through the collection set of minimum data including a HCV test.
- Timing:
    - In the case of a deceased donor, 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.
    - In the case of living donors (except allogeneic bone marrow stem-cell and peripheral blood stem-cell donors, for practical reasons), blood samples must be obtained at the time of donation or if not possible, within 7 days post donation (this is the 'donation sample').
    - Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.
    - If, in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the 'donation sample' is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.
    - In the case of bone marrow and peripheral blood stem-cell collection, blood samples must be taken for testing within 30 days prior to donation.
    - In the case of neonatal donors, the biological tests may be carried out on the donor's mother to avoid medically unnecessary procedures upon the infant.

Other guidance

SaBTO:

- Type of test:
    - NAT tests for HIV, HBV and HCV are not mandatory for organ transplantation, but their use represents good clinical practice. Turnaround time will not always permit provision of NAT results prior to organ transplantation, but they should still be performed to ensure the rapid identification of the recipients of potentially infectious organs. If NAT tests are either not done, or the results are not available prior to organ donation, combined antigen and antibody assays (rather than antibody testing alone) are required for HIV, and

should be considered for HCV.

- NAT is not mandatory for deceased donors of tissues, nor for living donors of tissue and HPC, but it replaces the need for quarantine and the follow-up serological screening. Combined antigen & antibody assays rather than antibody testing alone are required for HIV when NAT results are not available prior to transplantation and should be considered for HCV.

- Timing of testing:
  - Deceased donors
    - Where ante-mortem blood samples taken for other purposes exist, these samples (taken up to seven days preceding death) are usually preferable to post-mortem samples.
    - Where no ante-mortem sample is available, a post mortem sample can be used, provided samples for testing are taken as soon as possible, and within 24 hours of circulatory arrest The sample should be inspected for haemolysis before testing - only in exceptional circumstances should a visibly haemolysed sample be used for donor testing.
  - Living donors
    - A blood sample taken up to 30 days before organ donation is considered to meet the requirements for testing, as long as the donor's risk status has not changed in the time between the sample being taken and the donation.
    - For tissues and cells, serological testing of a sample taken on the day of donation or up to 7 days post-donation, and of a subsequent sample taken 6 months later for donors of tissues and cells which may be stored before use, is considered to meet the requirements for testing.
    - Negative results on NAT for HBV, HCV and HIV of a blood sample taken on the day of donation, or up to 7 days after donation, from a seronegative individual avoids the need to quarantine cryopreserved donations and retest donors after six months.
  - Additional guidance for cord blood and for neonatal donations in document.

JPAC:

- JPAC recommend mandatory anti-HCV testing of tissues and cells, and optional testing with HCV Ag and/or HCV Ag/Ab or HCV RNA (2).

Reproductive cells

The donation of reproductive cells for assisted reproduction procedures can pose a risk of transmission of infectious diseases to the receiving partner, to any child being born from the procedure, and to staff who may be involved in handling or processing the donation. Legislative requirements for screening of reproductive cells for donation differ from other

tissues and cells as less stringent biological testing is considered to be justified if the donation is between partners with an intimate physical relationship.

Assisted reproduction can involve donation of gametes from a partner for direct use, donation of gametes from a partner with in vitro manipulation prior to use, or donation of gametes from a third party.

Legislation

COMMISSION DIRECTIVE 2006/17/EC and S.I. No. 158/2006 (5, 6):

- Partner donation for direct use:
  - If the procedure involves partner donation of gametes for direct use, donor selection criteria and laboratory testing do not need to be applied.
- Partner donation not for direct use:
  - If partner donated gametes will be stored or processed in any way, or will result in the cryopreservation of embryos Anti-HCV Ab must be performed.
  - In the case of sperm processed for intrauterine insemination and not to be stored, if the tissue establishment can demonstrate that the risk of cross contamination and staff exposure has been addressed through the use of validated processes, biological testing may not be required;
- Donation by third parties for assisted reproduction:
  - Third party donors require careful donor selection and testing for anti-HCV Ab. Blood samples must be obtained at the time of donation.
  - Sperm donations other than from partners should be quarantined for 180 days, after which repeat testing is required. If NAT is performed on the donation blood sample, a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

Under COMMISSION DIRECTIVE 2012/39/EU (7)of 26 November 2012 amending Directive 2006/17/EC

- for donations other than by partners, blood samples must be obtained at the time of each donation.
- For donation by partners (not for direct use), blood samples must be obtained within three months before the first donation. For further partner donations by the same donor, further blood samples must be obtained according to national legislation, but no later than 24 months from the previous sampling.'.

Other guidance

SaBTO:

- Sperm washing
  - In some circumstances assisted reproduction with in vitro manipulation is used to minimise the risk of HCV transmission e.g. by 'sperm-washing'. In such circumstance the sample for insemination is tested after processing to

confirm is free of detectable viral RNA (1).

- Donation of eggs
    - Not yet required by legislation that eggs be quarantined but risk can be reduced by careful donor selections, and NAT of each partner involved.
- Advanced therapeutic medicinal products (ATMPs)
    - Embryonic stem cells for therapy created from gametes or embryos that have not been cryopreserved
        - These are generally donated for use by third parties. Hence it is appropriate that like other tissues and organs for transplantation, appropriate history-taking and microbiological testing of both partners is undertaken.
    - Embryonic stem cells for therapy created from cryopreserved embryos
        - If donated to third party appropriate safeguards in terms of history, microbiological testing of the couple and clear traceability of procurement, processing and storage are needed. Where an embryo has been used to derive stem cell lines and it has not been possible to retrieve donor samples for testing, extensive in vitro testing of the ATMP may be used to identify any residual risk.

4. What is the quality of the evidence? To be considered if primary literature was reviewed.

4.1. How reliable are the studies in the body of evidence?

If there is insufficient evidence to answer the key question go to section 11. Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

SaBTO is a well respected body with a clear code of practice.

4.2. Are the studies consistent in their conclusions – comment on the degree of consistency within the available evidence. Highlight specific outcomes if appropriate. If there are conflicting results highlight how the group formed a judgement as to the overall direction of the evidence

SaBTO guidance exceeds legislative requirements

4.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise

Yes

4.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/ action implementable in Ireland?

Yes

4.5. Are there concerns about publication bias? Comment here on concerns about all studies coming from the same research group, funded by industry etc

n/a

5. Additional information for consideration

5.1. Additional literature if applicable e.g. Irish literature

n/a

5.2. Relevant national policy

Regulations on screening of SoHO and their donors in Ireland

The Health Products Regulatory Authority (HPRA) is the designated Competent Authority responsible for human blood and blood components and for tissues and cells. The HPRA and the HSE are the competent authorities responsible for organs intended for transplantation. Within the HSE, Organ Donation Transplant Ireland (ODTI) is responsible for implementation of legislation.

Institutions which undertake prescribed activities under the legislation must be licensed by the HPRA. In Ireland the Irish Blood Transfusion Service (IBTS) is the principal supplier of blood and blood products for human healthcare. The IBTS is licensed by the HPRA as a blood establishment. It is also licensed as a tissue establishment for Directed Cord Blood Donations, Ocular and Cardiovascular tissue. Other licensed blood and tissue establishments are listed on the HPRA website.

The HPRA is responsible for implementation of legislation, inspection and authorisation of licensed establishments and the receipt, evaluation and follow up of serious adverse reactions and events.

In Ireland, ODTI in conjunction with the HPRA have developed *A Framework for quality and safety of human organs intended for transplantation* as required by legislation(8).

Current practice in Ireland

All blood donated to the IBTS is tested for antibody to HCV virus. In addition, Individual Donation (ID)-NAT using a multiplex assay testing for HIV RNA, HCV RNA and HBV DNA is undertaken. IBTS also screen tissue and cell donors with NAT.

Screening of solid organ donors is done in the National Virus Reference Laboratory where combined antibody antigen tests are performed for deceased donors which exceeds the legislative requirements.

Practice in other licensed tissue establishments is not known.

In Ireland we do not have a national advisory body for the safety of blood, organs or tissues other than the competent bodies set out in legislation.

5.3. Epidemiology in Ireland if available and applicable

nil

6. Potential impact of recommendation

6.1. Benefit versus harm

What factors influence the balance between benefit versus harm? Take into account the likelihood of doing harm or good. Do the desirable effects outweigh the undesirable effects?

Benefit: implementation of best practice will reduce the risk of any transmission events.

6.2. What are the likely resource implications and how large are the resource requirements? Consider cost effectiveness, financial, human and other resource implications

There may be resource implications for some establishment who currently only comply with the minimum legislative requirements

6.3. Acceptability – Is the intervention/ option acceptable to key stakeholders?

Yes.

6.4. Feasibility - Is the intervention/action implementable in the Irish context?

NAT is current practice in the IBTS for blood, and products must be negative prior to release. Practice in under establishments is not known. Requirement for NAT may require referral to external laboratories for some centres.

6.5. What would be the impact on health equity?

Recipients of donated SoHO often have complex health needs and infection with HCV may cause further morbidity. Therefore prevention of transmission will have a positive impact.

7. What is the value judgement? How certain is the relative importance of the desirable and undesirable outcomes? Are the desirable effects larger relative to undesirable

Best practice, where it exceeds legislative requirements, should be implemented**.**

8. Final Recommendations

√Strong recommenda□on
□ Condi□onal/ weak recommenda□on

Text:

- Screening of blood, organ, tissue and cells donor should at a minimum comply with legislative requirements
- The following screening is also recommended:
- NAT of donors of blood, organs tissues and cells, including reproductive cells (except for partner donation for direct use) should be performed and the results available prior to donation
- For deceased donors of solid organs
    - Combined antigen and antibody testing should be done prior to transplantation.
    - NAT should also be done as soon as possible *but the results are not required prior to transplantation.
- Any laboratories undertaking microbiological screening of donors should be accredited by the Irish National Accreditation Board (INAB) to undertake testing in compliance with the International Standard ISO 15189 or the appropriate regulatory authority
- A national advisory committee on the safety of blood, organs and tissues should be convened to advise on best practice

*NAT should be done the next working day if the donation arises out of hours.

Level of evidence supporting the recommendations: moderate

9. Justification

The highest standards should be implemented to ensure safety and quality of donated SoHO. Combined antigen/ antibody test and NAT offers better sensitivity and specificity. It is a matter of urgency that a national advisory committee on the safety of blood, organs and tissues should be convened to advise on best practice
10. Implementation considerations
The competent bodies and licensed establishments will need to be consulted. The competent bodies are only responsible for implementation of legislative requirements. NAT may not be available in all laboratories. A national advisory committee for safety and quality of blood, organs and tissues similar to SaBTO in the UK is required.
11. Recommendations for research List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

Review by GDG

Date: 23/02/2017

Recommendation accepted

Consultation feedback and review by GDG

Please see *Report of the consultation process* for feedback received.

Recommendation adjusted based on review of further guidance and legislation highlighted through feedback from the competent authorities and other stakeholders in testing of donors of SoHO.

Final recommendation

Recommendation 19

19.1. Screening of donors of blood, organ, tissue and cells, including reproductive cells*, should at a minimum comply with legislative requirements**.

The following screening is also recommended:

19.2. NAT for HCV-RNA of donors of blood should be performed and the results available prior to the use of the donation. The test must be designed and approved for screening of blood donations.

19.3. NAT for HCV-RNA of donors of tissues and cells, including reproductive cells*, and living solid organ donors, should be performed in addition to current legislative requirements**.

19.4. For deceased donors of solid organs:

19.4.1. Anti-HCV and HCV-antigen testing should be done and the results available prior to donation***.

19.4.2. NAT should be considered where feasible. NAT results may not be available prior to transplantation but NAT should still be performed to ensure the rapid identification of the recipients of potentially infectious organs ***.

19.5. Any external laboratories used for microbiological screening of donors should be accredited and comply with the standards of the appropriate regulatory authority. Laboratories in Ireland should be accredited by the Irish National Accreditation Board (INAB) to undertake testing in compliance with the International Standard ISO 15189.

19.6. A national advisory committee on the safety of blood, organs and tissues should be established to advise on best practice in relation to donor selection, and testing of potential donors.

*In the case of partner donation of reproductive cells for direct use and when no storage or processing of samples will be undertaken, microbiological screening is not required.

**Please refer to the relevant competent authority for legislative requirements

***It is acknowledged that in some circumstances the balance of risk and benefit may favour the use of potentially infectious donations. Such a risk assessment should be conducted by the transplant centre in discussion with an appropriate microbiologist/ virologist.

Quality/level of evidence: moderate

Strength of recommendation: strong

References List

1. Advisory Committee on the Safety of Blood Tissues and Organs. Guidance on the microbiological safety of human organs, tissues and cells used in transplantation. London: Department of Health; 2011. Available from: https://www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation.
2. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Guidelines for the Blood Transfusion Services in the UK 8th Edition. JPAC; 2013.
3. Directive 2002/98/EC of the European Parliament and of the CouncilSetting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF.
4. S.I. No. 360/2005 - European Communities (Quality and Safety of Human Blood and Blood Components) Regulations. Available from: http://www.irishstatutebook.ie/eli/2005/si/360/made/en/print#.
5. Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF.
6. S.I. No. 158/2006 - European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006. Available from: http://www.irishstatutebook.ie/eli/2006/si/158/made/en/print.
7. Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC of the European Parliament and Council as regards certain technical requirements for the testing of human tissues and cells. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32012L0039.
8. Quality and Safety Framework Group. A Framework for Quality and Safety of Human Organs Intended for Transplantation. Dublin: Organ Donation and Transplant Ireland; 2014. Available from: https://www.hse.ie/eng/about/Who/organdonation/publications/ODTI_Quality_and_Safety_Framework_for_Human_Organs_Intended_for_Transplantation.pdf.

Appendices

Evidence search and results

International and national guidelines

HCV guidelines identified, reviewed, and quality appraised as described in the National Clinical Guideline.

Other guidelines reviewed

Guidelines on the microbiological safety of SoHO as identified by expert GDG members and key stakeholders.

Grey literature

Legislation.

Primary literature

Nil used.