SaBTO

Advisory Committee on the Safety of Blood, Tissues and Organs

Tissues and Cells: MSM* Donor Selection Review

July 2013

*MSM – men who have had sex with men

Table of Contents

Tables

Figures

1. Executive summary

1.1.Background

The scope of the group's work was to make recommendations on the selection criteria for donation of tissues and cells by men who have had sex with men (MSM). The context was the recent change for blood donors from a lifetime to a 12 month deferral from last MSM contact. The scope was agreed to include haematopoietic stem cells (family and friends, unrelated donors and cord blood); pancreatic islets; hepatocytes; banked tissues (skin, cornea, heart valves, amnion, bone and tendon); and gametes and embryos for reproductive purposes (ie not for derivation of cell lines).

1.2. Methodology

The working group reviewed the evidence base for selection of living and deceased donors of cells and banked tissues in the UK in relation to MSM behaviour. The group reviewed updated data on generic virus risks, and considered in depth any tissue-specific infection risks, notably HHV-8. It was noted that epidemiological data on donors in the UK was available only for tissue donors handled through the UK Blood Services; no comparable data exist for tissue donors handled through other tissue banks, nor for donors of stem cells, pancreatic islets, hepatocytes or gametes. The UK Blood Services have collected risk behaviour data on surgical bone donors since 2001. To date, MSM behaviour has not been disclosed as a risk factor for infection. However, unlike the work on blood components, calculations of residual virus risk according to different MSM deferral periods were not possible due to the small numbers of donors and because each donor donates only once.

The group therefore adopted a risk-based approach, and identified factors that would determine the overall risk/benefit balance. These included: therapeutic objective (life-saving versus life-enhancing); supply issues; need for donor/patient matching; depth of donor history taking; the opportunity to discuss the risks of an individual donor with the potential recipient's clinician, with or without the recipient; product testing and manufacture, and practicability. The group was also mindful of current legislation, guidance from different sources, and practice in other countries.

The group followed a three-step process to reach its recommendations for different tissues and cells:

a) A standard questionnaire was issued to group members to gather information on how the factors listed above applied to each type of individual tissue/cell product. In some cases, further information on current practice was sought through professional societies.

b)Based on the factors above, the products were divided into four groups.

c)Using data from the survey, risk-based assessments were carried out on the four groups of products.

1.3. Recommendations on donor deferral

1.3.1. Group 1: Haematopoietic stem cells, whether from family and friends, or unrelated adult donors, or from cord blood

This also includes related products from the same donor types eg donor lymphocytes, and virus-directed T cells.

1.3.1.1. For 'family and friend' donors

NO DEFERRAL. **This is current practice and represents no change.**

Retain the current individual risk/benefit donor assessment ie ensure documentation of MSM behaviour but place no specific restrictions regarding donation.

1.3.1.2. For unrelated donors joining a registry

NO DEFERRAL.

For Anthony Nolan this is current practice and represents no change.

For the British Bone Marrow Registry and Welsh Bone Marrow Donor Registry this would represent a change to current practice.

The British Bone Marrow Registry and Welsh Bone Marrow Donor Registry recruit via blood donation, so pending this review employ lifetime deferral. This therefore represents a change to guidance.

The MSM behaviour should be documented, to facilitate an in depth discussion should the donor be a potential match for a patient. This ensures that the current practice of individual risk/benefit assessment prior to donation is continued.

1.3.1.3. For cord blood donors

NO DEFERRAL. This represents a change to current practice.

Allow donation with documentation of, but no restrictions regarding, MSM behaviour of the partner, and retain the current individual risk/benefit assessment prior to use of the donation.

For Anthony Nolan this is a change from a lifetime deferral after sexual contact by the woman with a man who has ever had MSM behaviour.

For British Bone Marrow Registry this is a change from a 12 month deferral after sexual contact by the woman with a man who has ever had MSM behaviour.

1.3.2. Group 2: Pancreatic islets and hepatocytes

NO DEFERRAL. This is current practice and represents no change.

Retain the current individual risk/benefit donor assessment ie documentation of, but no specific restrictions regarding, MSM behaviour.

1.3.3. Group 3: Banked tissues (corneas, heart valves, amnion, bone, skin, and tendon)

MEN
ALLOW DONATION 12 MONTHS OR MORE AFTER LAST MSM SEXUAL CONTACT.

WOMEN
ALLOW DONATION 12 MONTHS AFTER LAST SEXUAL CONTACT WITH A MAN WHO HAS EVER HAD SEX WITH ANOTHER MAN.

This is not current practice and represents a change from the current lifetime deferral for both men and women. It is consistent with SaBTO guidance for blood donation.

1.3.4. Group 4: Sperm, eggs and embryos

NO DEFERRAL. **This is current practice and represents no change.**

Retain the current individual risk/benefit donor assessment ie documentation of MSM behaviour, but no specific restrictions regarding donation.

1.4. Other Observations

1.4.1. Observations on the collection of information on the donor's sexual history

The survey demonstrated that different terminology was used in the donor selection questionnaires of different organisations and in some cases the terminology used was inappropriate as it referred to sexual orientation rather than specific risk behaviour.

It is desirable that standardised terminology should be used by all tissue and cell providers. The wording currently used by UK Blood Services was considered to be appropriate, referring to "men who have ever had oral or anal sex with another man with or without a condom or other protection".

1.4.2. Observations on donation testing

The recommendations on deferral are NOT contingent on use of any testing regime over and above the options already defined in current guidance. However, the group noted inconsistencies in the use of nucleic acid testing (NAT) between different tissue and cell products, and between different providers of the same product, notably with regard to donation of corneas, bone and sperm. SaBTO issued guidance [1] in 2011 on the microbiological testing of organs, cells and tissues, and this document alluded to NAT as best practice, but stopped short of a firm recommendation for its use for all banked tissues. Therefore, when this guidance is next reviewed, SaBTO may wish to clarify the position with regard to the use of NAT eg recommending its use for all banked tissues and cells, and giving consideration to which markers and the pool size to be used or individual sample testing.

1.4.3. Observations on manufacturing

Additional processes to reduce viral risk were identified only with regard to bone (eg a combination of peroxide and peracetic acid). There is an ongoing study of a new processing method for living bone donations to remove residual cellular marrow. This was previously considered by SaBTO in the context of vCJD risk reduction, and a study of efficacy recommended. It is

proposed that when this study is complete, the data on safety and clinical effectiveness should be reviewed by SaBTO, (with a view to considering whether or not this method should become the standard of care).

1.4.4. Observations on bio vigilance

Reporting systems exist for the notification of virus transmission by all tissue and cell products considered in this review, and are mandatory under the Human Tissue (Quality and Safety for Human Application) Regulations 2007. Such reported, confirmed events are now rare.

However, and in contrast to blood, there is limited documentation and no central collation of incidence and risk factors of virus positive donors of cells, tissues (except within Blood Services) and gametes. Collation, analysis and publication of such data would be enormously helpful in formulating future policies for donor selection and testing, as evidenced by experience with blood donors.

Similar consideration applies to the collection and storage of archive samples from tissue and cell donors. These would be invaluable not only in the investigation of suspected transmissions, but also in the identification and assessment of emerging infections. It is suggested that options should be considered for how best such data could be collected, analysed and published. This could include reporting of clinical manifestations of viral infections in recipients eg Kaposi's sarcoma.

The storage of archive samples from tissue and cell donors would assist in investigation of suspected infection transmissions and timely recalls.

Both data collation and archive samples have value in the identification and assessment of emerging infections.)

2. Background

In 2011, SaBTO reviewed the evidence base for blood donor selection criteria relating to specific sexual behaviours. Following the review, SaBTO recommended that the blood donor deferral for men who had ever had sex with men (MSM) should be changed from a lifetime deferral to a deferral of 12 months since the last at-risk behaviour [2]. This recommendation was accepted by Ministers and implemented in England, Wales and Scotland on 7 November 2011.

It is desirable to have the same guidance for all providers of the same product, and to minimise discrepancies in selection criteria for donors of blood, tissue, and cells. Since the previous MSM review was limited to blood donors, the recommendations have resulted in inconsistencies in donor selection. For example, a man who has had sexual contact with another man more than 12 months prior to donation can be acceptable as a platelet donor, but currently not as a stem cell or tissue donor by the UK Blood Services. Moreover, the same individual could be deemed acceptable as a stem cell donor by a non-Blood Service organisation such as Anthony Nolan. Therefore, all tissue and cell establishments need definitive advice regarding MSM eligibility.

The scope of the group's work was to make recommendations on the donor selection criteria for donation of tissues and cells (as defined in section 2) by MSM. The group considered the impact of various options on product safety, supply and practicability. In generating its recommendations, the group was mindful of current legislation, guidance from different sources, and practice in other countries.

The group has also made some observations regarding donor testing which, though not strictly in the scope of this work, may be helpful in achieving consistency across provider organisations.

The group was conscious of the thorough work undertaken by the SaBTO blood donor selection steering group that had previously made recommendations on donation of blood by MSM. The intention was not to revisit or repeat work underpinning those recommendations, where they could be applied directly to tissue/cell donation. Therefore this review does not formally reassess the effect of different deferral periods on risk of human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) in donors of tissues and cells, as this was covered previously.

The group focussed its work on specific issues pertaining to individual tissue/cell products in their inherent benefits, adequacy of supply, and specific infectious risks, as well as the processes used to mitigate those risks during donor assessment, donor testing and product manufacturing.

3. Scope

3.1. In scope

The following cell and tissue products from UK donations[#] were considered by the group to be in scope, with the provisos shown:

a) Haemopoietic stem cells (HSC): family and friends *
b) HSC: matched unrelated *
c) HSC: cord blood
d) Pancreatic islets
e) Hepatocytes
f) Heart valves
g) Skin
h) Corneas
i) Bone: living, single donor
j) Bone: deceased, single donor[§]
k) Tendon
l) Amnion
m) Sperm, eggs and embryos[+]

[#] some products are imported to the UK eg HSCs from other donor registries or cord banks. Importing centres should ascertain donation rules in the country of origin.
* includes related products from same donor types eg donor lymphocytes, virus-directed T cells etc.
[§] often referred to as 'pooled' but the pool is taken from different bones from a single donor.
[+] for purposes of reproduction, NOT generation of embryonic stem cell lines.

3.2. Out of scope

The following were considered by the group to be out of scope:

a) Organs for direct transplantation, without banking, from living or deceased donors. These are all life-saving, and there is currently no MSM deferral for organ donors.
b) Haematopoietic stem cells for autologous use.
c) Recommendations regarding cell or tissue donation by commercial sex workers. The blood donation guidelines group reviewed this topic, and concluded that there were no firm data on infection risk which could provide evidence-based recommendations regarding blood donation. The same situation applies to tissue and cell donation.

The establishment of the working group was recorded in the minutes of the SaBTO meeting of 9 March 2012; the scope of the review was reviewed by

the main SaBTO committee on 11 September 2012, and the final terms of reference supplied to the committee on 10 December 2012.

The full terms of reference and membership are included in Appendix 8.1, and the participation and contribution of all members is gratefully acknowledged.

4. Factors considered in risk assessment of each tissue/cell product

The range of tissues and cells considered by the group is highly heterogeneous. Therefore, information was gathered by the lead experts on each separate product under the following headings (a blank proforma is attached at Appendix 8.4).

4.1. Is the product life-saving or life-enhancing?

Products sit along a spectrum from potentially lifesaving in the short term (HSC transplants), through life-saving over a longer time frame (pancreatic islets, heart valves) to life-enhancing (bone products, gametes, cornea, tendons). Some products eg skin, can be either, depending on the clinical indication (life-saving when used for burns; life-enhancing when used for leg ulcers). This is important in considering the risk:benefit balance.

4.2. Adequacy of general supply, and meeting of donor:patient matching requirements

Neither of these issues was a major factor in the review of blood donation by MSM, but both need to be considered here. For example, 25% of sperm donations used in the UK are currently imported, due to a shortage of UK donors. For this reason, there is currently no deferral for MSM sperm donors. Other products eg corneas, are barely in balance.

The requirements for donor:patient matching are relevant in considering the risks of excluding an MSM donor who might provide the best match for an individual patient. For example, the practice of stem cell transplantation absolutely depends on availability of donors who are a good HLA[1] match with the patient; this significantly predicts clinical outcome. Moreover, the chances of finding a well matched donor are significantly lower in certain ethnic groups, who are under-represented on bone marrow registries. For heart valves, there must be matching of donor and patient valve diameter, and for pancreatic islets the blood group must match.

[1] HLA: human leukocyte antigen. The HLA system determines the compatibility of transplant donors and recipients.

4.3. Source of donors and depth of donor assessment

The range of products considered here is mirrored in the different sources of donors, who may be living or deceased, a family member or an altruistic stranger. Sometimes the same product can be sourced from different types of donors eg haemopoietic stem cells can come from ‘family and friend’ donors or from unrelated living donors from a registry. Bone products can also come from living or deceased donors. This is relevant in considering the completeness of the information available regarding the donor’s sexual behaviours. For deceased donors, therefore, GP records are obtained as well as a history from next of kin.

It should be borne in mind, however, that for all tissue and cell products, whatever the source of donors, the history is taken in much greater depth than for blood donation. There is always direct questioning of either the donor or family members against a standard proforma, while donors of stem cells and gametes are assessed on at least two occasions before donation, with in depth face to face interviews.

4.4. Are there infectious agents of concern for individual tissues?

This area of work examined the evidence for transmission of specific infectious agents by different tissues, as well as considering their epidemiology and the different processing steps taken during manufacturing which can reduce the risk. It also took into account the impact of current manufacturing protocols. For blood donations, for example, processing to remove leucocytes has significantly reduced the risk of transmission of cytomegalovirus (CMV) by transfusion, but this step cannot be applied to stem cell donations.

4.5. Maximum number of recipients who could receive cells/tissues from a single donor

This is relevant in several contexts:

a) the deceased multi-tissue donor, from whom multiple individuals could receive organs immediately and tissues from the same donor over a period of up to ten years
b) the sperm, egg or embryo donor: a maximum of 10 family units can receive donations from the same donor
c) the unrelated stem cell donor: one donor may provide cells for up to two individuals on separate occasions.

4.6. Current practice regarding repeat testing of the donor

In line with the European Union Tissue and Cells Directives (EUTCD), where NAT testing is not used, repeat serology testing is built into current regulations for living bone donors, sperm donors and stem cell donors.

4.7. Whether there is the opportunity to discuss with the patient's clinician possible risks relating to an individual donor

This is not possible with blood donation, but is not uncommon in organ donation. Here, the situation varies among products, with such discussions possible for potential recipients of stem cell transplantation and pancreatic islet transplantation, but not for recipients of banked tissues.

4.8. Summary table

Table 1 summarises the tissue and cell types and areas considered in the risk assessments.

Table 1. Factors affecting risk of tissue and cell products: review of current practice. Blood and organs are shown for reference.

	DONOR						PRODUCT					
	Current MSM donor deferral	**Is a direct donor history taken?**	**Is an indepth donor history taken?**	**Is NAT testing routinely used?**	**Is there repeat testing of the donor?**	**Opportunity to discuss with the patient the risks relating to a specific donor?**	**Is the product life-saving?**	**Is there an adequate general supply?**	**Do donor:patient matching requirements affect supply?**	**Intrinsic risk of the final product transmitting an infection (High/Med/Low)**	**Does processing mitigate the risk?**	**Maximum number of recipients from a single donation**
Blood	1 year	Y	N	Y	N	N	N	Y	N	H	Y	8
Organs	None	N/Y[1]	Y	Y[2]	N/Y[3]	Y	Y	N	Y	H	N	9[4]
Haematopoietic stem cells: family and friends	None	Y	Y	N	Y	Y	Y	N	Y	H	N	1
Haematopoietic stem cells: unrelated	ANT: none BBMR: lifetime	Y	Y	N	Y	Y	Y	N	Y	H	N	2
Haematopoietic stem cells: cord blood	ANT: lifetime NHSCBB: 1y[5]	Y	Y	Y	N	N	Y	N	Y	H	N	1
Pancreatic islets	None	N	Y	Y	N	Y	Y	N	N	L	Y	1
Hepatocytes	None	N	Y	Y	N	Y	Y	N	N	H[6]	N	1
Heart valves[7]	Lifetime	N	Y	Y	N	N	Y	Y[8]	Y	L	N	>30[9]
Skin	Lifetime	N	Y	Y	N	N	Y/N[10]	Y	N	M	N	
Corneas	Lifetime	N	Y	Y[11]	N	N	N	Y[12]	N	L	N	
Bone – living donor	Lifetime	Y	Y	N[13]	Y[14]	N	N	Y	N	H	N[15]	
Bone – deceased donor	Lifetime	N	Y	Y	N	N	N	Y	N	L	Y	
Tendon	Lifetime	N	Y	Y	N	N	N	Y	N	L	N	
Amnion	Lifetime	N	Y	Y	N	N	N	Y	N	L	N	≤150
Gametes and embryos	None	Y	Y	N	Y[16]	Y	N	N[17]	N[18]	H/L[19]	Y	10

[1] Yes for living organ donors
[2] Usually retrospective
[3] Yes, of living organ donors
[4] Does not include tissues donated by some organ donors
[5] For maternal sex with MSM
[6] High risk of transmission of hepatitis if undetected by testing
[7] Usually from deceased donors
[8] Pulmonary valves can sometimes be in short supply
[9] One tissue donor may donate multiple tissues, which may be used for multiple recipients
[10] Life-saving in the treatment of burns
[11] NAT testing was introduced on 1 April 2013 at the Corneal Transplant Service Eye Banks and Moorfields Eye Bank; East Grinstead undertakes NAT testing when necessary including testing of immunocompromised donors
[12] Barely in balance
[13] Either NAT testing at donation, or serology at donation and six months later
[14] No repeat testing if NAT was used in the first instance
[15] A study is ongoing
[16] Sperm only
[17] 25% of sperm used in UK is imported, egg recipients often go overseas
[18] Matching for appearance only
[19] Sperm = high risk; eggs and embryos = low risk (very small number of cells).

5. Infectious agents relevant to tissues and cells, and their epidemiology in the UK

5.1. Considerations

Identification of the infections of interest warrants consideration of the complete range of infectious agents endemic in the UK and those imported by returning travellers, including sexually transmitted infections and those with an increased incidence and/or prevalence in MSM**.**

Several characteristics determine whether a specific micro-organism might pose a threat to recipients through transmission in a particular tissue or cell type. These include its life cycle, tissue or cellular tropism, capacity to cause disseminated versus localised infection and whether initial infection is symptomatic or subclinical. Is the infectious agent cleared following primary acute infection or does it persist in the body causing chronic or latent infection with the capacity for transmission to others?

Where a micro-organism persists, are reliable tests available *ie* can infection be reliably inferred (or excluded) by the detection of a positive (or negative) serological response or NAT testing in the individual? Detection of a microbial agent or its component organisms in blood indicates disseminated infection, and the potential for transmission of infection in any tissue or cell type. But many infectious agents, although not directly detectable in blood, may persist in other tissues/cells with the capacity for transmission to a recipient.

If the micro-organism is transmitted in a donation of tissue or cells, are there clinical manifestations? Can infection in the recipient be readily diagnosed? Is the risk of infection significantly greater in an immunocompromised individual? What is the associated morbidity and mortality? Is effective treatment available?

5.2. Key points re donor screening

- Employment of NAT testing for HIV, HBV and HCV greatly shortens the window period and facilitates the use of urgent (*eg* HSC) donations without the need for long quarantine periods and follow-up serological screening.

- NAT testing cannot be used as a substitute for antibody testing. Specific IgG [1]is generated following infection with the microorganisms which cause chronic infections. Detection of the specific IgG in a donor indicates previous or persistent infection with that agent and the potential for transmission in cells or tissues, regardless of whether it

[1] IgG: immunoglobulin G is an antibody isotype produced by the body in response to specific pathogens. IgG can be measured as a diagnostic test to determine presence of a pathogen.

can be detected in blood or other body fluids. Serological testing is therefore mandatory and cannot be replaced by the use of NAT.

- Whereas live tissue donors can provide their own sexual history directly, this safeguard does not apply to donations from deceased donors. Indeed the ability of the GP or next of kin to provide a reliable recent sexual history will be doubtful in many cases.

5.3. Epidemiology

The previous blood donor selection criteria review [2] examined the epidemiology of a number of blood borne infections which could be transmitted by sexual activity and investigated whether there was an increased risk of these infections in MSM. This document will provide an update on the epidemiology of these previously reviewed infections, and in addition, provide epidemiological information on other infections of importance in tissue and cell donors.

Table 2 shows the infections which were reviewed as part of the MSM blood donor review with additional infections of interest for tissue and cell donors. A summary of possible risk factors for transmission is included. Table 16 (Appendix 8.2) provides more details of the infection risks carried by each tissue or cell type.

Table 2. Infections included in blood donor and tissue donor selection criteria reviews

	Blood donors	**Tissue and cell donors**	
Micro-organism	**Reviewed?**	**Reviewed?**	**Risk factor**
HIV	Yes	Yes	Sexual transmission. High risk: MSM, sex in areas where there is a high prevalence of HIV infection
HBV	Yes	Yes	Sexual transmission - acute MSM/heterosexual
HCV	Yes	Yes	Intravenous drug user/MSM with HIV infection
HTLV	Yes	Yes	Endemic country/heterosexual sex
Treponema pallidum	Yes	Yes	Outbreaks in MSM
HAV	Yes	Yes	Outbreaks in MSM
HHV-8	Yes	Yes	Mainly saliva, sexual activity specifically oral sex. Increased risks in MSM
CMV	No	Yes	Saliva - no evidence of increased risk in MSM
Toxoplasma gondii	No	Yes	Food/animals
EBV	No	Yes	Saliva/kissing common route
Chlamydia trachomatis	No	Yes	Sexual transmission
Neisseria gonorrhoea	No	Yes	Sexual transmission
HSV	No	Yes	Sexual transmission
Varicella zoster virus	No	Yes	No - not sexual route

5.4. Infections of interest for which testing is currently mandatory

There are a small number of infections which are part of the mandatory screening for all blood and tissue donors. These include HBV, HCV, human T-cell lymphotropic virus (HTLV), HIV, and treponemal antibodies (syphilis). These infections are described below.

5.4.1. Hepatitis B virus (HBV)

HBV is a blood borne infection, transmitted parenterally by exposure to blood, perinatally from mother to child and horizontally by contact, often sexually, with an infected person. Depending upon the age when infection occurs, the infection may become persistent (termed a carrier state), commonly seen in infants, or be an acute self-limited infection, commonly seen in adults. The UK is considered an area of relative low prevalence (less than 2%) with an estimated prevalence for HBV carriage of around 0.3% [3]. Most HBV infection occurs in adulthood in the UK following intravenous drug use (IDU) or sexual exposure [4] and usually leads to a self-limited acute infection.

During 2007 national standards were introduced for the reporting of acute HBV cases, with the aim of improving the surveillance and public health follow-up of acute cases. However, risk exposure data is difficult to collect and may not be complete, and therefore should be interpreted with caution. The case definition depends upon detection of hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antigen IgM (anti-HBc IgM) in serum with or without compatible symptoms.

During the year January-December 2011 the local Health Protection Units reported 5,478 hepatitis B cases, of which 428 were confirmed as acute and 57 re-classified as probable acute [5]. After matching with laboratory data, a total of 589 acute or probable acute cases were reported (annual incidence of 1.13/100,000 population). The majority of cases were in men (71%) with men aged 25-44 years having the highest incidence of acute infections. Where possible, data was collected on the most likely source of hepatitis B acquisition for each case. Of these 589 cases only 296 had exposure information available; the most common risk factor was heterosexual sex (58% of cases) with sex between men being the next most common risk disclosed (20% of cases). The incidence in males remains high and the excess of male cases may be due to MSM, however, due to lack of information this is difficult to confirm. The Green Book [3] recommends that people who are at increased risk of acquiring hepatitis B should be immunised against hepatitis B, including MSM. Men who have sex with men are considered to be at increased risk of acquiring hepatitis B infection.

5.4.2. Hepatitis C virus (HCV)

HCV is a blood borne virus most commonly transmitted by parenteral exposure. Perinatal transmission from infected mother to child and horizontal transmission from sex with an infected person are much less common. Acute infection with HCV rarely causes illness but more than half of individuals with acute infections will become

chronically infected. The UK is considered an area of lower prevalence (0.4%) with the worldwide prevalence of chronic infection being 3% [5]. An increase in laboratory confirmed cases of HCV infections has been observed in England from 1,395 in 1995 to 9,908 in 2011 [7].

Enhanced surveillance of HCV in MSM began in January 2008 (Enhanced surveillance of newly acquired hepatitis C infection in MSM study, SNAHC) [8]. Between January 2008 and March 2010, 218 newly acquired HCV cases were reported, over 80% of which were reported from the London centres. The median age at diagnosis was 38 years and 94% of cases had already been diagnosed with HIV. HCV transmission is still ongoing in the MSM community; however, it appears to be decreasing over time. Transmission of HCV in MSM is associated with high-risk sexual practises.

Injecting drug use is still the most common risk associated with HCV. MSM are considered to be at higher risk of HCV infection if they already have HIV infection.

5.4.3. Human Immunodeficiency virus (HIV)

HIV is a blood borne virus most commonly transmitted through sexual intercourse with an infected person. It is also transmitted through parenteral exposure (injecting drug use, through sharing of drug-taking equipment) and vertically from infected mother to child. The risk with oral sex is very low but HIV transmission does occur; however given the lack of data, it is difficult to make summary estimates for the transmission risk through oral sex.

By December 2011 an estimated 96,000 people were living with HIV in the UK, with approximately 24% being unaware of their diagnosis. An estimated 40,100 MSM were living with HIV of whom 20% were unaware of their diagnosis. The risk of HIV in the MSM community remains high. Public Health England (PHE) estimates that if 3.4% of the adult male population are MSM then 1/20 MSM are living with HIV nationally (47/1000) increasing to 1/11 in London (83/1000). In 2011, 6,280 people were newly diagnosed with HIV in the UK, of whom an estimated 48% (3,010) acquired their infection through sex between men. Current data suggest that there is still ongoing and substantial transmission of HIV within the UK by sex between men [9].

5.4.4. Human T-cell lymphotropic virus (HTLV)

Human T-cell lymphotropic virus I (HTLV) is a retrovirus that is endemic in certain parts of the world including Japan, sub-Saharan Africa, and the Americas [10]. HTLV can be transmitted parenterally by blood transfusion, horizontally by sex and perinatally from mother to baby by breastfeeding. An increased risk of infection in women may reflect the much greater efficiency of male to female sexual transmission [11]. PHE collects data on all individuals who test positive for HTLV in the UK. To date only one deceased tissue donor has tested positive in England; however, eight cord blood donors tested positive for HTLV between 2001 and 2011. Current data suggest that HTLV is not associated with sex between men [12].

5.4.5. Treponema pallidum

The UK Blood Services have been screening for antibodies to treponemes since the 1940s. It is also a routine test for all tissue donors. The majority of donors who test positive have evidence of previous infection rather than acute infection. PHE collates and analyses data on sexually transmitted infections reported in England. It reports that in England during 2011, where a sexual orientation was reported, 75% of syphilis cases were diagnosed in MSM (1,955/2,622). This includes cases of primary, secondary and early latent syphilis. The majority of cases were aged between 25 and 44 with only a small number of cases diagnosed in those aged 65+ years [13]. MSM remain the group most at risk of syphilis infection. Syphilis infections declined through the 1980s and early 1990s, probably due to a change in sexual behaviour related to the HIV epidemic; however, since the late 1990s syphilis infections have increased year on year with reports of large outbreaks occurring in cities in the UK including Brighton and Manchester [14, 15]. From the available epidemiological data it appears that spread within MSM follows a different pattern to spread within heterosexuals with more scattered sexual networks being seen involving more potential contacts.

The available data suggest that MSM are at higher risk of acquiring syphilis infection.

5.5. Infections of potential significance for sperm, eggs and embryo donation

5.5.1. Herpes simplex virus (HSV)

Genital herpes can be caused by both HSV1 and HSV2; however there is little data on the prevalence of HSV in MSM. A seroprevalence study [16] looked at the prevalence of HSV in both HIV and non-HIV infected MSM using samples collected in the unlinked anonymous sera study. This used the residual sera from samples collected for syphilis testing. Of the 3,363 HIV seronegative MSM included in the study, 69% were seropositive for HSV1 and 17 % were seropositive for HSV2. The prevalence for both infections increased with age.

5.5.2. Chlamydia trachomatis

Sexually active young adults are at greatest risk of *C. trachomatis.* In most cases the infection is asymptomatic; however if left untreated, *C. trachomatis* may result in pelvic inflammatory disease and reduced fertility in women, and more rarely, epididymitis and Reiter's syndrome in men. In England the numbers of cases in MSM reported by sexual health clinics has risen from 1.300 in 2001 to 5,000. This increase may in part be due to the increased use of NAT for chlamydia infection. A study showed that the prevalence of chlamydia varied by anatomical site in MSM with chlamydia being more frequently isolated from the rectum (8%) compared with the urethra (5%) and pharynx (1%) [17]. Of particular concern are certain serotypes of *C.*

trachomatis, L1,L2,L2a and L3, which may result in Lymphogranuloma venereum (LGV), a condition associated with MSM sexual behaviours. Since 2003 there has been an ongoing outbreak of LGV in Europe and North America. In England the number of cases of LGV doubled between 2009 and 2010 with 99% of cases reported in MSM of which 80% were associated with HIV co-infection.

Chlamydia testing is of particular significance for the donation of gametes and SaBTO recommends that gamete donors (except in the case of direct partner donation) are tested for *C. trachomatis* using NAT.

5.5.3. Neisseria gonorrhoea

Gonorrhoea and chlamydia are the most common sexually transmitted infections in MSM. Data reported from genito-urinary medicine (GUM) clinics to PHE during 2011 show a disproportionate number of gonorrhoea diagnoses in MSM. A total of 7,299 cases were diagnosed in MSM with the infection being more common in those aged 25-34. During the same time period 5,734 cases were reported in heterosexual men. Gonorrhoea diagnoses increased by 61% since 2010, but some of this increase may be due to new testing guidelines and the availability of molecular testing [12]. However, these data suggest that there is still a high burden of disease within MSM. Again this is of significance in gamete donors.

5.6. Other infections of interest

5.6.1. Hepatitis A (HAV)

HAV is an enterically transmitted picornavirus which causes acute hepatitis A. Outbreaks amongst MSM have occurred related to sexual behaviours, but most infections result from exposure to contaminated food or water. HAV has an incubation period of two-six weeks and is associated with a short plasma viraemia in the week before and for the week after the onset of jaundice. Sentinel surveillance data are collected for HAV; however, there are limited data available on how many positive tests are from MSM. The number of males tested at GUM clinics may be used as a proxy measure but there are limited data available to calculate incidence in MSM [18]. Overall the prevalence of HAV in the UK is low; however, sex between men may increase the risk of becoming infected with HAV although the risk remains low.

5.6.2. Cytomegalovirus (CMV)

There is little seroprevalence data available on CMV in the UK. Seroprevalence was estimated from samples collected during 1991 and 2002. In 1991, 2,477 samples were available (43% from males), and 2,760 from 2002 (44% males). Samples were obtained from patients aged between 1 and 80+ years. An ELISA[1] was used to test

[1] ELISA: enzyme-linked immunosorbent assay, a commonly used laboratory test to detect antibodies in the blood.

CMV IgG and a model used to estimate burden across the general population. CMV is thought to be transmitted through close person-to-person contact and it is hypothesised that much of the transmission occurs during childhood by saliva. It was estimated that more that 80% of 65+ year olds have evidence of CMV infection. There are no actual seroprevalence data showing that HIV negative MSM are at greater risk of CMV infection [19].

5.6.3. Epstein Barr Virus (EBV)

There have been a small number of seroprevalence studies carried out looking at EBV in the general population. EBV is spread through saliva; however, there are reports suggesting that the number of sexual partners may be associated with risk of acquisition of EBV [20, 21]. Only a small number of MSM were included in these UK studies. A study carried out in the Netherlands looked at the prevalence of EBV in HIV positive and HIV negative MSM and heterosexual men. No significant difference was seen in the prevalence of EBV1; however, EBV2 was isolated from 67% of HIV positive MSM, 39% of HIV negative MSM and 6% of HIV negative heterosexual men [22].

5.6.4. HHV-8 / Kaposi sarcoma herpes virus (KSHV)

5.6.4.1. Background

HHV-8 warrants detailed consideration for several reasons: HHV-8 has a high seroprevalence in MSM with HIV infection, but HHV-8 is also much more common worldwide in MSM without HIV infection compared with the general population. Higher rates of infection are also seen in regions with classic or endemic Kaposi sarcoma. Non-immunocompromised individuals with HHV-8 infection do not have detectable HHV-8 viraemia, so the change in deferral of MSM from lifetime to 12 months has been deemed to be safe. The minimal risk attributed to blood donation, however, cannot be extrapolated to apply to cell and tissue donations. Indeed HHV-8 may be transmitted in donor organs causing life-threatening disease in recipients. The risk assessment in individual cases is hampered by the suboptimal sensitivity and specificity and lack of standardisation of serological tests. Nor can the absence of HHV-8 viraemia guarantee the safety of non-blood donations. If testing allowed identification of potentially infected donations, this would logically need to be extended to all groups with higher rates of HHV-8 infection.

The available data on HHV-8 have therefore been outlined at some length to facilitate consideration of the individual types of donation.

5.6.4.2. Introduction

HHV-8 is a human herpes virus, which long eluded identification as the transmissible agent responsible for AIDS[1] -related Kaposi sarcoma (KS). Sequences of this

[1] AIDS: acquired immunodeficiency syndrome

gamma herpes virus were eventually amplified from KS extracts in 1994 by Representational Differential Analysis. The virus is detectable in virtually all cases of the different variants of KS: classic, endemic, iatrogenic (immune-suppression related) and epidemic (AIDS-related) KS. HHV-8 is also aetiologically linked with primary effusion lymphoma and multicentric Castleman's disease [23].

5.6.4.3. Cellular tropism and natural history

Following primary HHV-8 infection, high HHV-8 viral loads are initially detectable in peripheral blood mononuclear cells and plasma. Viraemia is usually short-lived and does not recur unless the host is immunocompromised and/or develops HHV-8 related disease.

Following primary infection, HHV-8 establishes lifelong latency in cells of lymphoid origin. CD19+ B-cells are the natural reservoir of HHV-8. HHV-8 can also infect different cell types *in vivo* including endothelium-derived spindle cells, epithelial cells, macrophages and CD34+ haemopoietic progenitor cells [24, 25].

In latent infection the genome persists as a viral episome, with viral gene expression confined to half a dozen latency proteins including the latency associated nuclear antigen (LANA). LANA is needed for persistent infection, and may also have a role in oncogenesis[1]. Induction of the lytic or productive phase generates new infectious virions, principally in oropharyngeal B-lymphocytes and accompanied by the expression of virus-encoded inhibitors of apoptosis and promoters of cellular proliferation. The highest quantities of infectious virus are found in saliva, facilitating salivary transmission.

5.6.4.4. Clinical features

Primary infection is typically asymptomatic in immunocompetent individuals, but it may cause a mild rash illness with lymphadenopathy in MSM.

Non-neoplastic HHV-8 diseases may occur following solid organ or autologous/allogeneic HSCT. These include plasmacytic B-cell lymphoproliferation, bone marrow failure and hepatitis [26, 27].

The risk of HHV-8 associated KS, or more rarely primary effusion lymphoma and Castleman's disease, appears to be inversely related to immune function. Thus both epidemic and iatrogenic KS may be successfully treated by anti-retroviral therapy induced immune constitution or immune suppression dose reduction respectively.

5.6.4.5. Diagnosis

HHV-8 associated neoplasms are readily diagnosed on histopathological examination of tissue biopsies but diagnosis of HHV-8 infection is more challenging.

Despite significant limitations, serology remains the best way to identify infected individuals. The initial serological response is to structural viral proteins produced in the early phase of productive or lytic infection. Subsequently the antibody profile matures, and antibodies to the latency antigens (LANA) predominate. In contrast with other persistent virus infections, not all HHV-8 infected individuals test seropositive. This may be because of variable, unpredictable or unsustained humoral immune responses, and optimal antigenic targets may yet be identified. With widespread variation in the reliability of in-house and commercial assays, testing is neither standardised, nor automatable, with continued reliance on indirect immuno fluorescent assays (IFA) [28]. Currently optimal testing requires separate testing algorithms for antibodies to both lytic and latent (LANA-1) proteins, to maximise sensitivity and specificity [29]. These challenges have hindered the development of routine screening pre-transplant and in other risk situations [26].

HHV-8 infection cannot reliably be detected by NAT testing of blood. DNA is not usually detectable in the blood of immunocompetent individuals, nor necessarily in patients with KS. Saliva may be a more reliable sample for detection of HHV-8 DNA.

In patients with primary HHV-8 post-organ transplant, viral load monitoring may be useful in predicting the HHV-8 associated non-neoplastic diseases. However NAT testing appears to be of limited value in predicting or managing post-transplant KS and indeed 50% or more patients with post-transplant KS may test negative for HHV-8 DNA in blood [26].

5.6.4.6. Epidemiology and transmission

The prevalence of HHV-8 shows significant geographical variation, with high infection rates of over 50% in sub-Saharan Africa and the Amazon basin where KS is endemic.

Intermediate prevalence rates of 5-20% occur in Mediterranean countries, the Middle East and Caribbean, mirroring the occurrence of classic KS. The UK, the rest of Northern Europe, North America and Asia are low incidence zones with prevalences of less than 5% [23, 30].

Higher prevalences are seen in immunocompromised populations, compared with the general population, most notably among HIV-infected MSM, of whom 30-40% have HHV-8 infection. MSM in USA and UK who do not have HIV are much more likely to have HHV-8 infection than the general population [31].

HHV-8 is sexually transmitted among MSM. The risk of HHV-8 has been correlated with the number of sexual partners and particular practices including oral sex. Heterosexual transmission also occurs but appears to be a less efficient means of transmission than homosexual sex.

Infected individuals shed virus in saliva and saliva now appears to be the principle route of transmission, accounting for frequent childhood acquisition in regions with endemic or classic KS [31-33].

5.6.4.7. Congenital and perinatal transmission

Rare cases of congenital and perinatal infection, with HHV-8 DNA detected in neonatal blood, have been described in zones of both high and intermediate prevalence. Maternal HIV co-infection may increase the risk of vertical transmission. Di Stefano et *al* have demonstrated HHV-8 infection of placental cells *in vitro* and detected HHV-8 DNA and a latent viral antigen in placenta from seropositive women, but without infant follow-up or testing [34]. In a study of 245 pregnant women in Italy, 30 of whom were HHV-8 seropositive, HHV-8 DNA was not detected in the amniotic fluid (n=27) or cord blood (n=3) samples tested [35].

5.6.4.8. Semen / male gametes

Wide variation in the prevalence of HHV-8 in semen prompted a multicentre study which showed polymerase chain reaction (PCR) contamination in association with the use of nested PCR assays [36]. In the uncontaminated tests, HHV-8 DNA was detected in semen samples of 2 of 30 healthy donors and in 1 of 7 HIV-infected men. These results were not readily reproducible however, with the same samples yielding positive results in just 3 (1.6%) of the 184 PCR assays in which they were tested [36]. As the authors commented, “This suggests that HHV-8 DNA is present in semen at concentrations that can be too low to allow its consistent detection.”

In situ PCR, an exquisitely sensitive research tool, has been used to identify the cellular reservoirs of HHV-8 in the semen of HIV-1 infected and uninfected men. HHV-8 was detected in the spermatozoa and mononuclear cells of the semen of 64 of 73 (88%) HIV1 infected men. Co-culture studies suggested that the HHV-8 infected sperm could potentially transmit infectious virus to uninfected cells. HHV-8 was also detected in 2 of 45 semen specimens from HIV-1 uninfected men, and at lower frequencies – less than 1 in 10,000 sperm or mononuclear cells [37].

5.6.4.9. Blood transfusion

HHV-8 DNA is not as a rule detectable in the blood of seropositive individuals. Blood donors with recently acquired infection from endemic regions may be more likely to be viraemic.

In the USA, no blood donor has been found to carry HHV-8 DNA [38, 39]. In a 2010 study of 164 blood donors, including 7 testing seropositive, HHV-8 DNA could not be detected in peripheral blood mononuclear cells (PBMC), induced/cultured PBMC or B-cells of any donor [37]. In three North American studies, conducted prior to routine leucodepletion and HIV-risk donor deferral, no case of transfusion transmission was documented among 151 seronegative recipients of HHV-8 seropositive blood [38]. Two putative seroconversions in the US could not be linked to donor infection [38]. Similarly transmission by blood transfusion in a Ugandan study is in doubt, given the likelihood of familial infection and lack of seroconversion in the corresponding recipient in all 12 recipient pairs [38]. KS has not been associated with transfusion-acquired HHV-8.

In a recent study of 5,009 blood donors in Southeast England, representative of the UK blood donor population, just (36) 0.7% showed repeatable reactivity for the anti-HHV-8HHV8 IgG enzyme immune assay (EIA) screening assay [40]. No sample could be confirmed as positive however, despite extensive confirmatory testing including further lytic EIA, LANA IFA and PCR testing of both buffy coat and plasma. Leucodepletion and storage of red cell components at 4 degrees for up to 42 days is likely to further reduce the seemingly very small risk of infection in the UK.

5.6.4.10. Solid organ transplantation

Post-transplant KS has been reported at frequencies of 0.5-5.3%, reflecting the regional seroprevalence of HHV8 and the higher risk associated with renal transplantation [26, 30]. Recipients are at risk of transplant-transmitted primary infection or of reactivation of pre-existing HHV-8 infection [25, 41-44]. Primary infection has been estimated to cause disease in between 8% and 38.5% of renal transplant recipients, seemingly dependent on the intensity of immunosuppression, demographic factors and specific immunosuppressive agents [24, 26, 30].

Post-transplant KS occurs a median of 30 months post-transplant, with visceral involvement in 25%-35% of cases and mortality of 8%-14%. HHV-8 infected neoplastic cells in post-transplant KS have been shown to originate from the donor in some cases [45].

Early cases documenting transmission by organ donation suggested this was a substantial problem, but recent papers from France suggest infection is much more common than disease [46, 47]. In a prospective study of 4,969 renal transplant recipients, 31% of seronegative recipients with a seronegative donor seroconverted for HHV-8. Just 3.1% (2/64) of HHV-8 seronegative recipients with a seropositive donor and 13% (21/161) of seropositive recipients with a seronegative donor developed KS, and there was no difference in survival or graft loss compared with the seronegative recipient and seronegative donor group [46]. More recently in a study of liver, kidney and heart transplants, viraemia was detected only in liver recipients (4 of 89) and three patients developed KS over 2 years of follow-up [47]. While emergency pre-transplant donor screening to exclude positive donors is neither feasible nor indicated, given the lack of reliable, specific HHV-8 screening tests and low morbidity of primary HHV-8 infection, the authors suggest consideration of less urgent testing to identify at-risk recipients for monitoring. A further consideration would be the choice of antiviral and immunosuppressive regimens, given the anti-HHV-8 activity of val/gancivlovir and foscarnet and the anti-KS activity of the mTOR inhibitor sirolimus (Rapamycin), apparently mediated by augmentation of specific cytotoxic T lymphocyte responses [24, 26, 30].

5.6.4.11. Pancreatic islet and hepatocyte transplantation

HHV-8 transmission has been documented in recipients of kidney-pancreas transplants, but there appear to be no reported cases with islet or hepatocyte transplantation.

5.6.4.12. Haemopoietic stem cell transplantation (HSCT)

Italy has an intermediate prevalence of HHV-8, but in a study of 187 HSCT donor and recipient pairs no case of KS had occurred after a median follow-up of 6 years [48]. This was despite pre-transplant HHV-8 seropositivity rates of 13% and 11% respectively among donors and recipients. 28% (5 of 18) seronegative recipients from seropositive donors seroconverted, and viral DNA [49] was not detected in blood of any of the 5 [48]. Interestingly, another 14 (9%) recipients of 149 seronegative donors also seroconverted.

HHV-8 neoplasia is uncommon in HSCT recipients, with a total of just 10 (8 allogeneic; 2 autologous) published cases of KS, 3 of them fatal. HHV-8 has been associated with non-neoplastic manifestations post-HSCT including bone marrow hypoplasia [27].

For the most part, HHV-8 disease post-HSCT seems to result from virus reactivation in the recipient rather than transmission from the donor. Explanations for the surprising lack of cases post-HSCT include the clearance of HHV-8 by myeloablative conditioning, chemotherapy, total body irradiation and the inhibition of neoplasia by post-transplant alloreactivity and other mechanisms during immune reconstitution [26].

5.6.4.13. Cord blood

To estimate the risk of herpes virus transmission by cord blood transplantation, samples from 362 donors in Colorado were tested by NAT. HHV-8 DNA was not detected in any sample but only 16 of the donors were HHV-8 seropositive [50].

5.6.4.14. Tissues

There appear to be no published data on HHV-8 transmission following transplantation of cornea, skin, bone, amnion, tendon or heart valves from either live or deceased donors.

5.6.5. Conclusions on HHV8

HHV-8 transmission seems rarely to pose a serious threat to HSCT recipients – with any associated risk justifiable by a life-saving donation. There appear to be no data re HHV-8 transmission by pancreatic islets or hepatocytes.

For gamete donation, the available data suggest that HHV-8 is not generally detectable in HIV-negative semen donors; there is very little data available for HIV negative MSM and/or HHV-8 positive men. Single cell ova and embryos are unlikely to transmit HHV-8

Whereas sterilised tissues are safe, unsterilisable tissues, especially more vascular tissues with a significant lymphoid cell component such as skin or unprocessed bone,

could potentially transmit HHV-8. While such grafts do not warrant administration of immunosuppressive therapy, acquisition of HHV-8 in a tissue graft might pose a threat in patients with compromised immune function.

Given the lack of data in some of these areas and the diagnostic difficulty associated with HHV-8, it would be advisable to institute surveillance of non-HIV associated KS among recipients of unsterilised tissues, if lifetime deferral of MSM is replaced by 12 month deferral for MSM activity.

5.7. Epidemiology of infections in current UK donor population

The NHS Blood and Transplant (NHSBT)/PHE Epidemiology Unit collects data on infected tissue and live surgical bone donors in England, Scotland and Northern Ireland. Currently, there is no routine surveillance system for cornea or stem cell donors that collates epidemiological data. The Human Tissue Authority (HTA) collects information on serious adverse events and reactions.

Data are collected on the numbers of donors tested, and the number testing positive in the routine tests for HIV, HBV and HCV, HTLV, treponemal antibodies and HBV anti-core. Where appropriate, additional testing related to travel-related risks is carried out and these data are also collected.

5.7.1. Tissue and cord blood donors from England 2011

During 2011, 512 deceased donors and 4,337 living surgical bone donors were tested. Of the deceased donors one of the 512 tested positive for treponemal antibodies, probably due to a long-past syphilis infection, and one donor tested positive for HTLV, the first HTLV positive deceased donor since testing began. Of the surgical donors, six were positive for treponemal antibodies and two for HCV infection. To date, only one HIV positive donor has been detected: a deceased tissue donor. Cord blood is collected at six centres around London located in areas where the population is ethnically diverse. Mothers are usually routinely screened as part of their antenatal checks for HIV, HBV and treponemal antibodies. During 2011 one cord blood donor tested positive for HCV and one donor was HTLV positive.

5.7.2. Cumulative tissue donor data 2001-2011

Since the start of infected tissue donor surveillance in 2001 in England, 20 deceased donors and 98 surgical bone donors have been identified with positive markers giving rates of 496.2 and 282.0 infections per 100,000 donors tested respectively including anti-HBc, a marker not routinely used for blood donors.

5.7.3. Tissue and cord blood donors from Scotland (2005-2011) and Northern Ireland (2007-2011)

Surveillance of infections in tissue and cell donors tested by the Scottish National Blood Transfusion Service (SNBTS) commenced in 2005. Tissue and cell donors are

not split by donor type but most are surgical bone donors. To the end of 2011, 12 infections were identified in total, 9 of which were markers for treponemal antibodies, giving an overall rate of infection of 115.4 per 100,000 donations.

Tissue and cell donor surveillance of donations tested by the Northern Ireland Blood Transfusion Service (NIBTS) commenced in 2007. Cumulatively, two infections have been detected in surgical bone donors (one HCV and one treponemal antibody positive).

5.7.4. Anthony Nolan: stem cells, data supplied by Anthony Nolan

All donors undergo testing for markers of infection at the time of having extended or confirmatory HLA typing. Initial tests are carried out for HBsAg (HBV surface antigen), anti-HCV and anti-HIV. All repeat reactive tests are further tested at the Royal Free Hospital Foundation Trust using serology and NAT testing and confirmed at PHE Colindale. Donors with an infection are not routinely asked about risk history. Anthony Nolan registers donors from across the UK.

5.7.5. British Bone Marrow Registry (BBMR): stem cells

BBMR is managed by NHSBT and recruits donors from England and north Wales. All donors are blood donors who have given at least one screen-negative donation. There are currently almost 324,000 individuals registered, aged between 18 and 60. The rate of infections in repeat blood donors has been used to estimate the risk of infection in BBMR donors.

5.7.6. Comparison of blood and tissue donors

The rate of infections in blood donors is described as a rate per 100,000 donations whereas for tissue donors the rate is described as per 100,000 donors. The number of tissue donors is low in comparison to the number of blood donations screened and therefore only one positive donor will result in a high rate per 100,000 donors. This is appropriate, as very few if any tissue donors donate on more than one occasion. The number and rate of markers of infection in blood donations is always higher in new or ‘one-off’ donors as any prevalent infections are identified and such donors are permanently deferred from donation. Repeat blood donors therefore have very low rates of infections as they will have been previously tested. However, occasionally repeat donors do test positive for markers of infection. These are usually seroconversions, and are due to an acute infection being acquired due to high-risk behaviour in the interdonation interval. There is always a small risk that an acute infection will not be detected because it is a very recent infection and therefore in the window period and below the limitations of detection of current screening tests.

From 2001 to the end of 2011 in England there have been no cases of HIV or HTLV in surgical bone donors and one case of HIV and one of HTLV in deceased donors. The rate of treponemal antibodies appears high for both surgical bone and deceased donors across England, Scotland and Northern Ireland. However, these results are most likely due to past cases of syphilis. Surgical bone donors are usually aged 60+

years and therefore have had the potential to be exposed to blood borne infectious diseases for a longer period of time than most blood donors.

A comparison of markers of infections in blood and tissue and cell donors is shown in Table 3.

Table 3. Infections in England, Scotland and Northern Ireland donor population: blood donation 2011 and cumulative tissue and stem cell donor data

		HBV		HCV		HIV		HTLV		Treponemal antibodies	
England	**Total**	**n**	**Rate/100,000**	**n**	**Rate/100,000**	**n**	**Rate/100,000**	**n**	**Rate/100,000**	**n**	**Rate/100,000**
Blood – all donors[a]	2,044,422	71	3.5	71	3.5	19	0.9	13	0.6	65	3.2
Blood[a] - first time donors	174,568	67	38.4	66	37.8	7	4.0	10	5.7	54	30.9
Blood[a] – repeat donors	1,869,854	4	0.2	5	0.3	12	0.6	3	0.2	11	0.6
Surgical bone[b]	39,087	13	33.3	12	30.7	0		0		47	135.3
Deceased tissue[b]	4,543	1	22.0	4	88.0	1	22.0	1	22.0	8	176.1
Cord blood[d]	15,366	0		12	78.1	0		8	52.1	6	39
Scotland											
Blood - all donors[a]	231,103	13	5.6	10	4.3	3	1.3	0		13	5.6
Tissue cell donors 2005-2011	10,399	3	28.8	0		0		0		9	86.5
Northern Ireland											
Blood - all donors[a]	63,527	0		1	1.6	0		0		3	4.7
Surgical bone donors 2007-1010	737	0		1	135.6	0		0		1	135.7
Anthony Nolan 2001-2011[c]	17857	4	22.4	13	72.8	3	16.8				Not Tested

[a] England and north Wales blood donors 2011 data, rate per 100,000 donations
[b] 2001-2011 rate per 100,000 donors England
[c] 2001-2011, one donor tested positive for both HBV and HCV. HCV RNA data are not routinely available
[d] NHSBT recruits cord blood donors from hospitals in and around greater London to ensure that they are from a wide range of black, Asian and minority ethnic communities. HTLV is more common in certain parts of the world including South America, the Caribbean, parts of Africa and Japan. The higher rates of HTLV observed in cord blood donors are related to the greater ethnic diversity within this donor group. The main risks for acquiring HTLV are prolonged breastfeeding by an infected mother and sex with an infected partner. **Rate per 100,000 donors for tissue donors**
Rate per 100,000 donations for blood donors

5.7.7. Risk exposures, age and ethnicity of infected tissue and cell donors tested by NHSBT

All blood donors who have markers of infection are contacted by the relevant Blood Service, given advice about their infection and asked about potential risk factors. A similar approach is followed for surgical bone donors. However, it is not always possible to identify a possible risk and in some cases donors are embarrassed about past infections such assyphilis. In contrast to blood donor surveillance, the Blood Services have very little information about risk factors for surgical bone donors. In recent years our risk information data have improved. However, given the age of donors and the time from acquisition of infection, it may be difficult to assign a risk factor. Due to the lack of risk information it is very difficult to conclude anything about compliance with the donor selection criteria in this group of donors. However, given the way in which donors are recruited to donate, ie one-to-one, it could be thought that donors may be more likely to disclose any risks compared to blood donors.

There is no routine collection of risk information for deceased donors. Risk information for deceased donors is supplied by relatives or friends, who may not be aware of any behavioural risks in the donors. It is not possible to ascertain how accurate data on risk factors may be in this group of donors. Of the limited risk data collected it is known that most treponemal infections in surgical bone donors were past syphilis infections, acquired many years ago. Table 4 shows the age, ethnicity and risk exposures reported for infected deceased and surgical bone donors between 2001 and 2011, where available.

For surgical bone donors, in 52/76 cases (68%) no risk exposure was identified either because of incomplete follow-up (34/76) or because no risk was identified despite a post-test discussion (18/76). Where a risk exposure was available, six surgical bone donors reported ‘other’ blood contact as the possible source of their infection (including tattoo/acupuncture/body piercing, nosocomial exposure and/or possible occupational exposure) while five reported blood transfusion as their most likely risk (all five transfusions occurred prior to 1980). To date no male surgical bone donor has disclosed sex with another man as a risk factor for acquiring an infection. Other possible risk exposures reported by infected surgical bone donors are shown in Table 4. Where known, the majority of infected surgical bone donors were of white ethnicity (95%, 52/55).

Table 4. Age, ethnicity and risk exposures reported for infected tissue donors identified by NHSBT, 2001-2011[1]

Characteristics	Deceased[2]		Surgical bone[3]	
	Male	Female	Male	Female
Number	10	3	35	41
Mean age (years)	58.9	61.7	68.8	69.0
Ethnic background				
White	0	0	23	29
Black African	0	0	0	0
Black Caribbean	0	0	1	0
Chinese	0	0	0	1
Indian/ Pakistani/ Bangladeshi	0	0	1	0
Not available	10	3	10	11
Risk exposures reported				
Injecting drug use	0	0	0	1
Sex between men and men	0	0	0	0
Sex between men and women	0	0	2	5
Blood transfusion recipient	0	0	0	5
Other blood contact[4]	0	0	5	1
Mother to infant	0	0	0	2
Born in an endemic country	0	0	2	1
Interviewed – no risk identified	0	0	7	11
Incomplete follow-up	10	3	19	15

[1] Excludes donors with positivity for anti-HBc (HBV core antibody) only, ie HBsAg and/or HBV NAT positive only

[2] One donor with a dual infection (HCV/treponemal antibody positive)

[3] Three donors with dual infections (2 HCV/ treponemal antibody positive, 1 HBV/ treponemal antibody positive)

[4] Other blood contact includes tattoo/acupuncture/body piercing, nosocomial exposure and/or possible occupational exposure.

5.7.8. Age and gender of donors

The age and gender of English blood and tissue donors are reported in Table 5, and in charts provided in Appendix 8.3. As has previously been noted by other authors the age of blood donors is significantly different to that of tissue donors. There is a minimum age of 17 years for blood donation and assuming donors are well they may continue to donate beyond their 65th birthday.

Data are available for deceased tissue and living surgical bone donors in England. The deceased tissue donors range in age from less than 12 months to 91 years. The median age for male donors is 49 years compared to 53 for female donors.

Surgical bone donors in England range from 21 years to 96 years with a median of 61 years for males and 59 years for females. The difference in age profile between these donor groups may impact on the risk of infectious diseases in these donors.

Table 5. Summary of age and gender of blood and tissue donors in England 2011

	Age of donors (years)					
Type of donor	mean	median	mode	min	max	Total
New Blood donor						
Male	32	29	18	17	70	75,236
Female	32	29	18	17	73	98,293
Deceased tissue						
Male	54	49	64	<1	91	333
Female	54	53	65	<1	87	197
Surgical bone						
Male	66	61	64	21	96	1961
Female	67	59	63	23	95	2429

5.7.9. Post-transplant infections

Currently, as with blood transfusion recipients, there is no routine follow-up of transplant recipients to check for development of post-transplant infections. However, for both blood transfusion and tissue recipients there are systems in place for reporting of post-transfusion and other untoward events post–ransplant (SHOT[1]/SABRE[2] and the HTA respectively). These are all passive systems and rely on reporters to identify an infection in a recipient and then to identify the transfusion or transplant, and perform further work to confirm whether or not this was the cause of the infection. Work has been carried out by the World Health Organisation (WHO) with support from the EU on the

[1] SHOT: Serious Hazards of Transfusion (http://www.shotuk.org/)
[2] SABRE: Serious Adverse Blood Reactions and Events (http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Blood/)

vigilance and surveillance of substance of human origin (SOHO V&S http://www.sohovs.org/soho/). This has involved experts from throughout Europe. A library of papers and associated information relating to transmission of infectious diseases and other adverse events is available at http://www.notifylibrary.org/. The database is still under development but will provide a useful information source. During 2011 no infectious disease transmissions were reported to the HTA from tissue or cell transplants.

5.8. Estimates of residual risk of not detecting HBV or HCV window period infections in surgical bone donors

The estimated risk of HBV and HCV window period infections in surgical bone donors which would be missed by testing was most recently calculated in 2011. These estimates were based on donor data collected between 2005 and 2010. The residual risk of an infectious blood donation being released was calculated for HIV, HBV and HCV using two years of data. However, a modified method was needed for tissue donors because of the small number of observed positive donors. Incident infections in surgical donors are difficult to assess given that most donors will donate only once. Incidence data was derived from new blood donor data. Given the difference in age groups data were stratified into donors aged less than 50 years and 50+ years, and also on the basis of gender. There is a higher incidence of HBV in blood donors, mainly women aged under 50; this group is under-represented in bone donors.

Residual risk of an infectious donation being released for issue was only calculated for HBV and HCV and only for surgical bone donors in England. There have been no HIV infections reported to date in surgical bone donors so therefore the risk of a missed window period HIV infection cannot be estimated. During the period used in the risk estimate (2005-10) the window period for HCV testing was greater for bone donor testing than for blood donors, as 60% were tested using serology alone. This has some impact on the results. If HCV NAT had been used for all bone donors tested, the estimate would reduce from 0.34 to 0.04 per million. The small numbers of infections observed in bone donors adds to the uncertainty in the model. Residual risks were calculated using data over a five year time period; data were stratified into males and females and by age as less than 50 years and 50 years or older.

Risks calculated for the period 2005-2010 were estimated as 1 per 2.38 million for HBV and 1 per 2.96 million for HCV (or one every 500 years) (Table 6).

The risk of an undetected window period HBV or HCV infection among surgical bone donors in England between 2005-2010 was estimated to be very low. This very low estimated risk is due to the highly sensitive testing systems in place and the low estimated incidence of infections in this group of donors. The estimated risk for HBV among surgical bone donors was lower than among blood donations mainly due to the higher incidence in young female

blood donors. The estimated risk for HCV in surgical bone donors was higher despite a lower incidence in the donor population due to the sensitivity of the tests used over this period for blood donation versus surgical bone donors. There are limitations to these data; the low number of infections in bone donors gives rise to uncertainty around the estimates of incidence and prevalence used in the model and therefore the overall risk estimate.

These data suggest that one HBV positive will be missed in approximately 2.4 million donors tested, and an HCV positive in every 3 million donors tested.

These risks are very small when put in context of how many tissue donors are screened each year.

Table 6. Estimated risk of testing NOT detecting HBV and HCV window period infections in surgical bone donors in England and in donations from new donors in the UK, 2005-2010

	HBV	**HCV**
Risk due to window period	2005-2010	2005-2010
Surgical bone (England) [1] [2] [3]		
per million	0.42	0.34
1 per x million	2.38	2.96
Donations from new blood donors (UK) [4] [5]		
per million	4.28	0.06
1 per x million	0.23	17.27
Risk ratio (surgical bone:new blood donors)	0.1	5.7

[1] Prior to September 2008, some donors were tested on both initial and follow up samples - only initial testing is considered here.
[2] Surgical bone donors were tested for HBsAg (window period (WP) 66.8 days), HBsAg and anti-HBc (combined WP 38.3 days) or HBsAg, anti-HBc and HBV DNA (combined WP 38.3 days). The overall length of the window period was adjusted for the proportion of tests in use (ie 34%, 26% and 40% respectively) to give a weighted WP of 52.2 days.
[3] Surgical bone donors were tested for anti-HCV (WP 59 days) or anti-HCV and singleton HCV RNA (combined WP 4 days). The overall length of the WP was adjusted in the proportion of tests in use (60% and 40% respectively) to give a weighted WP of 37 days.
[4] Blood donors were tested for HBsAg (78%) or HBsAg and HBV DNA (22%) giving a weighted WP of 60.5 days.
[5] All blood donors were tested for anti-HCV and HCV RNA giving a combined WP of 4 days.

5.9. Emerging infections

All blood services are concerned about the possibility of the emergence of a previously unidentified infectious agent. Since 1980 over 25 new infections have been identified, the majority of which have been zoonoses which may have emerged due to changes in habitat or climate. In addition infections which were previously only seen in Mediterranean areas of Europe have spread further west eg West Nile Virus. Currently hepatitis E is of concern with the possibility of transmission by transfusion of immunocompromised individuals. Hepatitis E is a short-lasting, often asymptomatic illness in immunocompetent individuals but can result in chronic infection in those who are immunosuppressed.

Since the mid1980s when HIV was identified there have been great improvements in surveillance mechanisms both across blood services and also between international public health services. These systems are a useful early alert system for blood borne viruses and it is expected that any emerging infections will be identified within months rather than years.

6. Tissue-specific risk assessments

6.1. Process

The group considered the data on generic or tissue-specific risks, previously reviewed in section 4. It was noted that epidemiological data on donors was available only for tissue donors handled through the UK Blood Services; no comparable data exist for tissue donors handled through other tissue banks, nor for donors of stem cells, pancreatic islets or gametes. The UK Blood Services data are on small numbers of surgical bone donors and, to date, none of the donors with markers of infection in this limited dataset have disclosed MSM behaviour as a possible risk factor for acquisition of infection. Only one tissue donor, a deceased donor, has tested positive for HIV.

Therefore, unlike the work on blood components, calculations of residual virus risk according to different MSM deferral periods are not possible.

The group followed a two step process to reach its recommendations for different tissues and cells.

The first step was to categorise the types of products into groups, based on the criteria outlined in section 3. Other factors which were also considered were (a) safety of current practice, and (b) operational simplicity for providers

The second step was to make recommendations on deferral criteria for the resulting four groups of products.

Group 1: Haematopoietic stem cells, whether from family and friends, or unrelated adult donors, or from cord blood. As stated in the Terms of Reference, this also includes related products from the same donor types eg donor lymphocytes, and virus-directed T cells.

Group 2: Pancreatic islets and hepatocytes.

Group 3: Banked tissues: bone, whether from living or deceased donors: heart valves, corneas, skin, amnion and tendon.

Group 4: Sperm, eggs and embryos, for reproductive purposes (not for generation of cell lines).

It was recognised that some banked tissue products (skin, heart valves) can be life-saving. It was concluded, however, that to have different recommendations for specific banked tissues from the same donor was operationally over-complicated, with the consequent risk of error.

6.2. Haemopoietic stem cells (HSC) and lymphocytes

6.2.1. Background

HSC are used for allogeneic transplantation in a wide variety of malignant and non-malignant diseases [51]. Following transplantation, lymphocytes from the same donor may be requested to rescue engraftment or treat early relapse. Rarely, disease-specific lymphocytes may be selected and infused (such as CMV-specific T-lymphocytes).

There are three main sources of HSC:

- Bone marrow (BM). This is obtained surgically, with the donor under general anaesthetic. Bone marrow stroma and blood are extracted from the bone marrow space of the posterior ilium. Rarely, bone marrow may be extracted from the anterior iliac crests or sternum.

- Peripheral blood stem cells (PBSC). PBSC are harvested through peripheral blood leukapheresis (white cell apheresis). Prior to harvest donors are given a short course of granulocyte colony stimulating factor (G-CSF), which mobilises HSC into the peripheral circulation.

- Cord blood unit (CBU). The umbilical cord blood, and blood from the foeto-placental circulation, are collected immediately following delivery.

Donor lymphocytes are obtained in an identical way to PBSC (ie leukapheresis), except that mobilisation with G-CSF is unnecessary.

In the UK, the British Bone Marrow Registry (BBMR), the Welsh Bone Marrow Donor Registry (WBMDR) and Anthony Nolan provide unrelated adult donors. There are four cord blood banks, managed by NHSBT, Anthony Nolan, the SNBTS and the NIBTS. In 2011 Anthony Nolan and BBMR aligned to allow their donors to be searchable on a single register, and WBMDR will align in early 2013. As part of this registry alignment, Anthony Nolan now carry out donor medicals and harvests for BBMR donors requested for UK patients. However, BBMR continue to work-up and harvest their donors for non-UK patients.

6.2.2. Context

6.2.2.1. Is it life-saving or life-enhancing?

Haematopoietic stem cell (HSC) transplantation is life-saving. However, despite advances in technology and supportive care since its inception in the mid-20th century, it remains a therapy associated with significant treatment-related mortality and morbidity [52]. For this reason, its use in both malignant and non-malignant conditions has been limited to life-saving indications.

Within this limitation it is now an accepted modality of treatment in a wide range of conditions including chronic leukaemias, lymphoma, myeloma, aplastic anaemia, haemoglobinopathies, inherited metabolic diseases and disorders of the immune system, as well as a developmental approach in some autoimmune diseases [53].

6.2.2.2. Are there supply issues?

The availability of appropriate HSC donors for allogeneic transplantation is determined primarily by the diversity of the HLA system, located within the major histocompatibility complex (MHC) on chromosome 6 [54]. Many loci on each of the two copies of this chromosome have been shown to be significant in determining outcomes from transplant: of these, the class I HLA antigens (A, -B, -C) and class II antigens (DRB1 and -DQB1) are used to ascertain match grade in standard UK practice. A 10/10 allelic-level match for an adult unrelated donor is considered ideal, and many studies support the notion that patients transplanted with HSC from mismatched unrelated donors (defined as one or more antigen or allele-level mismatches at any of the above loci) have inferior survival [55-57]. Indeed this survival decreases incrementally with each additional mismatch [58].

To date, 6,725 class I alleles and 1,771 class II alleles have been identified, reflecting the enormous diversity of the HLA system [59]. As a result, the chance of two randomly selected Northern European Caucasoid individuals being HLA-matched is estimated to be 1 in 20,000 [59]._These odds would lengthen considerably if the same two individuals were of different ethnic origin. In order to beat these odds, large donor registries have been set up worldwide, and a level of global collaboration unrivalled in any other field of medicine has facilitated the provision of a searchable international donor panel of over 20 million volunteer donors [60].

The first choice of donor for HSCT is an HLA-identical sibling. Inheritance of the HLA regions on chromosome 6 follow a simple Mendelian pattern and thus an individual has a one in four chance of being HLA-identical to any one sibling. It is estimated that one in three in need of an HSC allograft will have an HLA-identical sibling who is medically fit to donate, based on an average UK family size. However, decreasing family sizes are likely to impact this, meaning a larger proportion of transplants will be performed with unrelated donors or other HSC sources.

For a patient without an HLA-identical sibling, the chance of finding a matched unrelated donor is dictated by his or her own HLA phenotype. The distribution of HLA phenotypes (defined here as a specific combination of HLA alleles) within a given population is unequal: genetic phenomena such as linkage disequilibrium and founder effects mean that a small number of phenotypes have a very high frequency within the UK population, whilst the majority of phenotypes are rare. Patients with a common phenotype will have the luxury of several hundred matched donors within the UK panel; those with rare phenotypes are likely to have few or none. From studies of the donations

provided by the Anthony Nolan donor panel, 43% of patients transplanted with Anthony Nolan donors had more than 10 matched donors on the UK panel, and 57% had 10 or fewer. 18% had just a single matched donor on the register (with permission, Professor Steven Marsh, Anthony Nolan). Approximately 20%-30% of Northern European Caucasoid patients will have no matches on the UK or international panels.

The situation is far worse for patients from ethnic minorities, where the chance of having multiple potential matches is small [61], and the majority of such patients will have no fully-matched donors on either UK or international panel.

A number of other factors increase the scarcity of 'ideal' donors. Even for those donors with a 10/10 matched unrelated donor, matching for specific genetic polymorphisms in non-standard loci such as HLA-DPB1, KIR and NOD2 may soon become standard practice. In addition, many secondary donor characteristics have been shown to influence outcome and are thus used for donor selection: these include CMV antibody status, donor age and gender, number of prior pregnancies in female donors and source of haematopoietic progenitor cells (HPC) (bone marrow or peripheral blood stem cell harvest) [62].

Furthermore, although a potential donor may be identified on initial search, such a donor may be unable or unwilling to donate for various personal or medical reasons, or the registry may be unable to make contact with that donor. This donor attrition ranges from 15% to 50%, depending on the registry [63, 64].

For cord blood, two main features of donor selection affect the success of the transplant: the degree of HLA match and the cell dose. When cord blood is used as the HSC source there is tolerance of higher levels of HLA mismatch between patient and donor than with adult HPC sources. This is because the T-cells in the cord blood are immunologically naïve and the severity and incidence of graft-versus-host disease is lower compared to transplantation using adult HPCs. CB transplants may be successful when only 4/6 HLA antigens (HLA A, B, DRB1) are matched. However, to obviate a possible increased risk of graft failure in such mismatched CB transplants it is recommended that a higher cell dose is transplanted. Eurocord investigators have suggested a "sliding scale" strategy in unit selection: 6/6 greater than 3, 5/6 greater than 4 and 4/6 greater than 5×10^7 total nucleated cells (TNC)/kg recipient weight [65]. Although there are more than 561,000 cord blood units in over 50 cord blood banks internationally, many of these are units with low cell doses that are not clinically useful.

To try to address the inequalities in the provision of HSCs for transplantation mentioned above many cord blood banks target collection from black and ethnic minority (BME) populations. The NHS Cord Blood Bank currently has a high proportion of rare HLA haplotypes and 40.5% BME representation in its inventory (BBMR 2012). Approximately 35% of issues are to recipients from BME groups. Thus, cord blood units with high TNC levels and wide representation of HLA haplotypes are a precious resource.

In summary, a combination of huge diversity in the HLA system, numerous secondary selection characteristics and donor attrition mean that, for the majority of patients, an ideal donor is a scarce resource.

6.2.2.3. Legislative/guidance requirements for donor selection or testing

Human Tissue Authority (HTA)

The HTA, as one of the Competent Authorities in the UK under the European Union Tissues and Cells Directive, has responsibility for regulating tissues and cells (other than gametes and embryos) for human application. The Directives were fully implemented into UK law on 5 July 2007, via the Human Tissue (Quality and Safety for Human Application) Regulations 2007. All bodies involved in the provision of human cellular products are bound by HTA regulations.

Standards for donor selection (including both related and unrelated donors) are detailed in the Guide to Quality and Safety Assurance of Human Tissues and Cells for Patient Treatments as implemented by HTA Directions 003/2012. Within this legislative document, selection criteria for allogeneic donors, and then specifically for living allogeneic donors, are set out in Annex A. Minimum standards for screening for infectious disease markers are set out in Annex B, and are summarised below in Table 7.

With regard to high-risk behaviour, the following statements from the HTA Directions 003/2012 are relevant:

> *2.2.1. Allogeneic living donors must be selected on the basis of their health and medical history, provided on a questionnaire and through an interview performed by a qualified and trained healthcare professional with the donor, in compliance with point 2.2.2.* ***This assessment must include relevant factors that may assist in identifying and screening out persons whose donation could present a health risk to others, such as the possibility of transmitting diseases or health risks to themselves.*** *For any donation, the collection process must not interfere with or compromise the health or care of the donor.*

However, the HTA does not specify such risk factors, and individual establishments are permitted to provide their own definitions and screening processes for high-risk practices.

WMDA

BBMR, WBMDR and Anthony Nolan are accredited by the World Marrow Donor Association (WMDA), a global association that fosters international

collaboration to facilitate the exchange of high quality HSC for clinical transplantation worldwide and to promote the interests of donors.

The WMDA issues consensus 'white papers', which provide guidance for unrelated donor registries and cord banks on minimum standards expected in the procurement of HSC and other cellular products. The WMDA guidance does not currently cover related donors. Guidance for assessment of donor health, including establishing risk factors for transmission of blood borne infections, is laid out in the *World Marrow Donor Association recommendations for evaluation of donor health* [66]. Whilst this document does advise on certain risk factors pertaining to sexual contact, such as for partners of those with HIV or viral hepatitis, it does not provide guidance on deferral of MSM.

The Joint Accreditation Committee-ISCT & EBMT (JACIE)

JACIE was established in 1998 for the purposes of assessment and accreditation in the field of HSC transplantation. JACIE's primary aim is to promote high quality patient care and laboratory performance in HSC collection, processing and transplantation centres through an internationally recognised system of accreditation. Accreditation is the means by which a centre can demonstrate that it is performing to a required level of practice in accordance with agreed standards of excellence. Essentially it allows a centre to certify that it operates an effective quality management system. However, accreditation is voluntary.

Minimum standards for assessment of allogeneic BM and PBSC donors are set out in the 5th edition of the JACIE standards, particularly section B6.4 "Additional requirements for allogeneic donors". This requires donor evaluation procedures to evaluate the risk of disease transmission from allogeneic donor products. Specific to infectious disease risk, the following is stated:

> *B6.4.2 Allogeneic donors shall be evaluated for risk factors for disease transmission by medical history, physical examination, examination of relevant medical records, and laboratory testing.*
> *B6.4.3 The medical history for allogeneic donors shall include at least the following:*
> *B6.4.3.1 Vaccination history.*
> *B6.4.3.2 Travel history.*
> *B6.4.3.3 Blood transfusion history.*
> *B6.4.3.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.*
> *B6.4.3.5 Questions to identify persons at risk of transmitting inherited conditions.*
> *B6.4.3.6 Questions to identify persons at risk of transmitting a haematological or immunological disease.*
> *B6.4.3.7 Questions to identify a past history of malignant disease.*

B6.4.3.8 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.

The JACIE standards do not provide guidance on deferral of MSM.

NetCord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration

These standards perform the same function as JACIE standards but for cord blood donation and banking. Accreditation to these standards is currently voluntary. Minimum standards for assessment of cord blood donors are set out in the 4th edition of the NetCord-FACT Standards, particularly section C5. Specific to infectious diseases the following is stated:

C5.3.3 A history for the mother's communicable disease risk behaviour shall be obtained and documented.
C5.3.3.1 The mother's communicable disease risk behaviour shall be obtained in a confidential manner.
C5.3.3.2 The history shall include the mother's prenatal communicable disease testing, if known, and results of other general medical testing that could influence communicable disease transmission.
C5.3.3.3 Previously obtained history for communicable disease transmission risk shall be updated to the time of delivery. This shall be completed within 14 days of delivery.
C5.3.3.4 In the case of a surrogate mother who carries an infant donor not genetically hers to delivery, a communicable disease risk history of the surrogate mother shall be obtained and documented.
C5.3.3.5 The communicable disease risk history of the sperm, egg or embryo donor shall be obtained and documented, if applicable.

Guidance provided with standard C5.3.3 states: "History of potentially blood transmissible diseases must be obtained from the mother, tracked with the CB unit, and released to the Clinical Program." Guidance also states "HIV and hepatitis B transmission through high-risk behaviour, for example, intravenous drug use, incarceration and prostitution, are well documented. CBBs must determine the necessity of including such CB units into the inventory, regardless of infectious disease testing results. CB units with a high-risk maternal behaviour that exposes a potential recipient to a risk of HIV or hepatitis transmission must be deferred."

The NetCord-FACT standards do not provide guidance on deferral of MSM.

6.2.2.4. Is there evidence of viral transmission by the tissue/cell?

It is very likely that HSC (either PBSC, BM or cord blood) can transmit most, if not all, of the infections present in blood, since these products all contain, or are derived from, blood.

HBV [67], HCV [68, 69], HTLV type I [70, 71], malaria [72], syphilis [73], Chagas disease [74] and Brucella [75] have all been reported to be transmitted through HSC. Whilst not reported, transmission of HIV through HSC transplantation is thought very likely if the donor is infected. There have been no documented cases of transmission of prion-related diseases through HSC and, whilst reported in recipients of blood and organs (including heart, lung, liver and kidney), West Nile Virus has not to date been shown to be transmitted through HSC.

It is worth noting that in rare circumstances, a donor with a known blood borne infection, such as viral hepatitis or even HIV, might be accepted as a HSC donor because the benefit of transplantation may outweigh the risk of virus transmission [76].

6.2.3. Donor

6.2.3.1. Donor selection

For a patient in need of allogeneic HSC transplantation, an HLA-identical sibling will usually be first choice as donor. If there is more than one HLA-identical sibling, then secondary donor characteristics (eg age, gender, CMV status, blood group) will identify the most ideal donor.

If there are no matched siblings, then the usual route is to identify potentially matched unrelated donors by searching national and international donor registries. In certain circumstances, particularly in paediatric practice, a cord blood unit may be preferred to an adult unrelated donor. Otherwise, search for a cord blood unit will be performed if no suitable adult unrelated donors are found.

On identifying a potentially matched adult unrelated donor, a process of confirmatory typing (CT) occurs, where the registry performs high-resolution HLA typing from a fresh donor blood sample. The purpose is to ascertain if there are any occult HLA mismatches that may not have been apparent on initial search. Concurrently, any unresolved secondary donor characteristics such as CMV status or ABO blood group may be established. For each patient, CT may occur for a number of potentially matched donors (usually 3-6), and may be requested from any one of the 67 donor registries currently listed in Bone Marrow Donors Worldwide. This process may take several weeks, depending on donor availability and laboratory turn-around times.

When CT is completed, the transplant centre may have the option of requesting a particular unrelated donor for work-up and harvest, on the basis of HLA match and most ideal secondary donor characteristics.

Once requested for work-up, the pathway is similar for both sibling and unrelated adult donors: a harvest date is established and the donor will have a medical assessment, including laboratory testing for infectious disease markers, within 30 days of the planned harvest date.

Cord blood selection and acquisition differ from other HSC sources. If a cord blood unit (CBU) is identified on national and international donor registries as the best potential match for a patient, a request will be sent to the cord blood bank to reserve that unit for the patient. At this point, high resolution HLA typing will be performed on a stored sample of cord if not already done. The maternal HLA type will be done to confirm linkage with the donated cord. Infectious disease testing will be done on the CBU and completed on the donor mother if not already done. Also, a blood film is reviewed by an expert neonatal haematologist and an updated medical history obtained on the CB donor from the family doctor. At request for shipment of the CBU, viability and colony-forming unit assays are done on post-thaw segments of CBU to ensure that the cells are capable of dividing and growing and STR (short tandem repeat) confirmation of the identity of the CBU is performed on an attached segment of the donation.

6.2.3.2. Identification of high-risk behaviours

Related donors

Related donors are assessed with a questionnaire designed to pick up high-risk behaviour, generally at the time of medical examination and infectious disease testing. This usually occurs one month prior to donation.

Unrelated adult donors

Anthony Nolan donors complete a medical and lifestyle questionnaire at recruitment (Appendix 8.5.1.1), and then another (more detailed) questionnaire at the CT stage (Appendix 8.5.1.2).

BBMR donors complete a donor health check (DHC) questionnaire at recruitment (Appendix 8.5.2.1) and staff complete a telephone survey with them at the CT stage (Appendix 8.5.2.2) when a donor will also be sent the DHC to complete with up-to-date information.

Donors selected for work-up complete a further medical and lifestyle questionnaire, and may be asked further questions, if relevant, by the donor physician.

Cord blood

Mothers are asked about risk behaviours at the time they give full consent for CB collection. The lifestyle questionnaires used are on page 1 of FRM2289 for the NHS Cord Blood Bank (NHSCBB) (Appendix 8.5.2.3) and DOC1608 CBBF-F1-2 for the Anthony Nolan Cord Blood Bank (ANCBB) (Appendix 8.5.2.4). If the mother answers yes to any of questions 1a-f (NHSCBB) or any of questions 1-20 (ANCBB) the collection will not be taken.

6.2.3.3. Current practice with MSM

Related donors

The decision to proceed with a donor lies with the recipient, the physician performing the medical examination, and the physician caring for the recipient. As mentioned previously, however, discussing such issues with the recipient may be fraught with difficulty.

Unrelated donors

BBMR/WBMDR recruit their HSC donors from the blood donor pool and, as a result, donors with current perceived high-risk behaviour would be deferred at recruitment. As at 2011, MSM who have not had sexual activity for at least a year were permitted to join as blood donors, but could not register as HSC donors. If a donor had been involved in MSM after recruitment and within 12 months of the request for a CT sample, they would be excluded from donation for the BBMR. They are not asked in the DHC about behaviour more than 12 months ago but are asked if they have ever been declined as a blood donor. If MSM occurred more than 12 months before CT, a CT sample could be taken and further information would be sought at donor medical as for the Anthony Nolan below.

Anthony Nolan do not ask about MSM at recruitment, but exclude those donors who self-declare as partaking in ‘high-risk sexual behaviour’. MSM behaviour within the previous year is asked about at both the CT stage and at the donor medical. If it is identified, there is an opportunity for medical staff working for the registry to undertake a thorough sexual health interview to establish other factors that may impact the risk of transmission of blood borne infections, such as number of partners and use of condoms. Following this, the assessing physician will make a judgement on whether the donor should be deferred, or whether to inform the transplant centre to allow them to make a decision.

If the last MSM activity was more than one year ago, then the donor will be allowed to proceed and the transplant centre will not be informed.

Cord blood

In the NHSCBB mothers are asked at the time of their consent to donation (FRM2289, appendix 8.5.2.3) if in the last 12 months they have had sex with a male partner who has ever had sex with another man. Their cord blood will not be collected if this is the case. The ANCBB will not collect cord blood if the mother has ever had sex with a man who has had MSM behaviour.

The current rationale for these exclusions is that the male partner may be continually infectious, and may pass on infection to the woman at any point up to delivery. She may thus be in the window period of an infection when tested.

6.2.3.4. Does the donor have to be matched to the patient?

Whilst a 10/10 HLA match is ideal, many patients will not have this option. In these circumstances, a 9/10 or (rarely) 8/10 match will be accepted. However, mismatched transplants are associated with inferior patient outcome [58].

Matching for cord blood is discussed under *Supply Issues* in the *Context* section above.

If there is no HLA-identical sibling, and neither an unrelated adult donor nor appropriate cord blood unit is identified, then a mismatched related transplant may be considered (haplo-identical transplant), for example from parent to child, or between mismatched siblings.

6.2.4. Testing

6.2.4.1. Testing regime (eg serology, NAT)

Related donors

Infectious disease testing of related donors varies between transplant centres. In general, all potential donors will undergo serological testing as stipulated by the HTA and JACIE (Table 7) within 30 days of donation. Additional testing includes CMV, EBV and Toxoplasma gondii antibodies, as well as other diseases, such as malaria or West Nile Virus, if a relevant travel history is present. Some units may also test all related donors for varicella zoster and herpes simplex.

If more than 30 days elapse between testing and donation, infectious disease marker tests are repeated.

Table 7. Biological testing of living donors of allogeneic tissues and cells mandated by HTA

Infectious disease	**Mandated testing**
HIV-1,2	Anti-HIV-1,2
HBV	HBsAg Anti HBc
HCV	Anti-HCV-Ab
HTLV (I&II)	HTLV-1 antibody (if relevant ethnic origin or exposure history)
Syphilis	Validated serological testing algorithm

Unrelated donors

The testing regimes for unrelated adult donors differ between the UK unrelated donor registries, and these are summarised in Table 8. As with related donors, CMV, EBV and toxoplasma antibodies are also tested.

Table 8. Testing regimes of the unrelated adult donor registries
(Triplex NAT includes nucleic acid testing for HIV, HBV and HCV)

	British Bone Marrow Registry	Welsh Bone Marrow Donor Registry	Anthony Nolan
At recruitment	Anti-HIV-1,2 HBsAg, Anti HBc Anti-HCV-Ab Anti-HTLV I+II Syphilis serology Triplex NAT	Anti-HIV-1,2 HBsAg, Anti HBc Anti-HCV-Ab Anti-HTLV I+II Syphilis serology Triplex NAT	Not performed
At confirmatory typing	Not performed	Anti-HIV-1,2 HBsAg, Anti-HCV Anti-CMV Syphilis	Anti-HIV-1,2 HBsAg Anti-HCV-Ab
At (or by the time of) donor medical	Anti-HIV-1,2, p24 antigen HBsAg, Anti HBc Anti-HCV-Ab Syphilis serology Triplex NAT	Serologic test for syphilis); HbsAg; Anti-HBc; Anti-HCV; Anti-HIV 1 & 2; HIV p24; Anti-HTLV I, II; Anti-CMV; Anti-EBV; Anti-Toxoplasma; Triplex NAT	Anti-HIV-1,2, p24 antigen, HIV RNA HBsAg, Anti HBc, HBV DNA Anti-HCV-Ab, HCV RNA Syphilis serology
At collection	Not performed	Not performed	Not performed

Cord blood

The HTA mandates tests on donor mothers with additional testing on cells stored for allogeneic use as shown in Table 9. These must be done at the time of or within seven days of donation. NetCord-FACT standards stipulate that CMV testing of the maternal donor is also required but testing the CB unit is optional. The CBU should be tested for the same pathogens (apart from CMV) before the CBU is issued for clinical use. The NHSCBB tests the CBU when it is reserved for a transplant.

Table 9. Testing requirements for umbilical cord blood, as mandated by HTA

	Testing at Time of Donation	**Testing When Stored for Allogeneic Use**	
Pathogen	**Serology Testing**	**Serology Testing After 180 Days**	**Alternative Analytical Testing**
HIV-1,2	Anti-HIV-1,2	Anti-HIV-1,2	HIV-NAT
HBV	HBsAg Anti HBc	HBsAg Anti HBc	HBV-NAT
HCV	Anti-HCV-Ab	Anti-HCV-Ab	HCV-NAT
HTLV (I&II)	HTLV-1 antibody (if relevant ethnic origin or exposure history)	HTLV-1 antibody (if relevant ethnic origin or exposure history)	HTLV-NAT*
Syphilis	Validated serological testing algorithm	Validated serological testing algorithm	Not required

*not currently undertaken by NHS CBB as no CE marked HTLV 1 or 2 NAT testing kits available

6.2.4.2. Is there scope to increase the detection rate of testing (funding permitting)?

Related and unrelated donors

Mandatory NAT for HIV, HBV and HCV would shorten the window period, most significantly for HBV. This is now routinely performed at the donor medical assessment at Anthony Nolan, BBMR and WBMDR. For related donors, however, use of NAT varies between transplant centres.

In addition, it is possible to test adult donors (both related and unrelated) at the time of collection. Indeed, this is the policy of the National Marrow Donor

Program in the United States. However, there are two limitations to this practice.

Firstly, to maintain cellular viability and reduce the risk of bacterial contamination, fresh HSC should be infused within 24-48 hours of collection (and at the most within 72 hours of collection); any testing would need to be completed within this time frame to prevent infusion of a potentially contaminated product.

Secondly, HSC collection is critically timed to coincide with completion of patient conditioning (pre-transplant chemotherapy and/or sclerotherapy). If the donation were not given, such as in the case of a positive donor infectious disease marker, then an urgent alternative source of HSC would be needed to rescue the recipient from aplasia. There is a valid concern that false positive results might unnecessarily delay transplantation, with potentially devastating effects on recipient outcome.

Despite this, it is feasible to repeat NAT at collection, and this may be offered on an ad hoc basis, such as when a high-risk behaviour is identified.

Cord Blood

For cord blood the mother is currently tested at the time of donation or within seven days. Most mothers are tested for HBV and HIV at booking for antenatal care such that only a very recent exposure should be missed by NAT testing at donation. The donor could be retested – see below – but the potential loss of donations would be substantial.

6.2.4.3. Is it possible to quarantine the donation and retest donor?

Related and unrelated adult donors

It is theoretically possible to cryopreserve HSC from PBSC or BM collection and retest the donor. However, due to concerns about reduced cellular viability and impaired engraftment with cryopreserved products [77, 78], most transplant centres prefer fresh cells. Unrelated donor registries will only allow cryopreservation in extreme circumstances where infusion is not possible, such as an acute medical deterioration in the recipient.

Cord blood

As cord blood donations are routinely cryopreserved it would be possible to retest the donor mother at a later time after donation. However, experience with trying to access donors for re-bleeds for other reasons at the NHSCBB has shown that it is very difficult to do so. Mothers have donated at the start of a very busy time in their lives and find it hard to make time for NHSCBB

staff to visit to take a blood sample. Home visits are labour-intensive for the NHSCBB staff but asking mothers to go to GPs for blood tests has been even less successful. Mothers donating at the NHSCBB also seem to move house a lot and it is very difficult to keep in touch with them. If a policy of mandating follow-up blood samples were introduced there would be a high attrition rate of those donations.

Currently, the NHSCBB seeks information on the health of mother and baby three months after donation and the ANCBB at six months. If the baby had been diagnosed with hepatitis or HIV infection after birth this information would be obtained then. The NHSCBB obtains updated information on the health of mother and baby at the time a CB unit is requested by a transplant centre. This is obtained by a phone call to their GP. This information is obtained for the majority of issues and it would be expected that a GP would flag up if the mother had become symptomatic and/or had been tested for a serious infection such as HBV, HCV or HIV since the delivery of her baby.

6.2.4.4. What is the practice in other countries?

There is general global harmonisation of donor screening processes to ease transit of donations across international borders. Certain countries may routinely screen for other endemic infections such as West Nile Virus, babesiosis and dengue. Transplant centres, donor registries and cord blood banks accredited by JACIE or NetCord-FACT will comply with the same standards, as well as following their own national regulatory frameworks.

The two largest unrelated HSC donor registries/centres in the world, the National Marrow Donor Programme (NMDP) in the USA and Deutsches Knochenmarkspenderdatei (DKMS) have differing practices. The NMDP perform NAT at each stage of donor testing (CT, work-up and at donation), as well as serology, for HIV, HBV and HCV. However, the practice at DKMS is very similar to the UK.

Practices with regards to MSM also vary widely from country to country: the main constraint is local legislation. For example, the Food and Drugs Administration (FDA) in the USA prohibit the use of donation from MSM if the last sexual activity was within five years. In practice, however, this ineligibility may be waived at the discretion of the receiving transplant centre. A recent survey performed by the WMDA (Appendix 8.5.3) showed that 58% of registries who replied deferred donors at recruitment with any history of MSM activity, 12% deferred if within five years, 6% if within one year, 12% did not impose a fixed deferral and 12% judged on a case by case basis. However, at donor selection for transplant, 49% deferred donors with any history of MSM activity, 32% judged on a case by case basis, 7% allowed MSM activity and the remainder imposed either one or five year deferrals.

There is currently no specific guidance from the WMDA regarding deferral of MSM.

6.2.5. Processing

HSC, whether sourced from BM, PBSC or cord blood, may undergo limited processing such as T-cell depletion, but it is not currently possible to reduce the risk of transmission of blood borne infections through cellular processing.

6.2.6. Recipient(s)

6.2.6.1. What is the maximum number of recipients that could be supplied from this donor (across all products)?

Once harvested, HSC (from BM, PBSC or cord) are used only for a single recipient. However, an unrelated adult donor may be asked to donate (on separate occasions) to a maximum of two recipients. Similarly, an individual may donate to more than one sibling if required, although such occurrences are extremely rare. There is currently no recommended limit on how often a relative may donate.

6.2.6.2. Is there an opportunity to discuss the risks from individual donors with the potential recipient?

There is always the opportunity to discuss the risks from individual donors with the potential recipient. In the case of an unrelated adult donor, once a potential risk is identified in the donor, the recipient's transplant centre will be informed. In such circumstances, it becomes the responsibility of the transplant centre to discuss such risks with the donor as they deem appropriate. Such discussions may be fraught with difficulty, particularly with regards to high-risk sexual behaviour. Both transplant centre and registry have to consider donor confidentiality, as it is feasible that the donor and recipient may meet in future.

These issues become even more difficult with related donors, where high-risk behaviours in siblings may not be known.

6.3. Pancreatic islets and hepatocytes

6.3.1. Background

Pancreatic islets of Langerhans and hepatocytes can be isolated from cadaveric human donor pancreata using a complex laboratory isolation technique and infused into the liver of the recipient via the portal vein under local anaesthetic.

The aim of islet transplantation is to reverse life-threatening hypoglycaemic unawareness in type I diabetic patients and while insulin independence is desirable, it is not the primary aim of treatment.

Islet transplantation has been commissioned nationally in the UK since 2009 and currently three laboratories undertake islet isolation for seven transplanting centres.

The aim of hepatocyte transplantation (HT) is to treat liver-based inborn errors of metabolism where the aim is to replace a single deficient enzyme or its product. Worldwide, there are reports of about 100 patients, including 16 children at King's College Hospital, who have been treated by HT, with the main indication to date being children with urea cycle defects.

Lately hepatocytes have also been used in the treatment of acute liver failure. The hepatocytes are encapsulated in alginate beads and transplanted into the recipient's peritoneal cavity to provide liver function for a few weeks while the native liver recovers or the patient receives a liver transplant.

6.3.2. Context

6.3.2.1. Is it life-saving or life-enhancing?

Pancreatic islet transplantation is both life-saving and life-enhancing. Hypoglycaemic unawareness is potentially life-threatening, however the fear of recurrent severe hypoglycaemic attacks significantly impacts on the quality of life of both the patients themselves and their families and carers.

Hepatocyte transplantation is life-saving as it is indicated in the treatment of end stage liver disease. The treatment is often used as an alternative to orthotopic liver transplantation (OLT). However, cell function often declines within a year with the result that patients then undergo OLT.

HT is also indicated in acute liver failure (ALF) in which it has been used to maintain liver function as a bridge to OLT or until regeneration of the native liver occurs.

6.3.2.2. Are there supply issues?

There are recognised supply issues within solid organ transplantation, with a significant shortage of pancreata available for transplantation. The New Pancreas Allocation Scheme was introduced in the UK in 2010 to facilitate patient directed allocation of cadaveric donor pancreata for both islets and solid pancreas transplantation; however current laboratory techniques only result in transplantable islet preparations in less than 50% of isolations. The majority of patients will also require two or more islet infusions to obtain a clinically effective result.

There is a significant shortage of hepatocytes available for transplantation. Human hepatocytes are isolated from liver tissues rejected or unused for transplantation, including livers from DCD (donation after circulatory death) donors.

Treatment is limited by the availability of human hepatocytes from unused donor livers. This would be greatly enhanced if good quality hepatocytes could be isolated from steatotic donor livers, which are becoming more common. Addition of the antioxidant N-acetylcysteine to the perfusion solution when isolating hepatocytes from fatty liver gives significant improvement in cell viability and metabolic function. Therefore this is now used routinely for isolation of hepatocytes for clinical use.

6.3.2.3. Legislative/guidance requirements for donor selection or testing

Human Tissue Authority (HTA)

The HTA, as one of the Competent Authorities in the UK under the European Union Tissues and Cells Directive, has responsibility for regulating tissues and cells (other than gametes and embryos) for human application.

The HTA has been appointed the Competent Authority to oversee the requirements of the EU Organ Donation Directive (EUODD) [79]. They have implemented a regulatory framework to oversee that the quality and safety standards of the EUODD are being met [80]. National legislation must apply the defined standards of the EUODD by August 2012.

NHS Blood and Transplant (NHSBT)

NHSBT has an internal guidance document on contraindications to organ donation. The guidance requires that all solid organ donors undergo physical assessment and screening for defined absolute and organ-specific contraindications as per UK consensus, as detailed below.

- Age >85 years

- Any cancer with evidence of spread outside affected organ (including lymph nodes) within three years of donation (however, localised prostate, thyroid, *in situ* cervical cancer and non-melanotic skin cancer are acceptable)
- Melanoma (except completely excised Stage 1 cancers)
- Choriocarcinoma
- Active haematological malignancy (myeloma, lymphoma, leukaemia)
- Definite, probable or possible case of human TSE[1], including CJD and vCJD, individuals whose blood relatives have had familial CJD, other neurodegenerative diseases associated with infectious agents
- Tuberculosis: active and untreated
- HIV disease (but not HIV infection)
- Insulin dependent diabetes (excluding intensive care unit-associated insulin requirement)
- Any history of pancreatic malignancy.

6.3.2.4. Is there evidence of viral transmission by the tissue/cell?

There is no evidence of viral transmission by islet transplantation. NICE Guidance IPG 257 details a case report of a patient who died of West Nile Virus encephalitis following transmission via a mosquito three years post islet cell transplantation [81].

There is no evidence of viral transmission in hepatocyte transplantation.

6.3.2.5. What is the practice in other countries?

All EU countries are required to comply with the EUODD.

6.3.3. Donor

6.3.3.1. Donor selection

The donor selection process is broadly the same as for solid organ donation. Cadaveric donors are routinely tested for HBV, HCV, HIV, syphilis, HTLV, CMV, Toxoplasmosis and EBV.

All donor information is relayed to the accepting transplant centre via a combination of verbal and electronic means. The maximum age of 65 years is the only additional criterion applied prior to offering the pancreatic islets. Acceptance of pancreatic islets is patient-specific.

[1] TSE: transmissible spongiform encephalopathy. Examples in humans include Creutzfeldt Jakob disease (CJD) and variant Creutzfeldt Jakob disease (vCJD)

In general all livers are offered as solid organs and are only considered for hepatocytes if unsuitable for transplantation following retrieval. Acceptance of livers for hepatocyte transplantation is patient-specific.

6.3.3.2. Identification of high-risk behaviours

High-risk behaviours are identified through completion of a Patient Assessment (PA1) questionnaire undertaken with the next of kin of the donor and completion of a medical history questionnaire completed by the GP. The PA1 is always completed prior to organ offering. Standard practice requires the GP questionnaire to be undertaken at the time of donation where possible but this is rarely possible out of practice hours.

6.3.3.3. Current practice with MSM

Current practice is similar to that for solid organs. There is currently no deferral of MSM donors for pancreatic islet transplantation. However evidence of high-risk behaviours may preclude acceptance by transplant centres, depending on the balance of risk for individual recipients

6.3.3.4. Does the donor have to be matched to the patient?

Matching is for blood group only.

6.3.4. Testing

6.3.4.1. Testing regime

Serological testing is undertaken at the time of donation with some isolation centres carrying out confirmatory NAT testing.

6.3.4.2. Is there scope to increase the detection rate of testing (funding permitting)?

Routine NAT testing may increase the detection rate.

6.3.4.3. Is it possible to quarantine the donation and retest the donor?

This is not possible as pancreatic islets and hepatocytes are obtained from cadaveric donors. Only blood taken at the time of donation will be available for testing.

6.3.5. Processing

The islet isolation and purification process appears to make viral transmission unlikely, and there are no additional risk reduction methods known that could be introduced to increase safety.

The same applies to hepatocytes. However, it is likely that hepatitis could be transmitted if present in the hepatocyte cell line.

6.3.6. Recipient(s)

6.3.6.1. What is the maximum number of recipients that could be supplied from this donor (across all products)?

One recipient per donation for islet cell transplantation.

Depending on the hepatocyte cell yield, hepatocyte cells could be used for multiple recipients.

6.3.6.2. Is there an opportunity to discuss the risks from individual donors with the potential recipient?

All recipients are consented for the transplant. Consent would require the discussion of any risks associated with both the procedure and the transplantation of donor material, as with solid organ transplantation.

6.4. Banked Tissues

6.4.1. Background

This section considers the following tissues, which may be banked after collection and stored for varying periods of time: cornea, limbal stem cell, sclera, bone, tendons, amnion, heart valves and skin.

6.4.2. Context

6.4.2.1. Life-saving or life-enhancing?

Bone

Bone (derived from either living or deceased donors) is used in a wide variety of clinical situations the vast majority of which are life-enhancing situations [82]. Approximately 60% of bone is used in revision hip surgery. Other common orthopaedic surgery where bone is used is in non-union of fractures, revision knee surgery and filling of bone cysts. It is also used quite extensively in spinal surgery, particularly in spinal fusion, and in children for correction of scoliosis.

Demineralised bone matrix is used widely in dentistry. Rarer uses of bone in the form of large allografts are used in an attempt to prevent amputation in cases of long bone tumours.

Tendons

Tendons are also frequently used in life-enhancing situations. Most often they are used in younger patients, following traumatic knee injuries, usually following sport injuries. One of the commonest uses is in anterior cruciate ligament repair, whereby the use of autologous tendons with the associated morbidity is avoided [83, 84]

Heart valves

Heart valves (particularly pulmonary) are used in planned procedures in children with congenital heart defects, and also urgently as replacement in acute heart failure following endocarditis. Human heart valves are very resistant to bacterial infection and they are by far the graft of choice in such circumstances [85].

Skin

The main use of skin is as a temporary cover in extensive burns. It prevents infection and excessive fluid losses. Depending on the percentage skin loss, skin grafts may therefore be either life-enhancing or life-saving [86].

Ocular tissue

Ocular tissue (including corneas, sclera, limbus stem cells and potentially conjunctiva) is life-enhancing. The improvement of vision after corneal transplantation can be dramatic. A person whose best visual acuity is 3/60 (able to see at 3 m what a normally sighted person would see at 60 m) is considered to be blind. The improvement in visual acuity after corneal transplantation is from a median of 6/60 to a median of 6/12. This leads to a dramatic improvement in a patient's quality of life, economic opportunities, and independence.

Amnion

Amnion is collected along with umbilical cord at childbirth by elective caesarian section. The membrane can be used as a replacement for damaged corneas to improve or restore sight for people with eye disease or injury, and to grow donated stem cells which can be used in sight-saving ophthalmological procedures. Blood vessels from the umbilical cord can also be used in surgery to replace a patient's own blood vessels.

6.4.2.2. Are there supply issues?

Supply of corneas has only recently been in balance and is dependent on including elderly donors. There are occasional shortages with pulmonary valves, though the recently introduced National Fulfilment Scheme by NHSBT is attempting to co-ordinate heart valve banking in the UK. This will help minimise any supply issues.

Large bone allografts are usually sized for a particular patient and the surgeon will work with the tissue establishment to get the allograft of the right size. This may incur some delay and occasionally large allografts have to be imported.

With these exceptions, there are no major supply issues with banked tissues.

6.4.2.3. Legislative Requirements

The HTA is the Competent Authority in the UK that has responsibility to regulate tissues and cells for human application. HTA's remit in the context of tissues used for human application is to ensure adherence to the EU directive 2004/23/ EC [87] and its daughter directives 2006/17/EC and 2006/86/EC [88, 89].

The HTA has issued Codes of Practice to support good practice and the section on donor selection is in code 3/2010 [90]. It does not specify specific risk factors *per se*.

In 2011 SaBTO issued updated guidance entitled 'Microbiological guidance for the safety of Organs Tissues and cells use in Transplantation.' It does not provide specific advice on behavioural aspects of potential donors, but it does provide detailed guidance on the tests to be performed on each potential donor.

For those tissue establishments that operate within the UK Blood Services, there are detailed questionnaires for both live and cadaveric donors. Sections of the relevant behavioural questions are reproduced below. Moreover there are Guidelines for the UK Blood Services for Donor Selection which specify in detail the deferral criteria and the reasons behind them [91]. The Ocular Tissue Advisory Group has formally advised adherence to the JPAC guidelines. Non-UK Blood Transfusion Services (UKBTS) operated banks report using procedures as summarised in Appendix 8.6.

6.4.2.4. What is current practice in the UK?

Bone from live donors

Approximately 5,000 fresh frozen femoral heads are issued to patients on an annual basis. 85% are issued as fresh frozen. Approximately 15% of bones collected are bacteriologically contaminated. These are processed using validated methods (most often including gamma irradiation). For a full review of processing methodologies please see Appendix 8.8.

Bone from deceased donors

A significant proportion of bone issued clinically is derived from cadaveric donors - the majority of whom are DCD. Most if not all is processed (most often using gamma irradiation).

Tendons (from deceased donors)

These are either issued as fresh frozen or frozen after surface decontamination (the majority of tendons issued in the UK). The decontamination procedure involves incubation for varying periods of time in cocktails of antibiotics. Such processes have an impact on surface contaminants only and are not meant to produce sterilised grafts. Tendons that are bacteriologically contaminated need to be processed using validated sterilisation methodology. This is most often gamma irradiation, although other validated methods exist, such as peroxygene compounds. However there is concern that these methods have a damaging effect on the tissue

structure, particularly in stress-bearing soft tissues such as tendons. Therefore such processed tendons are infrequently used.

Heart valves

The vast majority of heart valves are retrieved from two main sources. They may be retrieved from DCD donors, very often as part of a multi-tissue retrieval. A significant proportion (between 30% and 40%) are retrieved from DBD (donation after brain death) donors where the heart cannot be used for transplant for a variety of reasons. Very few are derived as part of a domino operation.

Since cell viability is required, end sterilisation is not possible. All heart valves are disinfected using various antibiotic cocktails and protocols. They are then frozen (controlled rate) followed by storage in vapour/liquid phase nitrogen at -160 °C.

Skin

Skin is retrieved from deceased donors in practically all circumstances. Skin is routinely disinfected using antibiotic cocktails and then frozen (controlled rate) with 25% glycerol. Skin that is significantly contaminated, bacteriologically, may be end sterilised using gamma irradiation, although this is not a tissue preferred by clinicians.

Corneas

Between 1998 and 2007, an average of 3,684 corneas were donated each year in the UK. Enucleation of the eyes has to take place within the first 24 hours post-mortem and the corneas are preserved and stored in either an organ culture warm medium for a maximum of 28 days or an hypothermic medium (Optisol) for up to 7 days. The corneas cannot be stored for longer periods due to deterioration of the cells that may occur. Both these storage media contain antimicrobials (antibacterial and antifungal agents). Samples from the tissue are not collected prior to preservation but are taken from the preservation media following storage and tested for bacteria and fungi prior to the corneas being issued for transplantation.

Amnion

Amniotic membrane is harvested from consenting seronegative (for HBV, HCV, syphilis and HIV) maternal donors during elective caesarian section. Under sterile conditions, the placental membrane is washed in a balanced salt solution (BSS) to remove clots and debris. The membrane is then bathed in a cocktail of antimicrobial medium for 24 hours, followed by a second wash in BSS. Subsequently, the amnion is separated from the chorion and divided into pieces measuring approximately 2cm by 2cm and mounted, stromal side

down, onto nitrocellulose cards. The membrane is then placed in a plastic container, and stored in 50% glycerol at -80°C for up to two years.

6.4.2.5. Is there evidence of viral transmission?

Numerous tissues have transmitted a variety of viruses, bacteria, fungi and even prions. The subject has been extensively reviewed and the review by Eastlund and Strong covers the topic extensively [92]. Numerous factors need to be taken into account when assessing the risk of transmission. These are shown in Table 10.

Table 10. Allograft characteristics affecting the ability to transmit disease
Reproduced from Eastlund [92]

Nonviable Allograft	Viable Allograft
Type	
Bone Dura mater Pericardium Tendon Costal cartilage Fascia Ear ossicles	Heart valve and vessels Cornea Skin Marrow Blood stem cells Vascularized organs Semen and oocyte Foetal tissue
Characteristics	
Non-viable Acellular Connective tissue Can be processed, sterilized	Contains viable cells May be antibiotic treated Cannot be sterilized

Some of the tissues in the above table are not banked in the UK - dura mater (banned due to vCJD risk), ear ossicles and fascia are examples. If banking of these tissues is taking place, it is in very small volumes. It does not mean however that imports are not taking place although it is probably in small quantities.

The infectious diseases transmitted by different tissues are shown in Table 11:

Table 11 Infectious diseases transmitted by tissue allografts.
Modified from Eastlund [92]

Allograft	Infectious Disease
Bone	Hepatitis C Hepatitis, Unspecified type HIV Bacteria Tuberculosis HTLV
Tendon	Bacteria Hepatitis C HIV
Cartilage	Bacteria
Cornea	Hepatitis B Rabies Herpes simplex virus Creutzfeldt-Jakob disease Cytomegalovirus (?) Bacteria Fungus
Dura	Creutzfeldt-Jakob disease Bacteria
Cardiovascular Tissue (including heart valves, cardiopulmonary patches and blood vessels)	Hepatitis B Hepatitis C Bacteria Tuberculosis Fungus Strongyloides (?) Rabies
Skin	Hepatitis C (?) Bacteria Cytomegalovirus (?) HIV (?)
Pericardium	Creutzfeldt-Jakob disease Bacteria

Rabies has also been transmitted from blood vessels.

It is important to note that the risk of transmission is dependent not just on the product type, as described above, but also on the robustness of the medical history, the testing that is done on the donor and the tissue and the type of processing that is done on the tissue. In general the more aggressive the processing is, the less is the quality of the graft and its clinical applicability. Much effort has been expended by numerous tissue producers to use end sterilisation procedures that have the highest sterility assurance level with the least impact on the quality and efficacy of the clinical graft.

6.4.2.6. Details of the donor selection process

EU Directive (Annex 2006/17/EC) [88] provides general guidance on donor selection in Annex 1. In the context of behavioural history it states:
History, clinical evidence, or laboratory evidence of HIV, acute or chronic Hepatitis B, Hepatitis C and HTLV I/II, transmission risk or evidence of risk factors for such infections.

Donor selection criteria for living and deceased tissue donors include detailed and specific questions regarding the past medical and behavioural history of the donor. The behavioural questions in Table 12 are asked by UKBTS services regarding deceased corneal and tissue donors, those in Table 13 are asked of living bone donors, and those in Table 14 are asked regarding deceased organ and tissue donors. Other forms may be used by non-BTS establishments.

Live bone donors are mostly interviewed face to face. The next of kin of deceased donors are interviewed on the phone (in most cases) and the interview is recorded.

Table 12. Behavioural risk assessment questionnaire used by UKBTS for deceased donors of corneas and tissue

BEHAVIOURAL RISK ASSESSMENT – KEEPING TRANSPLANTS SAFE

There are a number of infections that can be transmitted through tissue transplants; therefore we do not take donations from people who are at risk of contracting HIV or hepatitis. Your relative's blood will be tested, but in rare cases, these tests may be negative even though infection is present. The following is a list of groups of people from whom we cannot accept donations.

- Anyone who is or thinks they may be infected with hepatitis or HIV.
- Anyone who has ever injected or been injected with non-prescription/illegal drugs including body building drugs, even a long time ago or only once.
- Anyone who has ever been given money or drugs for sex.
- Anyone who has ever been in prison for more than three consecutive days within the last 12 months.
- **Male donors only** – Men who ever had sex with another man, even protected sex.

Anyone in the last 12 months who has had sex with any of the following groups

- Anyone who is, or thinks they may be infected with HIV or hepatitis.
- Anyone who has ever been given money or drugs for sex.
- Anyone who has ever injected drugs.
- Anyone who may ever have had sex in parts of the world where AIDS/HIV is very common (this includes most countries in Africa).
- **Female donors only** – A man, who has ever had sex with another man, even protected sex.

To the best of your knowledge is it possible that any of these apply to (name of donor)? Yes / No

Has (name of donor) had any sexually transmitted infection? Yes / No

Table 13. Behavioural risk assessment questionnaire used by UKBTS for living donors of bone

Donor Lifestyle		
23. Are you HIV or HTLV positive, or do you think you may be HIV or HTLV positive?		
24. Have you ever had hepatitis B or hepatitis C, or do you think you may have hepatitis now?		
25. Have you ever injected, or been injected, with illegal or non-prescribed drugs including body-building drugs? (You must answer "yes" even if it was only once or a long time ago). You may be able to give if a doctor prescribed the drugs. Please ask.		
26. Have you ever been given money or drugs for sex?		
Have you had sex in the last 12 months with:		
27. anyone who is HIV or HTLV positive?		
28. anyone who has hepatitis B or C?		
29. anyone who has ever been given money or drugs for sex?		
30. anyone who has ever injected drugs?		
31. anyone who may ever have had sex in parts of the world where AIDS/HIV is very common? This includes most countries in Africa. There are exceptions,.so please ask.		
32. anyone who has syphilis or any other sexually transmitted disease?		
33. **To be answered by men only.** Have you ever had oral or anal sex with another man with or without a condom or other form of protection?		
34 **To be answered by women only.** In the last 12 months have you had sex with a man who has ever had oral or anal sex with another man with or without a condom or other form of protection?		

Table 14. Behavioural risk assessment for organ and tissue donors (DBD and DCD) used by NHSBT

BEHAVIOURAL RISK ASSESSMENT			
28 Did your relative:			
(a) consume alcohol?	Yes ☐	No ☐	Unknown ☐
If YES, approximately how many units per week			
(b) smoke tobacco or any other substance?	Yes ☐	No ☐	Unknown ☐
If YES, give details			
29 Is it possible that any of the following apply to your relative?			
(a) is, or may be infected with HTLV, HIV or hepatitis B or C?	Yes ☐	No ☐	Unknown ☐
(b) has ever injected or been injected with non-prescriptive drugs, including body building drugs, even if it was a long time ago or only once?	Yes ☐	No ☐	Unknown ☐
(c) has ever been given payment for sex with money or drugs?	Yes ☐	No ☐	Unknown ☐
(d) *(for male patients only)* ever had sex with another man with or without a condom?	Yes ☐	No ☐	Unknown ☐
(e) *(for female patients only)* had sex in the last 12 months with a man who has had sex with another man with or without a condom?	Yes ☐	No ☐	Unknown ☐
(f) been in prison or a juvenile detention centre for more than three consecutive days within the last 12 months? **NB: This excludes those who have been in a police cell for <96 hours.**	Yes ☐	No ☐	Unknown ☐
(g) had sex in the last 12 months with:			
(i) anyone who is HIV or HTLV positive?	Yes ☐	No ☐	Unknown ☐
(ii) anyone who has hepatitis B or C?	Yes ☐	No ☐	Unknown ☐
(iii) anyone who had a sexually transmitted disease?	Yes ☐	No ☐	Unknown ☐
(iv) anyone who has ever been given payment for sex with money or drugs?	Yes ☐	No ☐	Unknown ☐
(v) anyone who has ever injected drugs?	Yes ☐	No ☐	Unknown ☐
(vi) anyone who may ever have had sex in any part of the world where AIDS/HIV is very common (this includes most countries in Africa)?	Yes ☐	No ☐	Unknown ☐
Having answered all the previous questions is there anyone else who you think may provide more information?	Yes ☐	No ☐	

6.4.3. Testing

6.4.3.1. Testing regime

For testing of living and deceased donors, Annex 1 of the EUTCD 2006/17/EC [88] requires serology for HIV 1&2, HBV surface antigen and anti-core antibody, HCV antibody and syphilis. HTLV 1 antibody testing is required for donors living in, or originating from high-incidence areas or with sexual partners originating from these areas or where the donor's parents originate from these areas.

UKBTS tissue establishments follow testing as required by the Red Book Guidelines 2007 [91] summarised in Appendix 8.8. Other establishments follow different procedures, with the results of a survey summarised in Appendix 8.6. SaBTO requirements, issued in 2011, are detailed in Appendix

8.9. It is clear that the EU directive provides the minimum standards and the UKBTS provide the more specific requirements.

Ante-mortem samples are always the preferred analyte (in contrast to post-mortem samples). However, testing on post-mortem samples can be done provided a validated test kit is used.

The eye banks request serology tests for HIV, HCV, HTLV, syphilis, HBV surface antigen, HBV core and when required HBV surface antibody. NAT testing for HIV, HBV and HCV will be undertaken routinely on all donors from the 1 April 2013 by the Corneal Transplant Service (CTS) Eye Banks and Moorfield's Eye Bank. East Grinstead Eye Bank undertakes NAT testing when necessary including testing of immunocompromised donors.

6.4.3.2. Is it possible to quarantine the tissues?

It is possible to quarantine all tissues as they all have long shelf lives and in practice there is normally a significant period (required for processing, quality assurance controls etc) between collection and release. Clearly it is not possible to test deceased donors twice. In the case of living donors quarantine is possible, however this is not required if NAT testing has been done; NAT testing is now routine practice in the UK. Retesting is also not required if processing includes an inactivation step that has been validated for the viruses concerned.

Corneas are limited by the time they are in storage (maximum 28 days for organ culture and 7 days for Optisol); they are not quarantined for use beyond these times. The donor can only be retested on the blood sample provided at the time of enucleation.

6.4.4. Processing

6.4.4.1. What processing is currently undertaken that could reduce the risk of transmission?

<u>Bone from live donors</u>

Bone can be washed or freeze dried and gamma irradiated (25KGY). Some clinicians prefer not to use irradiated bone. Other methodologies do exist that do not use irradiation, for example Peroxygen and alcohols and/or other solvents are included in some protocols. Many protocols are patented by commercial providers

A UKBTS (NHSBT/SNBTS) validated patented washing protocol has been developed (Peracetic Acid Sterilisation (PAS) and peroxide combinations) that removes up to six logs of infectivity, but it is not currently used in the UK (see below).

Ethylene oxide (ETO) is another option that is generally considered very effective. It can only be used on dried tissue prior to exposure, and its use nowadays is severely restricted for health and safety reasons.

Other bone formulations exist - demineralised bone matrix (for specific indications due to its osteoinductive properties) which is processed using a series of chemicals (most often sodium hydroxide) followed by terminal sterilisation.

Bone from deceased donors

As above. The significant majority of it is processed, most often by gamma irradiation.

Tendons

All tendons could be terminally sterilised. However as previously indicated, their clinical effectiveness is reduced.

Heart valves

Gluteraldehyde has been used historically for this type of graft, but is not used nowadays owing to concerns concerning toxic residuals and *in vivo* calcification.

Skin

High concentrations of glycerol may have some antimicrobial activity. Not currently used in the UK.

Corneas

As cellular viability is extremely important, corneas are stored in preservation media which contains antimicrobials (antibacterial and antifungal agents). Microbiological samples of the eyes are however, not taken prior to being placed in the preservation media. Prior to issuing for transplantation, samples of the preservation media are tested for bacteria and fungi, but not viruses.

Amnion

High concentrations of glycerol may have some antimicrobial activity.

6.4.4.2. Are there additional manufacturing steps that could be introduced (funding permitting)?

Bone

Increasing the radiation dose above 25 kGy improves the viral log kill, but at the detriment of its mechanical properties. To ensure sterility assurance level 10^{-6} for HIV, for example, a dose of more than 40 kGy is required. This will significantly affect the quality of the bone, in particular weight-bearing bone.

Bone can be imported. The only place that can provide adequate numbers is USA. However there are concerns with some of the deferral criteria (which are less stringent than in the UK) and there are also some concerns over some GMP (good manufacturing practice) aspects of some facilities.

All bone (including fresh frozen femoral heads) could be processed. If gamma irradiation is applied as the end sterilisation step there are concerns about the mechanical properties and clinical acceptability. Bones can be washed (singly in view of pooling concerns about prion transmission) and then processed using chemical means. (See Table 16 p84). This methodology has been developed in the UK by the UKBTSs. However there are concerns over cost benefit implications and about the fact that such bone has not been used clinically before.

Tendons

All tendons can be end sterilised. However as stated above the quality of graft is significantly inferior and there will be difficulties with clinical acceptability of such products.

Heart valves

Besides antibiotic decontamination it is not likely that much else can be done. Decellularisation is being introduced, primarily for other reasons such as immunological /rejection reasons rather than improved microbiological safety. It is not possible to import heart valves due to global shortages.

Skin

Gamma irradiation has a deleterious effect on skin and is not the preferred graft by clinicians. Limited imports of skin already take place for patients under 16 as a CJD precautionary measure.

Corneas

Corneas are stored in preservation media containing antimicrobials (containing antibacterial and antifungal agents). Further processing may

increase the risk of reducing cell quality and render the tissue unsuitable for transplantation.

The introduction of NAT testing of all eye donors will reduce the risk of viral transmission and potentially that of other micro-organisms. Eyes could be disinfected at and following enucleation and prior to processing which may help to reduce the risk of transmission. In addition, the use of separate instruments may be recommended for the enucleation of each eye.

Amnion

No further steps are available as amnion is retrieved in a sterile operating room environment.

6.4.5. Recipients

6.4.5.1. What is the maximum number of recipients that could be supplied from this donor (across all products)?

Bone from living donors

One or two recipients per donor.

Amnion

One placenta can provide amnion membrane for as many as 150 recipients.

Tissues from deceased donors

If skin, heart valves, tendons and bone are taken from the same donor, over 30 recipients can be exposed to risk.

Corneas

One cornea can be split into an anterior and posterior layer and supply two recipients. The periphery of the cornea (the corneoscleral limbus) can also be used to supply stem cells. Therefore, one corneoscleral disc can supply three recipients and scleral tissue can be used to supply more than two recipients.

Although not currently undertaken, limbal stem cells can be expanded *ex vivo* to supply more than one recipient.

6.4.5.2. Is there an opportunity to discuss the risks of specific donors with the potential recipient (as opposed to just general risks)?

No, only generic risks are discussed.

6.5. Gametes and embryos

6.5.1. Background

6.5.1.1. Sperm

Spermatozoa are the male gametes normally obtained for donation by ejaculation. Donor sperm are used to help a woman get pregnant in the cases where:

- her male partner is unable to produce sperm (ie is sterile)
- her partner's sperm count or quality is so poor that it is unlikely to result in conception unless intra-cytoplasmic sperm injection (ICSI) is carried out (and this is unavailable or unaffordable)
- her partner has a high risk of passing on an inherited disease and there is no ability to undertake pre-implantation genetic diagnosis
- there is no male partner.

Currently donor sperm used for fertility treatments is cryopreserved following ejaculation and quarantined in liquid nitrogen or vapour for at least six months before being used in treatment. The donor is screened for infectious diseases at the beginning and end of the quarantine period (six months after his last donation), and if these tests are clear, his samples may be released for treatment. Unfortunately, sperm from some men are damaged by the freezing process. This means that after freezing there may be a reduction in quality and for this reason many donors cannot be accepted.

Most donor sperm samples are used in a simple insemination procedure (intra-uterine insemination) where washed sperm are placed in a woman's uterus immediately prior to ovulation. This could be in a natural cycle or more commonly is done in combination with ovulation induction drugs.

Alternatively, donor sperm may be used in *in vitro* fertilisation where eggs are recovered from the woman (usually after a period of ovarian stimulation) and donor sperm is co-incubated with them in the laboratory to facilitate fertilisation. Any resulting embryos are allowed to develop in the laboratory from two to five days before one or two are replaced in the woman's uterus.

Occasionally, donor sperm may be used for ICSI where a single sperm is injected into each of the woman's eggs recovered. However, this is generally

not recommended with donor sperm. Any embryos resulting from ICSI are allowed to develop in the same way as those resulting from *in vitro* fertilisation (IVF).

Any embryos that are not transferred to the uterus can be frozen for use in the future.

6.5.1.2. Egg

An oocyte (egg) refers to the female gamete and can only be obtained via a surgical procedure called an egg-collection. Donated eggs can be used in cases where the woman:

- has no ovaries or has had them removed
- had cancer treatment which has damaged the ovaries
- is post-menopausal (or had an early menopause)
- is producing few or low-quality eggs
- has repeatedly tried to conceive unsuccessfully using fertility drugs or IVF, where egg quality is considered to be the underlying problem

or where there is a high risk of passing on a serious inherited disorder and there is no ability to undertake pre-implantation genetic diagnosis.

Normally eggs are collected following a period of ovarian stimulation (see above) using a needle guided by ultrasound. This may be done under a general anaesthetic or more usually under sedation.

Donated eggs are fertilised with the partner's (or a donor's) sperm by IVF or ICSI. The developing embryos are incubated in the laboratory for between two and five days as described above and are then transferred into the uterus. Any embryos that are not transferred can be frozen for use in the future.

Egg donors can either be women who:

- volunteer to be donors altruistically but are not undergoing fertility treatment themselves; or
- are undergoing fertility treatment and who agree to donate some of their eggs to others, usually in exchange for discounted treatment. These are generally called 'egg sharers'. In 2010 57% (n = 776) of the egg donors came from egg share.

6.5.1.3. Embryos

Embryos are generally donated by people who have completed their fertility treatment and have additional embryos that they no longer require. Donated embryos can include those created using a couple's own gametes, or can also include those created using donor eggs (see above), donor sperm (see above) or using both donor egg and donor sperm.

Treatment using donated embryos is relatively straightforward and simply involves introducing a thawed embryo into the recipient's uterus at the correct time of her ovarian cycle.

Donated embryos can be used in the cases where:

- Both partners have fertility problems, which means they're less likely to be successful using their own sperm and/or eggs
- Both partners have a serious condition that would be inherited by any children
- A single woman is unable to produce eggs, usually due to ovarian failure or as a result of a premature or normal menopause.

According to data provided by the National Gamete Donation Trust in 2013, in the UK:

- 34 clinics recruit sperm donors
- 43 clinics recruit egg donors
- 34 clinics treat with egg sharing
- 37 clinics treat for receiving embryo donation
- 45 clinics treat for receiving donated eggs
- 40 clinics treat for receiving donated sperm.

6.5.2. Context

6.5.2.1. Is it life-saving or life-enhancing?

Gamete donation is life-enhancing for the parents and life-creating for the children conceived. Around one in six couples may have difficulty conceiving; that is approximately 3.5 million people in the UK. This could be because of infertility, lack of a male or female partner, or a serious condition that would be inherited by any children. For some, sperm, egg or embryo donation is the only way of starting a family. In 2009 1,756 children were born through donor conception: 1,084 through sperm donation, 593 through egg donation and 79 through embryo donation.

6.5.2.2. Supply issues

Sperm

Many clinics report significant difficulty in obtaining adequate supplies of donor sperm. However, this is difficult to quantify. A working party set up by the British Fertility Society [93] calculated that 500 donors per year were needed to fulfil UK demand. This would include giving patients the option of choosing donors with similar physical characteristics to themselves, such as stature, hair or eye colour. However, this estimate assumed that all 500

donors would give consent for their sperm to be used in the treatment of the maximum number of recipients allowed by law (children born in 10 family groups). In 2010, the HFEA reported that 480 new sperm donors had been registered with them (although 24% (n=114) were donors recruited from overseas). However, no information is published by the HFEA about the consent given by donors and so it is not possible to establish how widely their samples can be used. It is clear that a number of UK residents do travel to clinics overseas to seek treatment because of supply issues [94] but no accurate UK figures are available. Moreover, evidence from the media would suggest that some patients seek unlicensed treatment using the insemination of un-screened samples provided by friends or men they have made contact with on the internet. There are no reliable estimates of this activity, although it clearly raises safety concerns (donor screening and lack of sample quarantining) and has a number of legal issues for paternity (see Pacey 2010 for a discussion [95]).

Eggs

There are severe shortages of donor eggs as demonstrated by the length of waiting lists and reports that many patients are travelling abroad in search of donor eggs [94].

Embryos

There are no data on the number of patients who require embryo donation and whether the limited supply of donor embryos is sufficient to meet demand. However, informal reconnaissance from clinics suggests that demand probably outstrips supply.

6.5.2.3. What are the current legislative/guidance requirements for donor selection? Who sets them?

General

All donation and treatment involving sperm, eggs and embryos is licensed by the Human Fertilisation and Embryology Authority (HFEA) which enforces the Human Fertilisation and Embryology Act 1990 [96] and its 2008 amendment [97]. The HFEA publishes a Code of Practice [98], which outlines the basic legal requirements for the procurement, testing and storage of donated material. More detailed guidance on the medical and laboratory screening of donors was published by the Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists [99].

In summary, all donors must be selected on the basis of their age, health and medical history, provided on a questionnaire and through a personal interview performed by a qualified and trained healthcare professional. This assessment includes relevant factors that may assist in identifying and screening out persons whose donations could present: (i) a health risk to those who receive donated material (such as a risk of acquiring a sexually

transmitted infection); (ii) a health risk to themselves (for example during the process of egg collection); or (iii) a risk of transmitting a heritable condition or disorder to any child born.

Before a prospective donor provides gametes, the recruiting centre will take a medical and family history. This will include consent to approach their GP for their opinion of the donor's suitability. For sperm, egg and embryo donation there are different recommended maximum age limits as outlined below.

Sperm

Sperm donors should be aged between 18 and 40 years. Current professional guidelines recommend that sperm should not be taken from donors aged 40 or over. Centres should normally observe the relevant donor age limit, however, due to less substantial evidence on age limits for sperm donors, centres can assess the possible effect of a donor's age on a case by case basis.

Eggs

Current professional donor guidelines state that eggs should not be taken from egg donors aged 35 or over. Centres are required to observe the age limit unless there are exceptional reasons not to do so.

Embryos

With embryo donation, the egg donor should be aged between 18 and 35, and the sperm donor between 18 and 40. In exceptional circumstances a clinic may accept donors outside these age ranges after performing the appropriate risk assessment.

6.5.2.4. Is there evidence of viral transmission by this tissue/cell?

There are only isolated case reports of viral transmission from sperm (eg Stewart *et al.,* 1985 [100]) but these are largely before current screening strategies were adopted. According to Broder *et al,* infections from sperm have an incidence of less than 1 per 10,000 inseminations [101]. There are no known cases of viral transmission in the case of egg and embryo donation, and indeed this would seem unlikely given the limited number of cells that are transferred to the recipient in these cases.

6.5.3. Donor

6.5.3.1. Details of donor selection process eg duration and depth of interview, targeted, related etc.

Because of the lifelong implications of creating donor-conceived individuals, interviews with prospective donors take place before donation begins. Donors

must now agree for their identity to be released to donor-conceived people once they reach the age of 18 and as a consequence, one or more counselling sessions are conducted with each prospective donor (as appropriate). The length of time that each donor is in contact with the recruitment centre depends on the specific situation, as follows.

For sperm donors, each accepted donor typically donates once or twice per week over a three to five month period. This means that because sperm samples are frozen and held in quarantine for six months, the donor may be in contact with the recruitment centre for about eight to twelve months. The only exception to this is in the case of 'known-donors' (where the donor is known to the recipient) and where the donor may only be donating for that person. In this case the donor may only donate once, but given that the need for quarantine still remains, the donor may still be in contact with the clinic for a six month period.

For both altruistic and egg share donors, it is typical for them to have an extensive work-up as they are matched to a(nother) patient before treatment starts. The synchronising of the menstrual cycles of donor and patient can take up to four to six weeks before treatment. The donation cycle will take three to four weeks. Because eggs are used fresh and there is no opportunity for quarantine, egg donors are typically in contact with the donation centre for two to three months, although they may return to donate again.

Embryo donors are ex-patients who have completed their families and finished treatment and so will already be known to the centre for many years prior to considering donation.

6.5.3.2. Are there any matching considerations between donor and recipient?

Most treatment centres use general information about the donor to provide some element of matching between the physical characteristics of the donor and that of the recipient's circumstances. This may include ethnicity of the donor, but also aspects of height, weight, skin colour etc., as outlined above. This is arguably more important for heterosexual couples, who may prefer the physical matching of sperm donor characteristics to that of the male partner. However, in situations of donor shortages this may not be possible.

The only significant medical matching that is recommended relates to the CMV status of the donor and recipient. The best practice guidelines published by the Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists recommend that it is preferable to match CMV positive donors with CMV positive recipients only where there is no alternative and when a CMV negative donor is unavailable [98]. This is to reduce the risk of congenital infection of the foetus, which can result in significant disability [102].

6.5.4. Testing

6.5.4.1. Testing regime (eg serology, NAT)

As outlined earlier, all donors should be screened according to Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists guidelines [99].

These guidelines recommend that for bacterial infections (eg syphilis, gonorrhoea and chlamydia) screening should be conducted according to the recommendations of the Association for Sexual Health and HIV [103]. This document did recommend the use of NAT testing in some instances, but it is clear that since it was written most laboratories have moved over to NAT-based tests where appropriate and recruiting centres have followed suit, although definitive data are not available.

However, with regard to CMV and other blood borne viruses the Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society, Royal College of Obstetricians and Gynaecologists did not recommend the use of NAT testing, citing advice from the Department of Health Advisory Group on AIDS that existing serological testing (along with the use of 180 day quarantine in the case of sperm donation – see below) should continue to be used.

Since that time, the 8th HFEA Code of Practice [98] states that if NAT testing is used for HIV, HBV and HCV “quarantining of the gametes and retesting of a repeat blood sample is not required”. There are no data to indicate how many UK recruitment centres undertake screening for blood borne viruses by serology, NAT or a combination of the two.

It is likely that the Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists will revise their guidance in the near future.

6.5.4.2. Is there scope to increase the detection rate of testing?

No, although we are unaware of how many UK centres are using NAT testing. Single NAT versus Pools may offer increased detection.

6.5.4.3. Is it possible to quarantine the donation and retest the donor?

With current technology only fresh (unfrozen) eggs are used for donation. These cannot be quarantined although arguably the risk of infection is low given that only one cell is actually donated. Embryos are able to be quarantined, but their donation relies on retrospective testing although this is arguably again low risk.

Semen presents a higher risk of infection to the recipient because it contains many cells including leucocytes. However, with the tried and tested screening for known/tested pathogens and (180 day) quarantine strategies the risks are reduced to negligible levels. Arguably sperm processing methods (see below) reduce the risk still further.

6.5.5. Processing

6.5.5.1. What processing is currently undertaken that could reduce the risk of transmission?

Sperm preparation is normally undertaken prior to use in treatment and this would certainly reduce (but not eliminate) the viral or bacterial load. In the case of eggs, only one cell is being used in donation and so it is unlikely to carry a significant viral load. The same is true of embryos and both are processed and cultured between gamete production and treatment use.

6.5.5.2. Are there additional steps that could be introduced (funding permitting)?

No.

6.5.6. Recipients

6.5.6.1. What is the maximum number of recipients that could be supplied from this donor (across all products)?

Under current UK law, a maximum of 10 families can be created using a particular donor, although donors can specify a smaller number if they wish (such as in the case of known donation). Some family groups may also seek a genetically related sibling and this is permitted if donated material still exists to allow this.

6.5.6.2. Is there an opportunity to discuss the risks of a specific donor with the potential recipient (as opposed to just general risks)?

This is necessary from time to time, particularly with regard to ‘Known donors’ who might be family members or close friends of the recipient.

7. Recommendations and observations

7.1.Recommendations on donor deferral

7.1.1. Group 1: Haematopoietic stem cells, whether from family and friends, or unrelated adult donors, or from cord blood.

This also includes related products from the same donor types eg donor lymphocytes, and virus-directed T cells.

7.1.1.1. From 'family and friend' donors

NO DEFERRAL. This is current practice and represents no change.

Retain the current individual risk/benefit donor assessment ie ensure documentation of MSM behaviour but place no specific restrictions regarding donation.

7.1.1.2. From unrelated donors joining a registry

NO DEFERRAL.

For Anthony Nolan, this is current practice and represents no change.

For the British Bone Marrow Registry and Welsh Bone Marrow Donor Registry this represents a change to current practice.

The British Bone Marrow Registry and Welsh Bone Marrow Donor Registry recruit via blood donation, so pending this review employ lifetime deferral. This therefore represents a change.

The MSM behaviour should be documented to facilitate an in depth discussion should the donor be a potential match for a patient. This ensures that the current practice of individual risk/benefit assessment prior to donation is continued.

7.1.1.3. From cord blood donors

The SaBTO committee agreed that there should be as few barriers as possible to availability of this life-saving product. Sex with an individual who has ever had MSM

behaviour has not been identified as a risk factor in cord donors with positive virus markers.
Therefore it is recommended that a policy of

NO DEFERRAL is implemented. **This represents a change to current practice.**

Allow donation with documentation of, but no restrictions regarding, MSM behaviour of the partner, and retain the current individual risk/benefit assessment prior to use of the donation.

For Anthony Nolan this is a change from a lifetime deferral after sexual contact by the woman with a man who has ever had MSM behaviour.

For British Bone Marrow Registry this is a change from a 12 month deferral after sexual contact by the woman with a man who has ever had MSM behaviour.

The eligibility criteria for cord donors are summarised in Table 15.

Table 15. Impact on cord blood donor selection of the proposed changes to MSM criteria

Donor Scenario[1]	**Current eligibility**	**New eligibility**	**Implication for practice**
1. Mother not aware of any partners having MSM activity	Eligible to donate cord blood	Eligible to donate cord blood	No change
2. Mother knows that a partner she has had sex with in the previous 12 months has ever had oral or anal sex with another man, even if they used a condom or other protective	Not eligible to donate cord blood	Eligible to donate cord blood	**NHSCBB:** Change from 12 month deferral **ANCBB:** Change from lifetime deferral
3. Mother has had sex more than 12 months ago with a partner who had oral or anal sex with another man	**NHSCBB:** Eligible to donate cord blood **ANCBB:** Not eligible to donate cord	Eligible to donate cord blood	**NHSCBB:** No change **ANCBB:** Change from lifetime deferral

[1] It is recognised that where a mother knows that a partner she has had sex with in the previous 12 months has (a) had sex in an area with a high risk of HIV or (b) ever injected drugs, she will not be eligible to donate cord blood. However this is out of scope for this report.

	blood		

7.1.2. Group 2: Pancreatic islets and hepatocytes

NO DEFERRAL. This is current practice and represents no change.

Retain the current individual risk/benefit donor assessment ie documentation of, but no specific restrictions regarding, MSM behaviour.

7.1.3. Group 3: Banked tissues (corneas, heart valves, amnion, bone, skin, and tendon)

MEN
ALLOW DONATION 12 MONTHS OR MORE AFTER LAST MSM SEXUAL CONTACT.

WOMEN
ALLOW DONATION 12 MONTHS AFTER LAST SEXUAL CONTACT WITH A MAN WHO HAS EVER HAD SEX WITH ANOTHER MAN.

This is not current practice and represents a change from the current lifetime deferral for both men and women. It is consistent with SaBTO guidance for blood donation.

7.1.4. Group 4: Sperm, eggs and embryos

NO DEFERRAL. This is current practice and represents no change.

Retain the current individual risk/benefit donor assessment ie documentation of MSM behaviour, but no specific restrictions regarding donation.

7.2. Impact of proposed changes to MSM donor selection criteria on deceased tissue donors

When the eligibility of a deceased donor is being considered, one of four different scenarios may apply. These are summarised in Table 16, along with the current and proposed eligibility criteria. The only situation where eligibility to donate tissues and cells would be changed is when a deceased male potential donor is known by his family or next of kin or GP or the hospital to have engaged in MSM activity in the past, but there is certainty that he has had no MSM sexual activity in the previous 12 months.

Table 16. Impact on deceased donor selection for tissue donation of the proposed changes to MSM criteria

Donor Scenario	Current eligibility	New eligibility	Implication for practice
1. Family / next of kin / GP / hospital not aware of any MSM activity. No evidence of MSM activity	Eligible to donate tissues	Eligible to donate tissues	No change
2. Male known by family / next of kin / GP / hospital to be engaged in MSM activity and is presumed/known to be sexually active in the 12 months before death	Not eligible to donate tissues	Not eligible to donate tissues	No change
3. Male known by family / next of kin / GP / hospital to have engaged in MSM activity in the past. Family unaware of date of last MSM activity	Not eligible to donate tissues	Not eligible to donate tissues	No change
4. Male known by family / next of kin / GP / hospital to have engaged in MSM activity in the past, but known to have had no MSM sexual activity in previous 12 months	Not eligible to donate tissues	Eligible to donate tissues	**Change**

7.3. Observations on the collection of information on the donor's sexual history

The working group conducted a survey of the donor screening processes used by organisations that provide services in this area. Different wording was used in the donor selection questionnaires of different organisations, and in some cases the terminology used was inappropriate as it referred to sexual orientation rather than specific risk behaviour.

It is desirable that standardised terminology should be used by all tissue and cell providers. The wording currently used by UK Blood Services was considered to be appropriate, referring to "men who have ever had sex with another man, with or without a condom or other protection".

7.4. Observations on donation testing

It was not within the group's scope of work to make recommendations regarding testing of cells and tissues. It must be emphasised that the recommendations on deferral have taken into account current (and potential) testing practices, and are NOT contingent on any new recommendations regarding testing. However, the group noted inconsistencies in the use of nucleic acid testing (NAT), both between different tissue and cell products, and between different providers of the same product - notably with regard to donation of corneas, bone and sperm.

At present, guidance on all tissue and cell products specifies the serological tests to be carried out. Guidance, however, is less clear on the need for NAT.

SaBTO issued guidance in 2011 on the microbiological testing of organs, cells and tissues [1]. This document alluded to NAT as best practice, but stopped short of a firm recommendation for its use for all banked tissues. Therefore, when this guidance is next reviewed, SaBTO may wish to clarify the position with regard to the use of NAT eg recommending its use for all banked tissues and cells, and giving consideration to which markers and the pool size to be used or individual sample testing

7.5. Observations on manufacturing

During the risk assessments, information was gathered on current manufacturing practices, and whether technologies exist that could reduce the viral load of tissue products even further. As with testing, it was out of scope to produce recommendations for manufacturing, and the recommendations for donor acceptance are made within the context of current manufacturing regimes. Additional processes were identified only with regard to bone eg a combination of peroxide and peracetic acid. Such methods may impact on bone quality and therefore require careful risk/benefit and cost/benefit analyses. It was noted that there is an ongoing study of processing of living bone donations, and the group proposed that SaBTO should review the data on safety and clinical effectiveness when they are available (with a view to considering whether or not this method should become the standard of care).

7.6. Observations on bio vigilance

Reporting systems exist for the notification of virus transmission by all tissue and cell products considered in this review. Collation and publication of such incidents varies, probably because such events are now rare.

There is, however, very limited documentation of risk factors found in virus positive donors of cells, tissues (except within Blood Services) and gametes. Collation, analysis and publication of such data would be enormously helpful in formulating future policies for donor selection and testing, as evidenced by experience with blood donors.

Similar consideration applies to the collection and storage of archive samples from tissue and cell donors. These would be invaluable not only in the investigation of suspected transmissions, but also in the identification and assessment of emerging infections.

8. Appendices

8.1. Terms of reference

Background

1. The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) recently reviewed the blood donor deferral and exclusion criteria in relation to specific sexual behaviours. Following the review, SaBTO recommended that the blood donor deferral for men who have ever had sex with men (MSM) should be changed from lifetime deferral to 12 months from the last at-risk behaviour. This recommendation was accepted by Ministers and implemented in England, Wales and Scotland on 7 November 2011.

2. The UK Blood Services have generally tried to adopt common donor selection procedures for blood, tissue, and stem cell donors. The previous MSM review was limited to blood donors, but this has resulted in an inconsistency in donor selection for the UK Blood Services. For example, a man who has had MSM contact more than 12 months prior to donation can be acceptable as a platelet donor, but currently not as a stem cell or tissue donor with the UK blood services. The same individual could be deemed acceptable as a non-blood services stem cell donor. Therefore, all tissue and stem cell establishments need definitive advice regarding MSM eligibility.

Remit

3. The Working Group will review the evidence base for selection of living and deceased donors of cells and banked tissues in the UK in relation to MSM behaviour and make recommendations to SaBTO on the most appropriate ways to ensure the safety of the supply.

4. Its remit includes:

    - Evaluating the evidence base for deferral and exclusion policies;
    - Defining the infections of interest, whether currently screened for or not;
    - Reviewing the UK epidemiology of relevant infections;
    - Assessing the performance of current testing procedures;
    - Determining the residual risks for specific infections;
    - Reviewing relevant policies in other countries;
    - Evaluating the operational impact of any recommendations;
    - Evaluating the cost/benefit ratio of any recommendations;
    - Evaluating the impact of any recommendations on overall availability of supply;
    - Recommendations for disseminating the outcome of the review.

5. It is recognised that both organs and bankable tissue may be taken from the same deceased donor. Therefore the scope is described in terms of the material for which the recommendations will apply, rather than the donor.

6. In scope

   From donors who are alive at the time of donation:
   - Banked tissues;
   - Haematopoietic and non-haematopoietic stem cells and immunotherapies, to include cord blood, 'family and friend' donors and unrelated donors from registries;
   - Gametes and embryos for reproductive use.

   From donors who are deceased at the time of donation:
   - Banked tissues, including eyes;
   - Gametes and embryos for reproductive use;
   - Cells eg pancreatic islet cells.

7. Out of scope
   - Solid organs, which cannot be banked, from living or deceased donors.
   - Commercial sex workers and their sexual partners.

<u>Terms of Reference</u>

8. In formulating and communicating its advice, the Working Group will:

   - Take account of the scientific evidence available, including the nature of uncertainties and assumptions used to reach conclusions;
   - Take account of the infectivity risk of different tissues including the effects of processing;
   - Take account of the differences in risk/benefit for different types of tissue and cellular products;
   - Identify specific areas of research where further work is required to reduce uncertainty;
   - Take account of the risk of policies being perceived as unfairly discriminatory;
   - Consider the impact of its advice on all stakeholders in the supply chain, including but not exclusively donors, patients, the UK blood services and the wider NHS;
   - Take account of the need to maintain the safety of cells and tissues under the remit of the Precautionary Principle;
   - Take account of any legal requirements;
   - Take account of any other SaBTO recommendations;
   - Be ultimately accountable to SaBTO.

Membership

9. Membership of the group will be as follows:

Name	Position	Role on Working Group
Dr Lorna Williamson (Chair)	SaBTO member (Medical Director of Blood Service) Medical and Research Director, NHSBT	Chair on behalf of SaBTO
Dr George Galea	SaBTO member (Blood/Transplant Service Manager) Head of Tissue Services, SNBTS	Tissues expert
Dr Eithne MacMahon	SaBTO member (Microbiologist/Bacteriologist/Virologist) Consultant Virologist, Guy's and St Thomas' NHS Foundation Trust	Infection expert
Prof Marc Turner	SaBTO member (Haematologist) Medical Director, SNBTS	Stem cell expert
Mr Elwyn Nicol	SaBTO member (Patient Representative)	Layperson
Dr Phil Yates	Chair of Standing Advisory Committee on Tissues and Cellular Therapy Products Consultant, SNBTS	Tissues expert
Dr Su Brailsford	Consultant in Epidemiology and Health Protection NHSBT and HPA	Epidemiology expert
Dr Stephen Thomas	SaBTO Secretariat Safety Programme Coordinator, NHSBT	Secretariat support
Mr Andrew Broderick	SaBTO Secretariat	Secretariat support
Dr Allan Pacey	Senior Lecturer Academic Unit of Reproductive & Developmental Medicine, Sheffield University	Representing British Fertility Society
Dr Liezl Gaum	Royal Liverpool and Broadgreen University Hospitals NHS Trust	Representing NHSBT Ocular

		Tissue Advisory Group
Prof Francisco Figueiredo (or nominee)	Professor of Ophthalmology & Ocular Surface Disease Royal Victoria Infirmary & Newcastle University	Representing RCOphth Ocular Tissue Transplant Standards Group
Dr Mickey Koh	Consultant Haematologist St George's Hospital, London	Representing British Society for Blood and Marrow Transplantation
Dr Joan Power	President BATB	Representing British Association of Tissue Banks
Mr John Casey	Consultant Transplant Surgeon The Royal Infirmary of Edinburgh and St John's Hospital, Livingston	Representing British Transplantation Society
Dr Robert Lown	Medical Officer of ANT and Registrar at The Royal Marsden	Representing Anthony Nolan
Dr Yusef Azad	Director of Policy and Campaigns National AIDS Trust	Representing National AIDS Trust
Mr Carl Burnell	Chief Executive Officer GMFA	Representing GMFA and LGBT Partnership
Mr James Taylor	Senior Health Officer Stonewall	Representing Stonewall
Ms Clare Lewis-Jones	Chief Executive Infertility Network UK	Representing Infertility Network UK
Ms Laura Witjens	Chief Executive National Gamete Donation Trust	Representing National Gamete Donation Trust
Ms Catherine Davies	External Affairs Manager NHS Blood and Transplant	Communications lead
Ms Triona Norman	Head of Policy, Organ and Tissue Transplantation Department of Health	Observer
Mr Emyr Harries	Senior Policy Manager - Cell Therapy and Regenerative Medicine Department of Health	Observer
Ms Kim Hayes	Policy Manager, Assisted Reproduction & Embryology Policy	Observer

	Department of Health	

Work programme

10. The work of the Group is expected to be completed by December 2012, according to the following schedule:

Subgroup meeting	**Milestone**	**SaBTO meeting**
April 2012 (Telecon)	Agreement of Terms of Reference. Review of JPAC paper. Identification of any further work needed.	Document briefing in place of 29 May 2012 meeting
16 July 2012 (Face to face)	First face to face meeting of full group. Discussion of remit and membership. Identification of areas where additional information needs to be gathered.	11 September 2012
24 September 2012 (Face to face)	Review of additional information and preliminary outline of report.	-
26 November 2012 (Face to face)	Formulation of recommendations, and drafting of report.	10 December 2012
29 January 2013 (Face to face)	Approval of final report.	5 March 2013

11. The Working Group may meet in person or by telecon.

12. Administrative issues will pass to the SaBTO Secretariat who will also maintain a document library.

13. Members of the Working Group are asked to claim expenses from their employing organisation. Where this is not possible, they can be claimed from the Department of Health. Expenses in relation to travel and subsistence necessarily incurred in carrying out the work of the Group are payable in line with Departmental rates for individuals who serve on committees. This is standard class for rail travel and economy class for air travel. Members of the Working Group are asked to make every effort to use public transport where possible, rather than taxis, although these may be used for local journeys (under five miles). Receipts must be submitted with claims.

14. Papers will be circulated no later than seven days prior to any ordinary meeting.

Communications

15. The establishment of the working group was recorded in the minutes of the SaBTO meeting of 9 March 2012.

16. The Working Group will include stakeholders as detailed in section 9, and will consult those stakeholders listed at item 19. It will consider whether it is appropriate to conduct any other consultations when formulating its recommendations, although it is expected that sufficient expertise is included within the group. Unless specifically stated, members of the working group are not considered to be representatives of the organisations listed in section 9.

17. The recommendations of the Working Group will be published in a report and recommendation to SaBTO, with discussions and outcomes recorded in the public minutes of the meeting. A communications plan will be formulated.

18. This document will be appended to the report, so that the membership of the group is made public.

19. The Working Group will draw up a list of stakeholders that should be informed of SaBTO's recommendations and/or any decision by ministers. This will include:

- UK Departments of Health
- Human Tissue Authority
    - The HTA is the UK regulator for tissues and cells, and has agreed to assist with communication of any SaBTO recommendations to licensed establishments
    - HTA has also confirmed that Annex 1 of Directive 2006/17/EC does not require amendment to reflect any changes based on these recommendations.
- Medicines and Healthcare products Regulatory Agency
- Human Fertilisation and Embryology Authority
- UK Blood Services
- Health Professional organisations (in addition to those represented on the working group)
- Royal Colleges
- Patient groups
- Groups representing MSM (in addition to those represented on the working group)
- Fertility groups (in addition to those represented on the working group).

8.2.Review of infection risk

Table 17. Review of infection risk carried by each tissue or cell type

	Current mandatory testing					Cell/tissue dependent testing					Not tested		
Infection	**HIV**	**HBV**	**HCV**	**HTLV**	***T pallidum***	**CMV**	**EBV**	***T gondii***	***C trach***	***N gonor***	**HSV**	**HAV**	**HHV-8**
Increased incidence/prevalence if MSM donor?	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**
	Added risk of transmission if 12m v lifetime deferral?												
Blood	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Organs	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**Y**
HSC: family and friends	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**?**
HSC: matched unrelated	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**?**
HSC: cord blood	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**?**
Hepatocytes	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Pancreatic islets	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Heart valves	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Skin	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**?**
Corneas	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Amnion	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Bone – living donor	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**?**
Bone – deceased donor	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Tendon	**N***	**N***	**N***	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N?**
Assumes serological testing and quarantine, or NAT testing													

8.3. Age and gender distribution of blood donors, live bone donors, and deceased donors

Figure 1. Age distribution of new male blood donors 2011

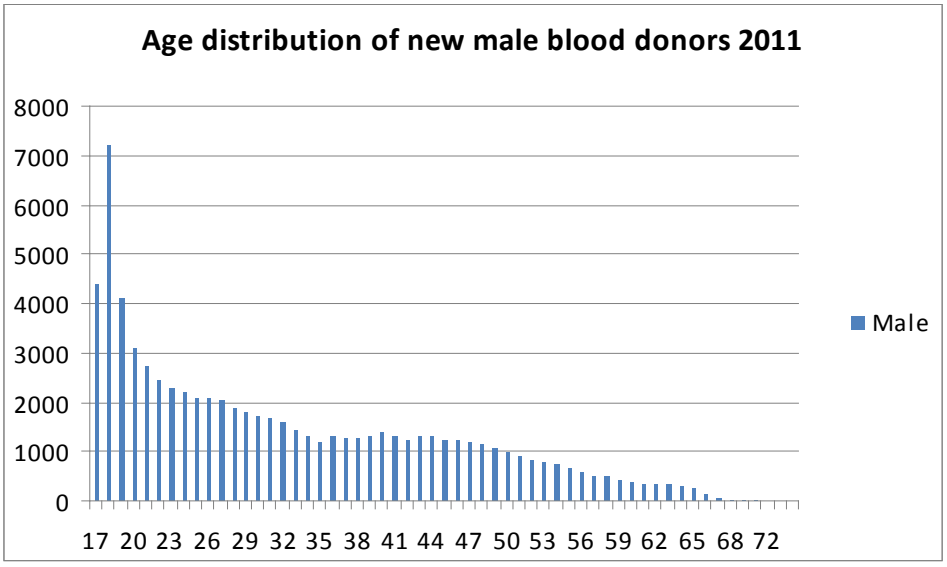


Figure 2. Age distribution of new female blood donors 2011

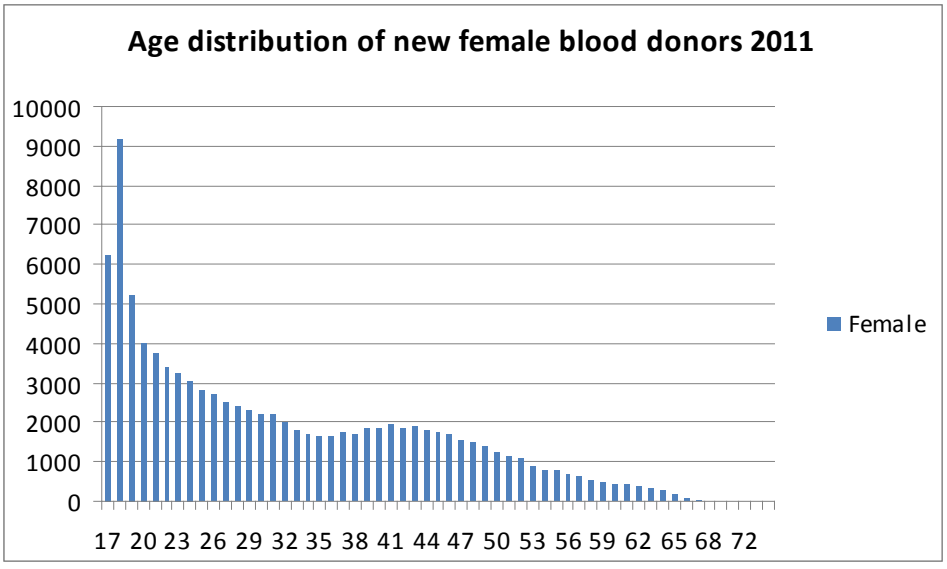


Figure 3. Age distribution of male surgical bone donors 2011

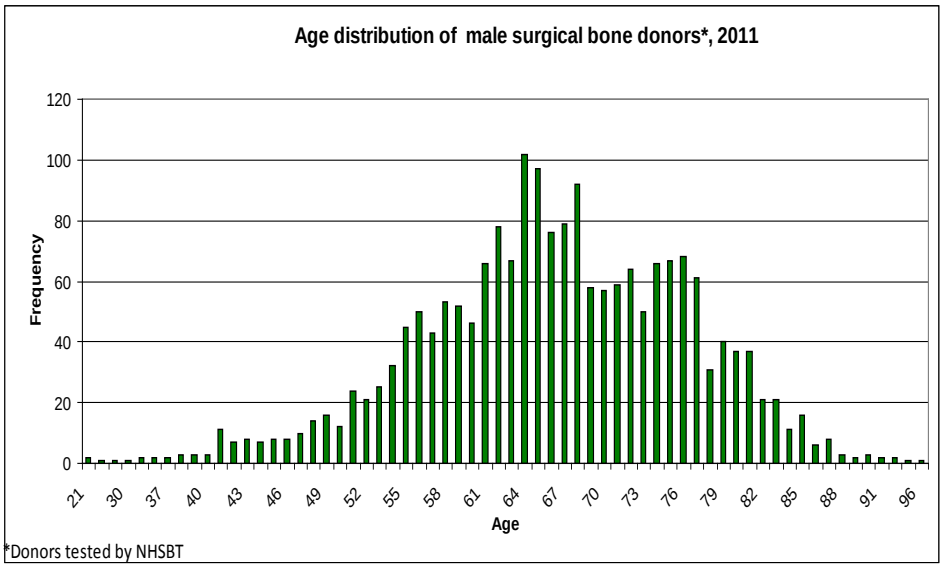


Figure 4. Age distribution of female surgical bone donors 2011

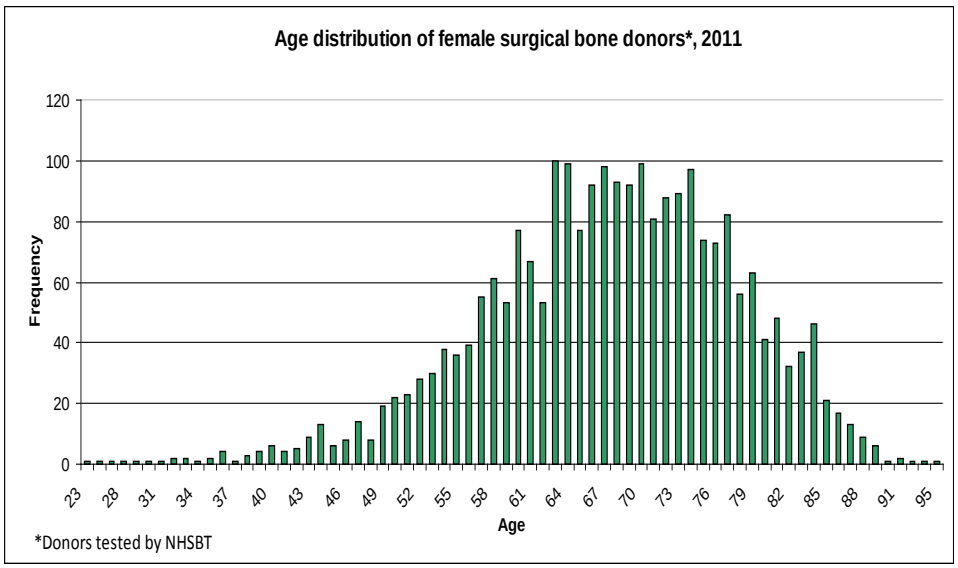


Figure 5. Age distribution of male deceased donors 2011

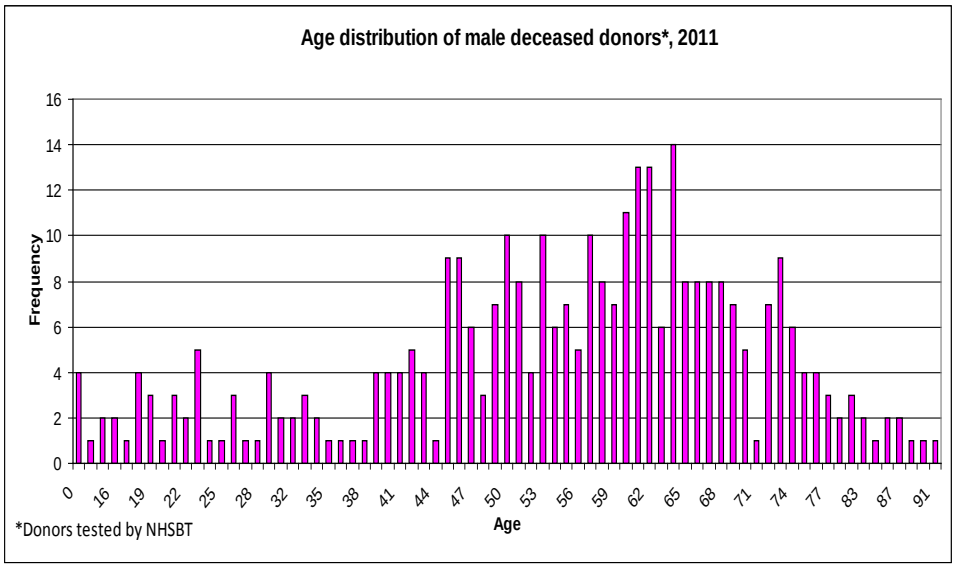
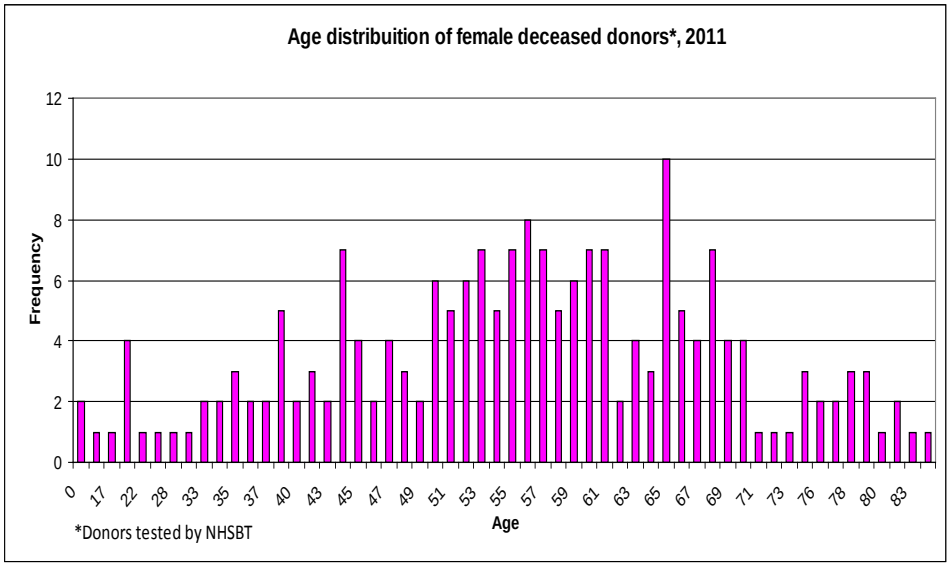


Figure 6. Age distribution of female deceased donors 2011



8.4. Blank proforma used for data collection for each tissue and cell type

Completed proformas may be provided on request to the secretariat, but are not included here for brevity – the text in the main report was derived from information gathered using this template.

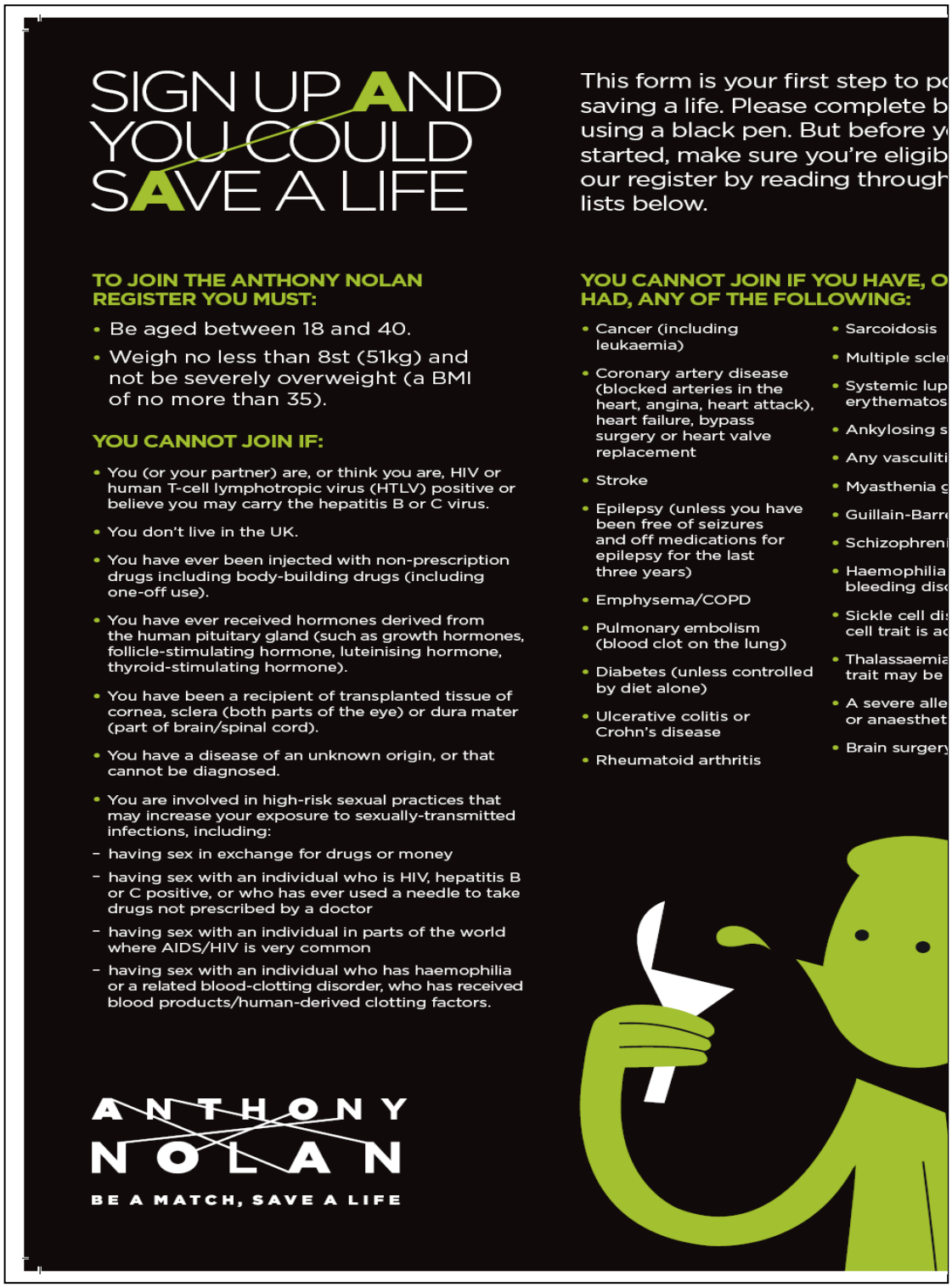
1. Tissue or cell	
2. Context	
Is it life-saving or life-enhancing?	
Are there supply issues?	
Legislative/guidance requirements for donor selection or testing.	
Is there evidence of viral transmission by this tissue/cell? Give details.	
What is current practice in the UK?	
What is current practice in other countries?	
3. Donor	
Details of donor selection process eg duration and depth, targeted, related etc	
Does the donor have to be matched to the patient?	

4. Testing	
Testing regime (eg serology, NAT)	
Is there scope to increase the detection rate of testing (funding permitting)?	
Is it possible to quarantine the donation and retest donor?	
5. Processing	
What processing is currently undertaken that could reduce risk of transmission?	
Are there additional steps that could be introduced (funding permitting)?	
6. Recipient(s)	
What is the maximum number of recipients that could be supplied from this donor (across all products)?	
Is there an opportunity to discuss the risks from individual donors with the potential recipient?	

8.5. Donor screening and consent documentation for haematopoietic stem cell donation

8.5.1. Adult donors

8.5.1.1. Anthony Nolan recruitment questionnaire



SIGN UP AND YOU COULD SAVE A LIFE

This form is your first step to p saving a life. Please complete b using a black pen. But before y started, make sure you're eligib our register by reading through lists below.

TO JOIN THE ANTHONY NOLAN REGISTER YOU MUST:

- Be aged between 18 and 40.
- Weigh no less than 8st (51kg) and not be severely overweight (a BMI of no more than 35).

YOU CANNOT JOIN IF:

- You (or your partner) are, or think you are, HIV or human T-cell lymphotropic virus (HTLV) positive or believe you may carry the hepatitis B or C virus.
- You don't live in the UK.
- You have ever been injected with non-prescription drugs including body-building drugs (including one-off use).
- You have ever received hormones derived from the human pituitary gland (such as growth hormones, follicle-stimulating hormone, luteinising hormone, thyroid-stimulating hormone).
- You have been a recipient of transplanted tissue of cornea, sclera (both parts of the eye) or dura mater (part of brain/spinal cord).
- You have a disease of an unknown origin, or that cannot be diagnosed.
- You are involved in high-risk sexual practices that may increase your exposure to sexually-transmitted infections, including:
  - having sex in exchange for drugs or money
  - having sex with an individual who is HIV, hepatitis B or C positive, or who has ever used a needle to take drugs not prescribed by a doctor
  - having sex with an individual in parts of the world where AIDS/HIV is very common
  - having sex with an individual who has haemophilia or a related blood-clotting disorder, who has received blood products/human-derived clotting factors.

YOU CANNOT JOIN IF YOU HAVE, O HAD, ANY OF THE FOLLOWING:

- Cancer (including leukaemia)
- Coronary artery disease (blocked arteries in the heart, angina, heart attack), heart failure, bypass surgery or heart valve replacement
- Stroke
- Epilepsy (unless you have been free of seizures and off medications for epilepsy for the last three years)
- Emphysema/COPD
- Pulmonary embolism (blood clot on the lung)
- Diabetes (unless controlled by diet alone)
- Ulcerative colitis or Crohn's disease
- Rheumatoid arthritis
- Sarcoidosis
- Multiple scle
- Systemic lup erythematos
- Ankylosing s
- Any vasculiti
- Myasthenia g
- Guillain-Barr
- Schizophreni
- Haemophilia bleeding dis
- Sickle cell di cell trait is a
- Thalassaemia trait may be
- A severe alle or anaesthet
- Brain surgery

ANTHONY NOLAN

BE A MATCH, SAVE A LIFE

Please fill this form in BLACK or BLUE ink. Cross the appropriate boxes and wr
within the boxes in CAPITAL LETTERS

Show your choice

A YOUR GENERAL DETAILS

Military pers
Service num

Are you Male? ☐ Female? ☐ Title Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Dr ☐

First name

Middle name

Surname

Address

Town/City

Postcode

Date of birth (DD/MM/

Email address

Home phone number

Work phone number

Mobile phone number

It is important we are able to cor
you by mobile and Email. Mark h
if you are happy for us to do so.

Occupation

GP Practice name

GP Practice town/city

GP phone number

Ethnic group. (Your ethnicity is the description that best describes your ancestors' origin. This will help identify a potential
this is not your nationality)

☐ Eastern European
☐ African Sub-Saharan
☐ British/Irish
☐ Scandinavian/Northern European
☐ Middle Eastern/Northern African
☐ Central/Southern European
☐ African Caribbean
☐ Asian (Indian Subcontinent)
☐ Other/Mixed

Why do you want to join the register? Please select the ONE most appropriate to you.

☐ I could be someone's only chance of a life-saving transplant
☐ Because of my community or religious
☐ In memory of someone I've lost to cancer
☐ To encourage others to follow my exa
☐ I'd want someone to help me if I needed a transplant
☐ Other

We would like to keep you informed about our vital work and fundraising activities, if you do not want to receive this information please let us know by cr

B OTHER CONTACT DETAILS

Please do not provide the same address as above.

In case we lose contact with you, please give
of a close friend or relative who will know wh
This person must not live with you.

First Name

Surname

Address

Town/City

Post code

Home phone number

Mobile phone number

OFFICE USE ONLY

Evaluator's signature

Name

Date (DD/MM/YY)

Facebook ☐ Poster ☐
TV ☐ Newspapers ☐
Letter/Email ☐ Friend ☐

Attach barcode he

C YOUR MEDICAL DETAILS

1A. What is your height?

centimetres or feet and inches

1B. What is your weight?

kilograms or stone and pounds

2. Have you ever donated blood? Yes No

3. Have you ever been refused as a blood donor? Yes No

If yes, please state why.

4. Have you ever received a blood transfusion

If yes, in which country and when?

Year received

5. Do you have any relatives who have been d nosed with Creutzfeldt Jacob Disease (v C.

6. Have you received treatment with human pituitary extracts such as growth hormone and gonadotrophins?

7. Please cross which, if any, of the following condition you have EVER had.

01) Asthma or breathing problems	**06)** Back and neck pain including fractures	**11)** Eczema	**16)** Malaria
02) Anaemia	**07)** Slipped discs	**12)** Psoriasis	**17)** Severe allergi
03) Bleeding problems	**08)** Colitis	**13)** Heart murmurs	**18)** Arthritis
04) Blood clots or deep-vein thrombosis	**09)** Chest pain	**14)** Sickle-cell trait or thalassaemia trait	**19)** ME
05) High blood pressure	**10)** Depression	**15)** Tuberculosis (TB)	

Please give details of the condition, whether it was resolved, details of treatments and investigations (for example, medication, operations, scans and tests)

Condition number from the table above	Was the condition resolved? Yes	No	Year diagnosed	Details of treatments and investigations
Condition number	Yes	No	Year diagnosed	Details of treatments and investigations
Condition number	Yes	No	Year diagnosed	Details of treatments and investigations
Condition number	Yes	No	Year diagnosed	Details of treatments and investigations

Please provide any other information or comments on your health including medications and operations which have not

D YOUR CONSENT

Your full name:

I, on D D /

have read the terms in the giving your consent and your privacy sections over the page and I agree to them. I voluntarily give you my consent to put my name on the Anthony Nolan Register.

Your signature:

This is a screening questionnaire. We may need to ask you for more details. If you have any questions please contact
www.anthonynolan.org • 0303 303 0303 • info@anthonynolan.org • Registered charity no 803716/SC038827

MAKE YOUR SUPPORT GO FURTHER
Set up a direct debit and help **save more lives.** This will help us recruit more donors, collect and store new stem cells, and fund lifesaving research.
The more funds we have the more lives we can save. It's that simple

Instruction to your Bank/Building society to pay by Direct Debit.

I would like to make a regular gift of: ☐ £10 ☐ £15 ☐ Other £

I wish to pay: ☐ Monthly ☐ Quarterly ☐ Yearly I would like my donation to come out on: ☐

The first payment will come out approximately one month after you send us back this form – we will write to confirm to you your first payn the first gift leaves your account.

giftaid it

Make your donation go further at no extra cost to you. Using Gift Aid means that for every pound you give we g from HM Revenue & Customs in tax relief and government supplements.

☐ I confirm that I am a UK Taxpayer and would like The Anthony Nolan Trust to reclaim the basic rate tax on my donations. I would li made in the current and previous four financial years, and any future donations that I may make until I notify you otherwise to be t donations. I have paid UK Income Tax and/or Capital Gains Tax at least equal to the tax that The Anthony Nolan Trust reclaims on the appropriate tax year (currently 25p for each £1 given).

Name :

Address: Postcod

To the manager: bank/building society

Bank address: Postcod

Name/s of account holder

Bank sort code: / / Account number:

Please note that banks and building societies may not accept direct debit instructions for some types of accounts.
Please pay The Anthony Nolan Trust from the account detailed on this instruction, subject to the safeguards assured by the direct debit understand that this instruction will remain with The Anthony Nolan Trust, and, if so, details will be passed electronically to my bank/buil

Your signature: DIRECT Debit Anthony Nolan identity number

GIVING YOUR PERMISSION – PLEASE READ THE FOLLOWING

1 I have read the booklet 'Be a match, save a life'. I've thought about what registering as a possible donor means. As far as I know, I am not at risk of transmitting infectious diseases.
2 I want to apply to join the Anthony Nolan register and what this means.
3 I am not on any other bone marrow or stem cell register. (You only need to be on one donor register.)
4 I understand that once I am on the register, I may need to give several blood samples for further matching tests. I am willing to do this.
5 I understand that to donate bone marrow or blood stem cells I will need to:
- have a medical examination in London to check whether I am suitable to donate,
- receive a five-day course of injections of a growth factor and have a peripheral blood stem cell collection (PBSC) carried out or spend two nights in a London hospital donating bone marrow under general anaesthetic,
- take time away from work or my normal dutires (one day for PBSC and around five to seven days for bone marrow) to recover after the donation.

6 I understand that if I join the register and I am a match, I will be expected to donate to a patient who may live anywhere in the world.
7 I understand I won't know who the patient is and they won't know who I am.
8 I understand that during the matching process my blood will be screened for infectious diseases including HIV, hepatitis B, hepatitis C ad syphilis.
9 I understand that samples of my blood or DNA v for testing in the matching procedure and may b research. I also understand that I will be contacte permission if the samples are needed for any oth
10 I give you my permission to collect, hold and pro personal information (including sensitive persona such as medical information and ethnic group) ir the Data Protection Act (1998).
11 I will let you know straight away about any chang personal details such as name, health status and
12 I understand that I may withdraw from the Antho register at any time, but I seriously intend to stay
13 If I am identified as a possible match but I can't b I agree that you may get my contact details from authorities, including my GP.

YOUR PRIVACY

We value your support and promise to respect your (and our subsidiary company Anthony Nolan Marketi the information we gather and keep in line with the D Act (1998). We will use this information to help our r you as a member of the Anthony Nolan register and t with you about our work as a fundraising charity, bl register and scientific research institute, if you do not this information please indicate so in section A of th

We will not give your details to anyone else without except where we need to carry out our work of if we

You can find more details about how we use your in **www.anthonynolan.org**

ANTHONY NOLAN
BE A MATCH, SAVE A LIFE

ANTHONY NOLAN
2 Heathgate Place
75-87 Agincourt Road
London NW3 2NU

0303 303 0303
www.anthonynolan.org
info@anthonynolan.org

Illu
Re
80
OF

8.5.1.2. Anthony Nolan CT medical update questionnaire

ANTHONY NOLAN

BE A MATCH, SAVE A LIFE

ANTHONY NOLAN
2–3 Heathgate Place
London, NW3 2NU
Tel 0303 303 0303
Fax 020 7284 8226
www.anthonynolan.org

Reg charity no

OFFICE U
Extend
Confirm
Other

MEDICAL UPDATE

POTENTIAL BLOOD STEM CELL/BONE MARROW DONOR

Important: in block capitals, please complete pages 1–8, and return this completed form as soon as

Donor ID | Male | Female | Mr, Mrs, Miss, Ms, Dr, Other

First name | Middle name

Last name | Date of birth D D M M Y Y | Age

What is your height? centimetres **or** feet and inches

What is your weight? (see notes 1&2) kilograms **or** stone and pounds

(1) MINIMUM weight is 8 st
(2) Volunteers who are se
may not be accepted as th
increase risk of complicati
with the administration of

Occupation

DATA PROTECTION STATEMENT Anthony Nolan values your support and promises to respect your privacy. The data we gather and hold is r
accordance with the Data Protection Act (1998) by us and our subsidiary company Anthony Nolan Marketing Ltd. We would like to keep you
about our vital work and fundraising activities, if you do not want to receive this information please let us know by ticking this box ☐
We will not, without your consent, supply your details to any third party except where this is necessary to carry out our activities or required

Address to which post/sample kits should be sent:

Postcode

Home tel | Work tel

Mobile

Email – work

Email – personal

KEEPING IN TOUCH If you move home we could lose contact with you. Please give below the nam
someone with an address different from yours who will always know how to reach you. We will onl
information to contact you if absolutely necessary.

First name

Last name

Relationship

Address

Postcode

Home tel | Work tel

Mobile

Email – work

Email – personal

V3/J

YOUR GP DETAILS

Name of GP

Address of GP

Postcode

GP telephone

Your NHS number (if known)

DONOR CONSENT

Are you on any other register for bone marrow/blood stem cell donors, if yes please give details: Yes

I have read the booklet *You're a match what happens next?* and I understand that to donate bone m cells I would be required to:

- Undergo a medical examination in a designated specialist hospital to assess my fitness to donat
- Spend two nights in a hospital and undergo a general anaesthetic for a bone marrow harvest/or 4/5 day course of injections of a growth factor followed by a peripheral blood stem cell collectic
- Take time away from work or my normal activities: (7-10 days for bone marrow/1-2 days for PBSC) Yes
- My preferred method of donation is: bone marrow PBSC No pr
- To the best of my knowledge I am not at risk of transmitting infectious diseases.
- I understand that I may be required to give several blood samples over a period of time for furth I am willing to undertake this as and when requested.
- I understand that I may be found to be compatible with any person in need of a bone marrow/b cell transplant, in any part of the world. I am willing to donate to anyone for whom I am consider suitable match.
- I understand that, as part of the process of matching and donor selection, I will from time to tim Anthony Nolan information about me which includes information which is defined as 'sensitive p under the Data Protection Act 1998, such as my medical history and ethnic origin.
- I give permission for Anthony Nolan to use information about me, including sensitive personal d matching and donor selection, in accordance with the terms of the Data Protection Act 1998.
- If I am identified as a possible match but cannot be found, I agree the Anthony Nolan may get m details from local health authorities including my GP surgery.
- I agree to the storage of frozen samples of my blood/DNA and understand that these may be us detailed tissue typing at a future date.
- I give permission for my blood to be screened during further tests for infectious disease markers Hepatitis B, Hepatitis C and HIV.
- I understand that if any of the tests prove positive* I will be contacted in complete confidence b Director or the Medical Officer of Anthony Nolan for appropriate consultation and counselling. ***Please note that a substantial proportion of the tests which initially appear positive are, on re not confirmed as positive.**

YOUR PREFERRED CONTACT METHOD

Should the test appear to be positive, I would like the Medical Director or the Medical Officer to cor by the preferred method below. *Please state day time or evening*

Please sign below if you agree to the above statement:

Signature of donor Date

MEDICAL UPDATE

Please ensure that you complete the following questionnaire as accurately as possible. The purpose
health screen is for us to assess if it would be safe for you to proceed as a potential bone marrow/b
cell donor. All disclosures will be treated as strictly confidential and will only be used in assessing y
as a volunteer donor.

1. Have you ever had or do you suffer from:

a) Ankylosing Spondylitis? Yes ☐ No ☐

b) Cancer? (excluding Basal Cell Carcinoma of the skin) Yes ☐ No ☐

c) Crohn's Disease or Ulcerative Colitis? Yes ☐ No ☐

d) Diabetes (insulin dependent or medication controlled)? Yes ☐ No ☐

e) Myasthenia Gravis? Yes ☐ No ☐

f) Pernicious Anaemia? Yes ☐ No ☐

g) Severe Psoriasis? Yes ☐ No ☐

h) Severe Eczema? Yes ☐ No ☐

i) Rheumatoid or Psoriatic Arthritis? Yes ☐ No ☐

j) Reactive Arthritis (Reiter's Syndrome) Yes ☐ No ☐

k) Rheumatic Fever? Yes ☐ No ☐

l) Sarcoidosis? Yes ☐ No ☐

m) Schizophrenia or other mental illness under psychiatric care? Yes ☐ No ☐

n) Sickle Cell Anaemia (tick 'no' if you only have the trait or are a carrier)? Yes ☐ No ☐

o) Lupus (SLE , Systemic Lupus Erythematosus)? Yes ☐ No ☐

p) Thalassemia (tick 'no' if you only have the trait or are a carrier)? Yes ☐ No ☐

If your answer is 'yes' to any of the above please contact your Coordinator before completing this form.

2. Have you ever used a needle, even once, to take drugs not prescribed by a doctor? Yes ☐ No ☐

3. Have you ever given or taken money or drugs in exchange for sex? Ye

4. Have you ever had sex with:

a) an individual who may be HIV positive Ye

b) an individual who may have had Hepatitis B or C or Yellow Jaundice Ye

c) an individual who has been given money or drugs in exchange for sex Ye

d) an individual who has ever used a needle to take drugs not prescribed by a doctor (even once) Ye

e) an individual with haemophilia or a related blood clotting disorder, who has received blood products/ human derived clotting factors Ye

f) an individual who has been sexually active in parts of the world where AIDS/HIV is very common Ye

5. Have you ever tested positive for:

a) HIV Ye

b) HTLV Ye

c) Hepatitis B Ye

d) Hepatitis C Ye

If your answer is 'yes' to any of the ab
contact your Coordinator before com
this form.

V3/JU

Note: People with lower back problems have to be carefully screened for their own safety as bone marrow is drawn from the pelvic bone. For this reason please give us as much detailed information as possible on question 6 (if you do have back problems you may be only able to donate via the PBSC method).

6. Do you, or have you ever suffered from any form of lower back injury, lower back or sciatica? (if no go to question 7) Yes ☐ No ☐

If yes:

a) When did the problem start? D D M M Y Y

b) Was there a cause (e.g. accident, sports injury)? If yes, give details: Yes ☐ No ☐

c) What investigations have been made, and what were the results?

d) What diagnosis or name has the condition been given?

e) What treatment have you received? e.g. surgery, manipulation (chiropractic care, physiotherapy, osteopathy etc.)

f) Do you still suffer from pain and discomfort? Yes ☐ No ☐

g) Can you lift heavy objects or participate in vigorous sports? Yes ☐ No ☐

h) Does the problem cause any limitations to your lifestyle? Yes ☐ No ☐

If yes, describe the limitiations:

i) How much time have you had off work or normal duties?

j) Please list any medication you take for your back condition (name and dose)

k) Has your back problem been resolved? Ye

7. Do you drink alcohol? Ye
If yes, how many units per week?
(1 unit = 1 small glass of wine/half-pin

8. Have you had any pregnancies? (If no, go to question 9) Ye
If yes, please state the number, inclu terminations and miscarriages.

Date of last birth: D D

It is our standard policy not to test d are pregnant or who have a baby les year old. Please advise us if this is th you are, therefore, not able to provid sample currently.

9. Have you ever donated blood? Ye

If yes,
when did you last donate? D D

10. Have you ever been refused as a blood donor? Ye

If yes, please state when and why.

11. Have you ever received any blood transfusions (including plasma or other blood products)? Ye

If yes, why, when (approximately wha how many units and in which country

12. Have you had a tattoo, body piercing acupuncture in the last 4 months?

Tattoo Ye

Body piercing Ye

Acupuncture Ye

If yes D D M M Y Y

For acupuncture; what was the name person and of the practice performin acupuncture?

13. Have you ever had anaemia or any blood disorder? Yes ☐ No ☐

If yes, please give details/date

14. Are you a carrier of:

a) Sickle cell trait Yes ☐ No ☐

b) Thalassemia trait Yes ☐ No ☐

15. Have you ever had malaria? Yes ☐ No ☐

If yes, when?

16. Have you or anyone in your family had CJD (Creutzfeld-Jakob Disease)? Yes ☐ No ☐

If yes, please provide details:

17. Have you ever had brain surgery? Yes ☐ No ☐

If yes, please provide details:

18. Have you ever had epilepsy? (if no go to question 19) Yes ☐ No ☐

a) When was the last fitting episode?

b) Are you on medication for epilepsy? Yes ☐ No ☐

If yes, please give medication name and dosage:

19. Have you ever been treated with human pituitary extracts, such as growth hormones or gonadotrophins? Yes ☐ No ☐

If yes, please give dates

D D M M Y Y to D D M M Y Y

20. Do you have any thyroid conditions including Graves' and Hashimoto's Disease? (if no go to question 21) Yes ☐ No ☐

a) If yes, have you ever received radioiodine, carbimazole or propylthiouracil? Ye

b) What other treatment or medication have you received?

21. Do you suffer from depression? (if no, go to question 22) Ye

a) If yes, what medication, if any, have prescribed (name and dose)?

b) Are you receiving any therapy or counselling for your depression? Ye

c) Do you feel your depression is well-controlled? Ye

22. Do you have any severe or life threatening allergies (including latex and general anaesthetic)? Ye

If yes, what are the triggers?

23. Do you have Coeliac Disease? Ye

24. Do you suffer from asthma? (If no, go to question 25) Ye

a) If yes, is it well-controlled? Ye

b) Have you ever had an asthma attack requiring admission to hospital? Ye

If yes, when were you last admitted to hospital? D D

c) Have you ever had an asthma attack requiring admission to a high dependency or intensive care unit? Ye

d) Do you use inhalers? Ye

If yes, please give details:

V3/JU

e) Do you use Theophylline tablets? (e.g. Nuelin SA, Slo-Phyllin, Uniphyllin Continus) Yes ☐ No ☐

f) Montelukast tablets? Yes ☐ No ☐

g) Steriod tablets or injections? (e.g. Prednisolone) Yes ☐ No ☐

h) Any other asthma medication? Give details:

25. Have you ever had Tuberculosis? Yes ☐ No ☐

If yes when? D D M M Y Y

26. Have you ever suffered from any other lung conditions? Yes ☐ No ☐

If yes please provide details

27. Do you suffer from high blood pressure? Yes ☐ No ☐

a) If yes, is your blood pressure being monitored by your GP? Yes ☐ No ☐

b) Please give date and details of your last reading (please ask your doctor or practice nurse):

c) Are you on medication for high blood pressure. Yes ☐ No ☐

If yes, please give medication name and dosage:

28. Have you ever had:

a) A heart attack? Yes ☐ No ☐

b) Chest pain/angina? Yes ☐ No ☐

c) A heart murmur? Yes ☐ No ☐

d) Any heart surgery (including keyhole) or any other procedure (e.g. angioplasty)? Yes ☐ No ☐

e) Any other heart disease/condition? Yes ☐ No ☐

If yes to any above questions; please or example, date of diagnosis, detail investigations (e.g. ECG - Electrocar

29. Have you ever had a blood clot (e.g. deep vein thrombosis or pulmonary embolus)? (if no, go to question 30) Ye

a) Has this happened on more than one occasion? Ye

b) Where was the most recent clot (e.g

c) When did this occur? D D

d) Were there any factors that may have contributed to this event? Ye

If yes, please give details:

30. Do you suffer from gout? (if yes, please be aware that you will only be able to donate bone marrow, not PBSC) Ye

31. Have you ever had ME or Post-viral Syndrome? Ye

If yes, is it: Ongoing ☐ Resolved

32. Have you been diagnosed with any condition not stated in this questionnaire? Ye

If yes, please provide details:

33. Are you taking any other medication not previously mentioned? Yes ☐ No ☐

If yes, please provide details:

34. Have you undergone/ are awaiting any surgery including dental? Ye

If yes, please give the following deta

- date of diagnosis.
- the nature of the condition, e.g. ong intermittent, any limitations it impos lifestyle/activities (please make it cl the condition has now cleared and i it lasted)
- if appropriate, the names and dosag medication you are taking

SIGNATURE OF DONOR

DATE

Thank you for updating your details. Please provide your ethnic origin on the following page and return the form to us as soon as possible.

V3/JU

YOUR ETHNIC ORIGIN

POTENTIAL BLOOD STEM CELL/BONE MARROW DONOR

This is required as it helps us to identify the best matches for patients of a similar ethnic backgrou

(Please tick the appropriate)

United Kingdom & Ireland (WHITE)

English ☐ Scottish ☐ Welsh ☐

Northern Irish ☐ Republican Irish ☐

Any other combination of UK/ Irish descent
(e.g. Welsh Mother, English Father)

Northern & Central European (WHITE)

Austrian ☐ Belgian ☐ French ☐ German ☐

Dutch ☐ Swiss ☐ Scandinavian ☐

Any other combination of Northern or
Central European descent
(e.g. Danish Mother, Dutch Father)

Southern & Eastern European (WHITE)

Italian ☐ Portuguese ☐ Spanish ☐ Turkish ☐

Greek ☐ Other Balkan ☐ Eastern European ☐

Any other combination of Southern or
Eastern European descent
(e.g. Spanish Mother, Czech Father)

Other (WHITE)

Any other white or combination of these
(e.g. French Mother, Scottish Father)

African-Caribbean & African (BLACK)

Caribbean ☐ African (excluding North Africa) ☐

Any other African or African-Caribbean
descent (excluding North African)

South Asian (ASIAN)

Indian ☐ Pakistani ☐ Bangladeshi ☐

Any other South Asian descent

East Asian (ASIAN)

Japanese ☐ North Korean ☐ South Kor

Chinese ☐ Taiwanese ☐ Thai ☐

Indonesian ☐ Burmese ☐ Malaysian ☐

Vietnamese ☐ Philippine ☐ Cambodian

Lao ☐

Any other combination of East Asian desc
(e.g. Chinese Mother, Malaysian Father)

Central Asian (ASIAN)

Eastern Russian ☐ Kazakhstani ☐

Uzbekistani ☐ Mongolian ☐

Other (please state)

Other (ASIAN)

Any other combination of South, East or
descent

(e.g. Chinese Mother, Mongolian Father)

Other (OTHER)

North African & Middle Eastern ☐

Jewish ☐

South American ☐

Central American ☐

Mestizo ☐

Any other Non-European descent

Mixed Race

Mixed White & Black ☐

Mixed White & Asian ☐

Mixed White & Other ☐

Mixed Black & Asian ☐

Mixed Black & Other ☐

Mixed Asian & Other ☐

Mixed Other

Other (please state)

Don't Know ☐

Declined To Answer ☐

8.5.2. Cord blood

8.5.2.1. BBMR regular donor health check forms

Donor Health Check for regular donors

Please answer the following questions in blue or black ballpoint pen. If you are uncertain of any answer, leave the box blank and speak in confidence to the nurse. Please do not use correction fluid if you make a mistake on this form.

A Your lifestyle - Since your last donation...	Yes	No	Staff
A1 ...have you tested positive for HIV?			
A2 ...have you had hepatitis B or hepatitis C or think you may have hepatitis now?			
A3 ...have you injected yourself or been injected with illegal or non-prescribed drugs including body-building drugs or cosmetics?			
A4 ...have you been given money or drugs for sex?			
A5 **Since your last donation, have you had sex with:**			
a anyone who is HIV positive;			
b anyone with hepatitis B, hepatitis C or HTLV;			
c anyone who has ever been given money or drugs for sex;			
d anyone who has ever injected drugs;			
e anyone who may ever have had sex in parts of the world where AIDS/HIV is very common (this includes most countries in Africa);			
A6 **Male donors only;** Since your last donation have you had oral or anal sex with a man, with or without a condom?			
A7 **Female donors only;** Since your last donation have you had sex with a man who has ever had oral or anal sex with another man, with or without a condom?			

B Your health - Since your last donation...	Yes	No	Staff
B1 ...have you been told that you should no longer give blood?			
B2 ...have you had a serious illness or seen a doctor about your heart?			
B3 ...have you had any hospital investigations, tests or operations?			
B4 ...has there been any **addition or change** to your prescribed medicines, tablets or therapy (except HRT for the menopause, the pill or other birth control)?			
In the last 7 days...			
B5 ... have you taken any prescribed aspirin or painkillers or taken any other medicine or tablets that you have bought yourself?			
B6 ...have you seen a doctor, dentist or any other healthcare professional or are you waiting to see one (except for routine screening appointments)?			

Change of details – If we have your details wrong, please give us the correct information below.

Title.....Forename.....Surname.....

Address.....

Postcode.....Home no.....Work no.....

Mobile.....Email.....DoB: DD / MM / YYYY

C Risks of infection	DT CODE	Y
C1 **In the last 2 weeks** have you had any illness, infection, or fever or do you think you have one now?		
C2 **In the last 4 weeks** have you been in contact with anyone with an infectious disease?		
C3 **In the last 8 weeks** have you had any immunisations, vaccinations or jabs?		
Since your last donation...		
C4 ...have you had jaundice or hepatitis?	J	
C5 ...have you had your ears, face or body pierced, had a tattoo or any cosmetic treatment that involved piercing your skin?	S	
C6 ...have you had acupuncture?	S	
C7 ...have you been exposed to someone else's blood or body fluids eg through a needle prick or bite or broken skin?	S	
C8 ...have you had a blood transfusion?		
C9 ...has anyone in your family been diagnosed with CJD?		
C10 **Female donors only**; Have you ever had treatment for infertility?		

D Travel outside the UK - Since your last donation...	DT CODE	Y
D1 ...have you been outside the UK (including business trips)? *If **'Yes'** please answer D2, D3 and D4* *If **'No'** ignore the following questions D2 D3 and D4* *(If 'yes': staff must **also** check previous long stay or malaria)*	R L/V	
D2a. ...have you lived or stayed outside the UK for a continuous period of 6 months or more?	L	
b. If 'yes' have you been outside the UK since you returned?	L	
D3 ...have you visited Central America or South America for a continuous period of 4 weeks or more?	R	
D4a. ... Have you had malaria or an unexplained fever which you could have picked up while travelling?	M	
b. If 'yes' have you been outside the UK since then?	V/F	

(IN CAPITALS) **Forename**.....(IN CAPITALS) **Surname**.....

Your Signature.....**Date**.....

STAFF USE ONLY	CLINICAL NOTES
	☐ Suspend until...../...../..... ☐ Withdraw ☐ Accept
Withdraw/suspend until ...../...../..... ☐ Attention Clinical Support Team ☐ Medical Referal Form attached ☐ Set medical bar	Date...../...../..... CST/Donor Records signature.....

Page 1 c

Version 5 01/05/12 **DONATION RECORD - REGULAR DONOR** :

Surname Group

Forenames

Title DOB Sex Donor No

Address

Tel No

Occupation

Tel No. (day)

Outcome of Attendance

01 Donated
02 Low Hb
03 Other samples only
04 No Donation - No numbers
05 No Donation - Numbers Issued
06 No Donation - Pack labelled

PACK HOLD CODE

Signature.....

Donation

Code

BBMR

Total

Award

Award Given Y☐ N☐

Attendance Outcome

Date

Panel

Sub Panel

P:
T:

DONATION TYPE: Whole Blood ☐ | Platelets Only ☐ | Platelets & Plasma ☐ | Autologou

Plasma for FFP ☐ | Red Cells Only ☐ | Granulocytes ☐ | Other ☐

I have completed my tasks in accordance with SOPs	Signatures
Registration	
Health Check☐ Hb Pass☐ Low☐	
Session Hb result ..... g/L	
Machine/Pack set up	
LA	VP
Needle Removal	
Dressing/PD advice	
Final Pack/Sample Check	
Reconciliation	

Incident Record

Malaria (MA)
R DD MM YY
L DD MM YY
T DD MM YY
M DD MM YY
V DD MM YY
F DD MM YY

T-Cruzi (TC)
R DD MM YY
L DD MM YY

HBV (AC)
S DD MM YY
J DD MM YY
C DD MM YY
E DD MM YY

West Nile Virus (WN)
R DD MM YY
W DD MM YY

Discre Testin
R = Ris
L = Lo
T = Tra 1st a r
M = Ma
V = Re are illr
F = Ur
W = W illr
S = Sk
J = Ja
C = Co
E = En

Donor Consent - to be signed in the presence of a member of NHSBT staff

1. I have today read and understood the Welcome Booklet. I have been given the opportunity to ask questions and they have been answered.
2. To the best of my knowledge I am not at risk of infection or of transmitting the infections listed in the Welcome Booklet.
3. I agree that my blood donation will be tested for HIV and other conditions listed in the Welcome Booklet. I understand that if my donation gives a positive result for any of these tests I will be informed and asked to participate in a post-test discussion.
4. I understand the nature of the donatic and the possible risks involved as expla Welcome Booklet.
5. I agree to NHS Blood and Transplant h information about me, my health, my and donations, to contacting my doct information and using my donation fo explained in the Welcome Booklet.
6. I give my blood to NHS Blood and Tran used for the benefit of patients. This n direct transfusion to a patient or for o as explained in the Welcome Booklet.

Date DD MM YY Donor Signature _____

Pa

FOR STAFF USE ONLY

8.5.2.2. BBMR follow-up questionnaire forms

FORM FRM3077/1.2 Effective: 15/10

Donor Response Questions – Hematos

BBMR Donor Questionnaires for task G5002 ***Donor Name*** ***Donor ID No.***

G011 ***Stem Cells: Donor Health Check Form at CT Request***

1	International patient or lapsed blood donor?	YES	NO		
2	Donor Health Check form explained to donor?	YES	NO		
3	Verbal consent obtained for mandatory IDM testing?	YES	CONSENT REFUSED		NO
4	DHC signed by donor	NO	YES		
5	DHC return date	.....			

G006 ***Stem Cells: Record Donor Response***

1	Willing to proceed?	YES	NO		
2	Donor height in metres	.....			
3	Donor weight in kilograms	.....			
4	Donor height (Imperial)	.....			
5	Donor weight (Imperial)	.....			
6	*Donor height and weight confirmed?	Confirmed	Estimated		
7	Body Mass Index	.....			
10	Are you currently seeing or waiting to see a Health Care Practitioner?	NO	YES		
11	If Yes, please specify	.....			
12	On medication?	NO	YES		
13	If Yes, give details	.....			
14	*Any back pain now or in the past?	NO	YES		
15	If Yes please give details.	.....			
17	Do you have any allergies, including latex?	NO	YES		
18	If Yes, give details	.....			
19	Piercings, tattoos or acupuncture in last 4 months?	NO	YES		
20	If Yes, please specify	.....			
23	Travel to malarial area in last 12 months?	NO	YES		
24	If Yes, please detail	.....			
25	Any travel outside the UK in last 12 months?	NO	YES		
26	If Yes, give details	.....			
29	Have you lived for more than 1 year in any tropical country?	NO	YES		
30	If Yes, give more details	.....			
31	Blood transfusions?	NO	YES		
32	If Yes, detail number and dates	.....			
33	Number of pregnancies (to term and incomplete)?	.....			
35	Child <1, pregnant or trying for baby?	NOT APPLICABLE		YES	NO

(Template Version 07

Cross-Referenced in Primary Document: SOP645 Page 1

Donor Response Questions – Hematos

G006 ***Stem Cells: Record Donor Response - continued***

41 Consultant/MO/Nurse Practitioner Referral? NO YES

42 Consultant/MO/Nurse Practitioner Response? .....

43 Check Personal Details are current &/or update NO YES

44 GP Surgery Name .....

45 GP Surgery Contact Name .....

46 Record donor ethnicity and update record

White Irish	White British	Other White Background	Unknown	Chinese	Asian – Pakistani	Asian - Indian	Asian – Bangladeshi
Black – African	Black - Caribbean	Mixed White and Black African	Mixed White and Black Caribbean	Other Black Background	Any Other Group	Other Mixed Background	Mixed white and Asian

48 Test from stored DNA? YES NO

49 Consent to test stored DNA given by donor? NO YES

50 Donor can proceed to CT/ET? YES NO

51 Donor withdrawn? Not Applicable Permanently T

G010 **Stem Cells: Record donor response (lapsed)**

1 Have you had or come into contact with Hepatitis? NO YES

3 If Yes, please give further details

4 Have you had or come into contact with other Infectious Disease? YES NO

5 If Yes, please give further details .....

6 Have you ever been advised not to donate blood? NO YES

7 If Yes, give more details .....

8 Have you ever been unwell after donating blood? NO YES

9 If Yes, give more details .....

10 Since your last donation have you had any serious illnesses? NO YES

11 If Yes, give more details .....

12 Have you seen anyone at an STD, GUM or VD clinic? NO YES

13 If Yes, give details .....

14 Have you lived for more than 1 year in any tropical country? NO YES

15 If Yes, give more details .....

16 Have you ever had malaria? NO YES

17 Consultant/MO/Nurse Practitioner Referral? NO YES

18 Consultant/MO/Nurse Practitioner Response? .....

Date of Interview.....Signed By.....

8.5.2.3. NHSCBB donor screening form

FORM FRM2289/3 Effecti

CORD BLOOD DONOR SCREEN

SECTION A ENROLMENT and CONSENT

MOTHER'S DETAILS

Mother's name……

Mother's DOB ……(must be 17yr or older)

Home tel no……

Second contact no……

GP name…… ……

Address……

……

Tel no. ……

Affix donor mother's donation num

Estimated date of delivery……

Father's name ……

Donor Hospital……

Additional Languages……

LIFE-STYLE QUESTIONNAIRE

1 I now need to ask you about risk behaviour. These questions are mostly about sexual contacts. We I I am going to read out a list of behaviours to you. If any apply please tell me. You can answer at th unclear and you would like me to repeat it or discuss it please tell me.

Have you ever:

a) injected drugs for non-medical reasons?
b) received money or drugs in exchange for sex?
c) had HIV, Hepatits B or C?

In the last 12 months have you:

d) had sex with a partner who has had sex with someone in exchange for money or drugs?
e) had sex with a partner who has hepatitis B, C or HIV, a man who has had sex with another man, a m for non-medical reasons?
f) had Gonorrhoea?

Do any of the above points apply to you? YES NO

MEDICAL HISTORY

	YES	NO	Details
2 Is this pregnancy a result of IVF (in vitro fertilisation) or a surrogate pregnancy?			*If yes, was the baby conceived usin embryo?*
3 Is this a multiple pregnancy?			
4 Have you ever been diagnosed with epilepsy?			*If yes, state medication*
5 Have you ever lived outside of the UK for a period of 6 months or more at any time in your life from birth?			*If yes -Give details of places & date*

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Cross-Referenced in Primary Document: SOP1744

CORD BLOOD DONOR SCREEN

6 Have you ever had malaria?			*If yes - Give date*
7 Have you ever had an unexplained illness where fever was the main symptom, while you were abroad, or within 6 months of return to the UK?			*If yes - Give date & places visited*
8 Were you or your mother born in Central or South America?			
9 Have you ever lived or worked in rural subsistence farming in Central or South America for a continuous period of 4 weeks or more?			*If yes – give dates & places*
10 Have you ever had an organ or tissue transplant, or any surgery on the brain or spine for a tumour or cyst?			*If yes - give full details & dates*
11 Have you ever had any other major operations or suffered from any serious illnesses including blood or bone marrow problems?			
12 Have you or your immediate family ever been diagnosed with, or investigated for cancer?			*If yes - give full details & dates*
13 Has any one in your family been diagnosed with Creutzfeldt Jakob Disease (CJD)?			*If yes - give details of relationship to the baby*
14 Has anyone on either side of your baby's family got thalassaemia, sickle cell anaemia, or unusually shaped red blood cells, or had leukaemia?			*If yes - give details, including relationship to the baby*
15 If preconsented record ethnicity.			*e.g. 1A, 2I, 1C etc.*

Comments

Interviewer

Name..... Date.....

Signature..... Time.....

(Template Version 07/10/08)

FORM FRM2289/3 Effecti

CORD BLOOD DONOR SCREEN

SECTION B *(Completed at the bedside, post delivery)*

Affix donor mother's donation number barco

Confirmation of identity (Mother's ID Card)

Correct name of mother YES / NO

Correct date of birth of mother YES / NO

Correct address YES / NO

	YES	NO	Details
1 Have you travelled outside the UK in the 12 months before your baby was born?			
2 Have you ever had a blood transfusion?			*Give full details including date, rea*
3 In the 12 months before your baby was born did you have acupuncture*, tattooing, body piercing, cosmetic treatment that involves piercing the skin, or an accidental needlestick injury?			**Was the acupuncture done by a c premises? If not give name of acu* *Date*
4 Have you ever had injections for growth or fertility?			*If yes - give full details, including h*
5 Have you had any injections or vaccinations in the last 12 months?			*If yes – give details*
6 Were there any complications during delivery?			*If yes – give details*
7 Did your baby require admission to the special care unit?			*If yes - give full details*

BLOOD SAMPLES TAKEN (after delivery)

Please tick which samples were obtained: HI Micro PPT

Signature if different from interviewer: Date:

Check that labels used to label mother's blood samples are identical to labels used for consent pack pape

Interviewer

Name..... Date.....

Signature..... Time.....

(Temp

Cross-Referenced in Primary Document: SOP1744

FORM FRM2289/3 Effecti

CORD BLOOD DONOR SCREEN

OFFICE USE ONLY:

SECTION C ADDITIONAL TESTS REQUIRED *(completed at NHSCBB)*		
Malaria antibodies	Yes/No	Signature..... Date.....
T Cruzi	Yes/No	

SECTION D FOLLOW UP MEDICAL ASSESSMENT
(completed by a trained CBB staff member at least 12 weeks after delivery, usually by te

Interviewer	*Confirmation of identity (check front page)*
Name	Correct name of mother
Signature.....	Correct date of birth of mother
Date.....	Correct date of birth of baby

	YES	NO	Details
1 Has your baby had its 6-week check?			*Note any problems*
2 Have you had your 6-week post-natal check?			*Note any problems*
3 When your baby was discharged, did the paediatrician have any concerns, or were you aware of any abnormal test results?			*If yes - give full details*
4 Having answered all these questions, is there anything else you think may make it inappropriate for your cord blood to be transplanted? If 'yes' give details.			
5 Finally, in the unlikely event of your baby or anyone in the immediate family goes to develop a serious illness, we would appreciate it if you could let us know using the contact details provided on your consent form.			*Please tick yes to confirm that mum this info*

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Cross-Referenced in Primary Document: SOP1744

8.5.2.4. Anthony Nolan Consent Form

HOSPITAL NUMBER: _____ EDoB: _____ F-F1-2 Consent Form 2

INSTRUCTIONS: PLEASE PUT A TICK IN APPLICABLE BOXES AND ANSWER TO THE BEST OF YOUR KNOWLEDGE	Yes	No
1 Is this a surrogate pregnancy (e.g. you are carrying the child to be raised by another couple)?		
2 Have you or the baby's biological father ever been infected by HIV, Hepatitis B or C, HTLV?		
3 Have you ever had malaria?		
4 Have you ever undergone infertility treatment with hCG (also known as human chorionic gonadotrophin)? (clomiphene/chlomid acceptable)		
5 Have you ever received hormones derived from the human pituitary gland (such as growth hormones, follicle stimulating hormone, Luteinising hormone, Thyroid stimulating hormone) or been a recipient of grafts (transplanted tissue) of cornea, sclera (both parts of the eye) or dura mater (part of brain / spinal cord)? If 'Yes'; please give details:		
6 Have you ever undergone brain (neuro) surgery?		
7 Have you ever been diagnosed with Creutzfeldt- Jakob disease, or variant Creutzfeldt-Jakob disease (also known as CJD, vCJD, human mad cow disease or human scrapie)?		
8 Have you ever received a transplant with tissue or organs including those from non-human (e.g. pig heart valve) origin?		
9 Have you ever been given money for sex?		
10 Have you ever injected yourself with recreational or body building drugs?		
11 Has anyone you have had sex with within the last 12 months injected themselves with recreational or body building drugs?		
12 Have you had sex with a known haemophiliac or anyone with a blood disorder?		
13 Have you had sex with a man who has ever had sex with another man?		
14 Have you had sex with anyone, no matter what their race, who has been sexually active in the parts of the world where HIV/Aids is common?		
15 Have you had sex with anyone, in the previous 12 months who may be HTLV positive, or may be a hepatitis B/C carrier?		
16 Have you had Chicken pox, shingles, or toxoplasmosis during pregnancy?		
17 In the previous 12 months, have you received a 'live' vaccine e.g. Rubella or Yellow Fever? If 'Yes'; please name/give target disease of vaccine?		
18 Have you received a blood transfusion or blood derived product since 1980?		
19 Do you have a history of disease of unknown origin, or that could not be diagnosed?		
20 Do you or the baby's biological father have a history of rapid progressive dementia or degenerative neurological disease (e.g. Parkinson's or Alzheimer's disease), including those of unknown origin?		

(Instructions for collector: If the answer to any of the above questions is 'Yes' or if there is documentary evidence of these arrangements or infections, please halt process and DO NOT continue consenting and DO NOT collect)

21 Have you had any acupuncture, tattoos or body piercing within the last 4 months? If 'Yes' for acupuncture please give date. Where was this performed and what was the name of the person performing the acupuncture? D D M M Y Y		
22 Have you travelled abroad in the previous 12 months? If 'Yes'; which country?		
23 Were you born in or have you ever, at any time of your life lived in Africa, Central America, Asia, or the Middle East for a period longer than 6 months? If 'Yes'; which country?		
24 Do you, your sexual partner or your parents originate from the Caribbean, Japan, South America, or Africa? If 'Yes'; which country?		

COMMENTS

Woman's name and signature:

Dedicated cord collector's name and signature:

Date: Date sent to the ANCTC:

page 1/2

25. In the table below, please check the boxes that apply to you and biological relatives (i.e. relatives by blood):	YOU	BIOLOGICAL FATHER	YOUR OR THE FATHER'S BIOLOGICAL BROTHERS OR SISTERS	YOUR PARENTS	BABY'S FATHER'S PARENTS	BABY'S BIOLOGICAL BROTHER OR SISTER
Have you or your family members ever suffered from a malignant disease (Cancer) e.g. Hodgkin's lymphoma, thyroid cancer, Leukaemia etc.? *If 'Yes' please write the disease below*	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐
Have you, or your family ever suffered from a blood disorders e.g. Glucose-6-phosphate dehydrogenase deficiency (G6PD), Spherocytosis, thalassaemia, thrombocytopenia, sickle cell disease, Chronic granulomatous disease, Hypoglobinulinemia? *If 'Yes' please write the disease below*	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐
Have you, or your family ever suffered from an autoimmune disease e.g. Arthritis, Ulcerative colitis, Crohns disease, Systemic Lupus Erythematosus (SLE), Myasthenia Gravis, Diabetes, Multiple Sclerosis? *If 'Yes' please write the disease below*	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐
Do you or your family suffer from any metabolic/ storage diseases e.g. Tay Sachs, Prophyria, Hunter syndrome, Krabbe disease? *If 'Yes' please write the disease below*	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐
Do you or your family suffer from any 'other' diseases e.g. Cystic fibrosis, Duchene's Muscular Dystrophy Myasthenia gravis, Celiac disease? *If 'Yes' please write the disease below*	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐	Yes ☐ No ☐ Don't know ☐

Woman's name and signature: _____

Dedicated cord collector's name and signature: _____

Date: _____ **Date sent to ANCTC:** _____

8.5.3. International practice

The World Marrow Donor Association (WMDA) conducted a survey of worldwide unrelated stem cell registries, with the purpose of determining how registries define high-risk behaviour, with specific mention of MSM. The key findings were summarised below by Rob Lown (Anthony Nolan).

Countries returning surveys:

Argentina
Armenia
Australia
Belgium
Canada
Czech republic
Denmark
France
Germany
Israel
Italy
Japan
Korea
New Zealand
Norway
Poland
Russia
Singapore
Slovakia
South Africa
Spain
Sweden
Switzerland
Taiwan
Thailand
The Netherlands
United Kingdom
United States
Wales

Registries enquiring about MSM

At recruitment

Yes – 47%
No – 27%
No answer – 22%
Other 3%

At donor selection for transplant

Yes – 58%
No – 22%
No answer – 19%

When MSM behaviour is asked about, what is the timeframe?

At recruitment

Ever – 30%
Within last 5 years – 14%
Within last year – 3%
No answer – 22%

At donor selection for transplant

Ever – 66%
Within last 5 years – 24%
Within last year – 5%
No answer 5%

<u>If MSM is identified, what is the effect on donor status?</u>

At recruitment

Deferred – 38%
Can join – 8%
1 year deferral – 4%
Case by case decision – 8%
5 year deferral – 8%
No answer 34%

At donor selection for transplant

Deferred – 37%
Can join – 5%
1 year deferral 5%
Case by case/transplant centre decides – 24%
5 year deferral – 5%
No answer – 24%

8.6. Survey of current practice

MSM Tissues & Cells

Survey of current practice

Survey responses

- 14 tissue retrievers / providers
- 4 stem cell providers
- 2 fertility clinics

Tissues (n = 14)

- 4 Blood and Tissue services
  - 3 x NHSBT
  - SNBTS
- 2 Eye banks
- 2 Heart valve banks
- 1 Eye and HV bank
- 5 Bone banks
- 1 Society (AATB)

Tissues Qs

- 8 use NHSBT; 1 uses SNBTS questionnaire
  - Eye and HV banks, NHSBT, SNBTS
  - "Men who have ever had sex with another man, even protected sex"
- 5 bone banks use in-house questionnaires
  - "Homosexual or bisexual"
  - "High risk group including homosexuals"
  - "High risk group for AIDS, including MSM"
  - "Must not donate if you are MSM"
  - "Any possible risk from HIV?"
- AATB
  - "Sexually active in the last 5 years?"
  - if so "did he have sex with another man?"

Tissue deferrals

- 13 x Lifetime
- 1 x Don't ask, don't defer
- AATB = 5 years

Testing (Tissues)

	HIV	HBV	HCV	HTLV	Syphilis	Note
Eyes	Sero	Sero (s + c)	Sero	Sero	Sero	Eye only donors
Bone	Sero (1 x NAT)	Sero (1 x NAT)	Sero (1 x NAT)	Sero	Sero	n = 5
HV	Sero + NAT	Sero + NAT	Sero + NAT	Sero	Sero	
Tissue Services	Sero + NAT	Sero + NAT	Sero + NAT	NAT / Sero	Sero	Pooled then ID if nec.

Location: 4 x in house; 1 x 3rd party; 8 x Blood/Tissue service

9 electronic transmission of results; 4 manual

Intervals (Tissues)

	Sample – donation	Donation - use
Eyes	<7 days pre-mortem or <24h post mortem	~14 days whilst results gathered
Tissue	<7 days pre-mortem or <24h post mortem	~14 days whilst results gathered
HV	<7 days pre-mortem or <24h post mortem	8 weeks (mention of TB)
Bone	<30 days pre-retrieval	6 m follow up, one site repeats serology, one for malaria risk only

Points of interest

- Paediatric donors
  - Assess mother if donor <18m or breast fed in last 12m
- Oxford HV bank
  - Retaining MSM donations in hope of change
- AATB
  - Note qualification of sample (colloids)

Stem Cell Qs

- 4 responses
- 4 different questionnaires used
  - 3 with similar wording to NHSBT blood Q as before
  - AN: "ever had sex with another man" but this does not appear in the list of high risk behaviours

SC deferrals

1. 1 year
2. Lifetime, but discretion used
3. 2 months (related donors)
4. none

Testing (SC)

	HIV	HBV	HCV	HTLV	Syphilis	Note
1	Serology HIV-1+2 NAT (ID)	HBsAg, anti HBc, NAT (ID)	Serology NAT (ID)	Sero I + II	Sero	
2	Sero Ag and Ab v HIV-1,2	HBsAg	Sero	Sero	Sero	Toxoplasma, HSV, EBV, VZV, Hep E, CMV
3	Serology + NAT HBc Ab	Serology + NAT	Serology + NAT	Sero	Sero	CMV, EBV, VZV, HSV, Toxoplasma, malaria if rec.
4	Ab p24 Ag	HBsAg, anti HBc	Ab and RNA	Sero I + II	Sero	CMV, EBV (VCA IgG NA IgG) Toxoplasma IgG VCV IgG

Location: Mixed - in house and at Blood/Tissue service

Transmission of results mixed, mostly electronic

Intervals (SC)

- Test – donation
  - <1 month
- Donation – use
  - none

Gametes (n = 2)

- Questionnaires
  1. "Sexual history" and "History of STIs"
  2. "Would you describe your sexual behaviour as hetero / homo / bi / other"
- Deferral
  1. No deferral if not high risk
  2. None

Testing (Gametes)

HIV	HBV	HCV	HTLV	Syphilis	Chlamydia	Gonnorrhoea	CMV
Serology + NAT	Serology + NAT	Serology + NAT	Serology	Serology	SDA	SDA	Serology
Serology	Serology	Serology	Serology	Serology	Serology	Serology	Serology

Donors tested every 3 or 6 months.

Quarantine of 2 months at one site.

Location: In house

Transmission of results mixed.

8.7. Sterilisation and disinfection methods for banked tissues

There are a number of different techniques available for the decontamination of tissue grafts. It should be noted that a given technique can be either a sterilisation or a disinfection protocol, depending on the conditions under which it is applied. The choice of which decontamination protocol is appropriate for each type of tissue graft is informed by the efficacy of the protocol, and by the deleterious effects it has on the biological and/or biomechanical properties of the graft. Generally speaking, the more effective a protocol is, the more damaging it is to the tissue.

8.7.1. Alcohols

Alcohol solutions, principally ethanol in a 70% aqueous solution, are used both as a surface disinfectant and as a soaking solution. They have multiple modes of action, some of which are best achieved by permitting the alcohol solution to evaporate from the surface being disinfected. Alcohols are most effective against vegetative micro-organisms, but are much less effective against spores. They are often used as carriers for other decontaminating chemicals, such as chlorhexidine gluconate. Alcohol disinfection may be used to treat the skin of deceased tissue donors prior to retrieval of tissues, as a surface swab prior to dissection of heart valves, and as a soak for the treatment of tendon allografts. The advantages of alcohols as disinfectants are that they are relatively mild, and have few deleterious effects on tissue properties. They are also much less toxic than other chemical decontaminants so retention of residuals and staff safety are not major concerns. This is counterbalanced however by the relative weakness and limited range of their antimicrobial activity.

8.7.2. Peroxygen compounds

Peroxygen compounds, principally hydrogen peroxide and per-acetic acid, are popular chemical decontaminants for tissues. They are used either as liquid soaking solutions, or as gas plasmas. When in contact with organic tissue (or certain metal ions) the compounds degrade, releasing reactive oxygen species ('free radicals') which exert killing effects. They have a wide range of activity, being effective versus vegetative micro-organisms, spores and viruses. They are generally supplied as high concentration, stabilised solutions, which are diluted prior to use, either with water or buffered saline. Per-acetic acid is more stable than hydrogen peroxide, and has been used extensively for the treatment of musculoskeletal allografts, principally in Germany. A particular preparation of 1% v/v per-acetic acid in aqueous ethanol solution has been validated as a sterilisation protocol.

In the UK, NHSBT has investigated the application of lower concentrations. Whilst the treatments performed well in development studies and were shown not to damage the tissues, in routine clinical application their efficacy was

inconsistent. NHSBT does however incorporate a wash in 3% hydrogen peroxide into its bone processing protocol, which has been shown to significantly deplete bio-burden. The advantages of per-oxygen compounds are their efficacy and wide range of action, and the fact that they degrade into non-toxic chemicals after application; hydrogen peroxide degrades to water and oxygen, and per-acetic acid to acetic acid and oxygen. There are thus no concerns regarding residuals remaining in the tissue, or staff safety in their application. Their limitations arise from their damaging effects to tissue structure. These effects depend on the tissue in question; for hard tissues, they are less pronounced, but their use in stress-bearing soft tissues, such as tendons or cardiovascular grafts, is not advisable without extensive validation.

8.7.3. Chlorine compounds

Chlorine gas or chlorine compounds are commonly used chemical disinfectants. They are not widely used in the treatment of tissues due to their deleterious effects on tissue properties. However hypochlorite compounds, such as sodium hypochlorite, are of interest due to their demonstrated anti-prion properties. The primary mode of action of chlorine and chlorine-based compounds is thought to be their dissolution in aqueous solution to form hypochlorous acid. The high concentrations (more than 20,000ppm) of hypochlorite required to inactivate prions renders this treatment unsuitable for tissue grafts; soft tissue grafts are partially dissolved by this treatment, and hard grafts are de-mineralised. It has been used in lower concentrations in the treatment of bone grafts, for its antimicrobial and bleaching effects, and also as a surface decontaminant for skin allografts, but it is not widely used for the treatment of tissue grafts. Its use nowadays is mostly restricted to the sterilisation of reusable instruments within tissue establishments.

8.7.4. Glutaraldehyde

Glutaraldehyde is a well characterised chemical decontaminant. It acts by crosslinking intracellular and extracellular proteins, and is effective against all classes of micro-organisms. When applied to tissues, it crosslinks extracellular matrix proteins which alters the mechanical and biological properties of the tissue. This can be advantageous if the crosslinking strengthens the tissue and makes it more resistant to degradation, but also has adverse effects as tissue thus treated is prone to calcify *in vivo*. Glutaraldehyde is also a carcinogen, which can leach out of an implanted graft over time. In tissue banking, glutaraldehyde has been used historically to treat dura mater and other membrane type grafts, but is rarely used today, if at all, owing to concerns regarding toxic residuals and *in vivo* calcification. It is used commercially for the preparation of xenogeneic heart valve grafts, derived from porcine tissue. In this situation, its excellent antimicrobial properties justify the use of xenogeneic tissue, and the crosslinking of the tissue lengthens the lifespan of the graft. However, *in vivo* calcification is a drawback with these grafts.

8.7.5. Ethylene oxide

Ethylene oxide is a toxic alkylating agent that is widely used to sterilise heat labile medical equipment. It has a broad range of activity, and is effective against all classes of micro-organisms. It is predominantly used as a gas, either at 37° or 55°C, and therefore one of its restrictions when applied to tissues is that the tissue must be dry before exposure. The presence of fluids in the tissue hinders gas penetration, and in the case of ethylene oxide also results in the formation of toxic by-products such as ethylene chlorohydrin and ethylene glycol that can persist in the tissue. It is therefore used to sterilise lyophilised tissues, predominantly bone allografts, although it has been used in the past to treat other freeze dried allografts such as tendon and skin. Its efficacy, combined with the availability of commercial sterilisers and the fact that it has no deleterious effects on the mechanical properties of the tissue, made it a popular choice for these grafts. As a gaseous sterilant, it is also easier to remove from tissues after use by aeration at high ambient temperature.

Until recently, this was the sterilant of choice for processed bone allografts as a reliable, broad spectrum sterilant that did not damage the tissue structural properties; it was ideal for this purpose. The only significant safety concern was the potential retention of residual amounts of ethylene oxide or its by-products in the tissue after sterilisation, and it was necessary to periodically validate the sterilisation protocol to ensure that these residuals were below a maximum safe level. However, recent advice from the Department of Health, to the effect that there was no effective safe level of residual ethylene oxide, and that it should only be used where there was no other alternative, has led to its replacement with gamma irradiation for sterilisation of bone grafts. Currently, ethylene oxide sterilisation is only permitted for weight-bearing allografts.

8.7.6. Antibiotic decontamination

Antibiotic decontamination involves soaking tissues in a solution of antibiotics, usually prepared in a buffered, physiological solution. This is a relatively weak disinfection process, which is only used in the treatment of tissues where cell viability is required, as it is the only decontamination process that will selectively target micro-organisms over cells.

It generally comprises a range of different antibiotics, including at least one anti-fungal compound, selected to have as wide a range of activity as possible against micro-organisms. The tissue grafts are immersed in the antibiotic solution, with or without agitation, for a set period of time. Incubation times of between 12 and 24 hours are most common.

Antibiotic disinfection is the method of choice for disinfecting grafts where cell viability is thought to be important for optimal graft performance, and was initially developed to treat cardiovascular allografts. It is also used to treat skin and meniscal grafts where cell viability is desirable. However, it is a relatively

weak disinfection process.

Antibiotic solutions have no anti-viral activities.

8.7.7. Gamma irradiation

Gamma irradiation is a physical decontamination method in which the material to be sterilised is exposed to high energy gamma rays from a decaying radioactive source (usually cobalt60).

Gamma irradiation is also used to sterilise a wide variety of medical consumables, such as bandages and syringes. It is generally a service offered by third party companies as it requires a separate specialist plant.

Gamma irradiation has been used to sterilise a number of different tissue grafts. It is primarily used to treat musculoskeletal grafts, where it has the advantage of being able to easily penetrate to the centre of the graft, even through thick cortical bone. It is also used to treat tendon allografts, and occasionally other types of graft. Gamma irradiation has recently been introduced to treat contaminated skin grafts, although in this case it was necessary to treat the skin with a radioprotective chemical (glycerol) to ameliorate the secondary effects of irradiation. The effects of irradiation on connective tissue proteins is complex; the primary effects cause scission of chemical bonds and weakening of the protein, whereas the secondary effects cause the proteins to cross link, making the matrix stiffer.

Irradiation leads to a dose-dependent reduction in the mechanical strength of structural tissue grafts. For this reason, many surgeons will not use irradiated grafts because of the risk of early mechanical failure. Efforts have been made to address these concerns - one approach has been to reduce the dose of irradiation applied to grafts, justified by assessing the bio-burden present before irradiation. Another has been to impregnate the tissue with a cocktail of radioprotective chemicals prior to irradiation, to ameliorate the secondary effects. It is also less effective against certain classes of micro-organisms, in particular bacterial spores and viruses. Where contamination with these organisms is suspected, higher dosages need to be applied.

8.7.8. Heat

Heat, either alone or in combination with steam and pressure, can be used to sterilise or disinfect. The most common form of heat sterilisation, autoclaving, cannot be used to sterilise tissues as it is too destructive to the mechanical and biological properties of tissue. It is however very useful for the sterilisation of single use and reuseable instruments. Milder forms of heat disinfection (pasteurisation) can be applied to tissues however.

Autoclaving, or steam sterilisation, requires exposure of an item to steam at high pressure and temperature. By containing the items to be sterilised in a sealed pressure vessel, and increasing the heat in the presence of water,

superheated steam is created which penetrates the items quickly and kills micro-organisms. A pressure of 15psi generates steam at a temperature of 121°C, which is effective against all classes of micro-organisms, although some classes, such as bacterial spores, are more resistant.

Pasteurisation is a gentler heat treatment, requiring heating of an item to a temperature of generally between 50° and 80°C for a defined period of time. The treatment time varies in accordance with the temperature, with higher temperatures requiring a shorter treatment time. To ensure even temperature distribution and to guard against accidental overheating, the item is usually immersed in fluid prior to treatment. Pasteurisation is not a sterilisation technique, but is effective against vegetative bacteria, fungi and viruses. Bacterial and fungal spores are resistant to pasteurisation.

Autoclaving is not considered a viable process for tissues, due to its immensely destructive effects on both biological and mechanical properties. It has been used historically in some situations to treat bone allografts that are not intended to have weight- or stress-bearing properties, but not for some time. It used to be common practice to incorporate a pasteurisation step (55-60°C, 3-4 hours) at the beginning of bone processing protocols, to reduce initial bio-burden prior to processing and to protect processing staff from any viral contaminants in the tissue. However, improvements in the asepsis of tissue retrieval, and of donor selection and screening protocols, led to this process being removed. A commercial pasteurisation system was also developed and marketed by a German company in the 1990s, aimed at pasteurising femoral heads by heating to 80°C for 30 minutes. This was developed to allow hospital-based bone banks without processing facilities to pasteurise their own grafts. However pasteurisation, even at lower temperatures, has deleterious effects on soft tissues and is only applicable to bone grafts, where the connective tissue proteins are afforded some protection by the mineralised matrix.

Dr George Galea, 8 Nov 2012

8.8. Testing requirements for tissue donors according to Guidelines for the UK Blood Transfusion Services

Reproduced from the Guidelines for the Blood Transfusion Services in the United Kingdom [91].

Table 22.1 Microbiological testing for tissue donors

Donor Type	Sample	microbiological testing requirements for blood samples																	
		Donation sample											post-quarantine sample						
		syphilis	HBsAG	anti-HCV	anti-HIV	anti-HTLV(pooled)	HCV-PCR pooled	anti-HBc	HIV-PCR pooled	HIV-PCR single	anti-HTLV single	HCV-PCR single	HIV-PCR single	syphilis	HBscAg	anti-HCV	anti-HIV	anti-HTLV pooled	HCV-PCR pooled	anti-HBc
living donor																				
surgical bone donor	single sample	Y	Y	Y	Y	Y	Y	Y	Y	Y										
amnion donor (maternal sample)	two samples	Y	Y	Y	Y	Y	Y	Y						Y	Y	Y	Y	Y	Y	Y
dead donor																				
deceased donor		Y	Y	Y	Y	–	–	Y	–	Y	Y	Y	Y							
Deceased Infant donor	infant sample	Y	Y	Y	Y	–	–	Y	–	Y	Y	Y	Y							
	maternal sample	Y	Y	Y	Y	Y	Y	Y	Y	Y										

8.9. SaBTO guidance on screening of candidate organ, tissue and cell donors

Reproduced from SaBTO Guidance on Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation [76].

Final version 1
Published 21.02.11

Table 3 – Screening of candidate organ, tissue and cell donors

	Available tests		Organs*	Tissues**	Haemopoietic progenitor cells (HPC) and therapeutic cells (TC)**	Reproductive cells***	Human embryonic stem cells
Infection	**Serological**	**NAT**					
HIV1/2	Anti-HIV1/2	HIV RNA	✓	✓	✓	✓	✓
HBV	HBsAg	HBV DNA	✓	✓	✓	✓	✓
	Anti-HBc (anti-HBs)	n/a	**a**	✓	✓	✓	✓
HCV	Anti-HCV	HCV RNA	✓	✓	✓	✓	✓
HTLV1/2	Anti-HTLV1/2	n/a	✓	✓	✓	✓	**f**
Syphilis	Anti-*T. pallidum*	n/a	✓	✓	✓	**e**	✓
T. gondii	Anti-*T. gondii* IgG/M	n/a	**b**	.	**c**	.	.
CMV	Anti-CMV	CMV DNA	**c**	.	**c, d**	**c**	.
EBV	Anti-EBV	n/a	**c**	.	**c**	.	**f**
C. trachomatis	n/a	*Chlamydia* DNA	.	.	.	✓	.
N. gonorrhoea	n/a	*N. gonorrhoea* DNA	.	.	.	✓	.

✓ = Mandatory Tests; n/a = not applicable; . = not required

* 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 testing 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.

*** Partner donation with direct use does not require microbiological testing.

a Anti-HBc screening is indicated for liver and for tissues but not for other organ donations. As other organs or tissues may be taken from the same donor, in practice the results of this test will often be available. Donors whose serum contains anti-HBc in the absence of HBsAg should be tested for anti-HBs to confirm immunity to HBV infection. Consideration should be given to confirming the specificity of sera which exhibit anti-HBc reactivity in the absence of other markers.

b Donations containing cardiac or skeletal muscle as major component which may contain tissue cysts.

c IgG tests facilitate matching of donor/recipient serological status and risk management in recipient.

d CMV NAT is performed to exclude CMV infection in cord blood donations.

e Syphilis testing of partners is not mandatory under the EUTCD but is routinely a part of antenatal screening; earlier detection of infection would allow treatment and prevention of long term sequelae.

f Good clinical practice

8.10. References

(1) SaBTO Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation. 21-2-2011. https://www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation.

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8.11. Glossary

ANCBB	Anthony Nolan Cord Blood Bank
BMDW	Bone Marrow Donors Worldwide
CBB	Cord Blood Bank
CBU	Cord Blood Unit
CIBMTR	Centre for International Blood, Marrow and Transplant Research
CT	Confirmatory Typing
CTL	Cytotoxic T Lymphocyte
DBD	Donation after Brain Death
DCD	Donation after Circulatory Death
DMSO	Dimethyl Sulfoxide
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein Barr Virus
EIA	Enzyme Immuno Assay
ETO	Ethylene Oxide
EUODD	European Union Organ Donation Directive
EUTCD	European Union Tissue and Cells Directive
GMFA	Gay Men Fighting Aids
GMP	Good Manufacturing Practice
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HHV	Human Herpes Virus
HLA	Human Leucocyte Antigen
HPC	Health Professional Council
HSCT	Haematopoietic Stem Cell Transplant
HSV	Herpes Simplex Virus
HTA	Human Tissue Authority
HTLV	Human T cell Lymphotropic Virus
ICSI	Intra Cytoplasmic Sperm Injection
IDM	Infectious Disease Markers
IDU	Intravenous Drug User
IFA	Immuno Fluorescent Assays
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee – ISCT (Europe) & EBMT
KSHV	Kaposi Sarcoma Herpes Virus
LGBT	Lesbian Gay Bisexual and Transgender
LGV	Lymphogranulona venereum
MHC	Major Histocompatibility Complex
MSM	Men who have Sex with Men
NGDT	National Gamete Donation Trust
NHSCBB	National Health Service Cord Blood Bank
OTAG	Ocular Tissue Advisory Group
PBMC	Peripheral Blood Mononuclear Cell
PBSC	Peripheral Blood Stem Cell
PEL	Primary Effusion Lymphoma
SNAHC	Surveillance of Newly Acquired Hepatitis C in Men who have Sex with Men
TNC	Total Neutrophil Count

UKBTS	United Kingdom Blood Transfusion Services
VZV	Varicella Zoster Virus
WBMDR	World Bone Marrow Donor Register
WMDA	World Marrow Donor Association