ADVISORY COMMITTEE ON THE SAFETY OF BLOOD, TISSUES AND ORGANS

FINAL MINUTES OF THE TWENTY SECOND MEETING
29TH APRIL 2014
SKIPTON HOUSE, LONDON SE1 8UG

Present:			
Professor	John	Forsythe	Chair
Members			**Area of expertise**
Professor	John	Cairns	Health Economist
Mrs	Gill	Hollis	Patient Representative
Mrs	Catherine	Howell	Nurse
Professor	Richard	Knight	Prion Disease Specialist
Dr	Harpreet	Kohli	Epidemiology/Public Health
Professor	Alison	Murdoch	IVF/Fertility/Stem Cells
Dr	Mallika	Sekhar	Haematologist
Professor	Tom	Solomon	Microbiologist/Bacteriologist/Virologist
Dr	Glyn	Stacey	Stem Cell Banking
Professor	Richard	Tedder	Microbiologist/Bacteriologist/Virologist
Professor	Marc	Turner	Haematologist
Professor	Anthony	Warrens	Immunologist
Dr	Lorna	Williamson	Medical Director, Blood Services
Observers			
Mr	David	Carter	Medicines and Healthcare products Regulatory Agency (MHRA)
Dr	Aileen	Keel	Scotland
Dr	Sheila	MacLennan	UK Forum
Dr	Willy	Murphy	Irish Blood Transfusion Service (IBTS)
Dr	Elizabeth	Reaney	Northern Ireland
Dr	Andrew	Riley	Wales
Dr	Amy	Thomas	Human Tissue Authority (HTA)
Secretariat			
Mr	Andrew	Broderick	Department of Health (DH)/NHS Blood and Transplant (NHSBT)
Mrs	Tina	Lee	DH
Others			
Ms	Samantha	Fletcher	NHSBT Communications
Mr	Andrew	Parker	DH Health Protection Analytical Team

Item 1: Welcome, introductions and apologies

1.1 Apologies had been received from Dr Paul De Sousa, Professor Kate Gould and Dr Eithne MacMahon (SaBTO members); Professor Adrian Newland (National Blood Transfusion Committee) and Ms Triona Norman (DH, Transplantation Policy Lead) (Observers), and Mr Mark Noterman (Secretariat).

1.2 The Chair welcomed Dr Glyn Stacey, who was co-opted onto SaBTO for 2014 to provide additional expertise in stem cell banking and cellular therapies, and who was a member of the Cell-based advanced therapies working group; Dr Amy Thomas, the

new HTA Observer, who was also a member of the Cell-based advanced therapies working group; and Ms Samantha Fletcher, who was resuming attendance.

1.3 The Chair also noted that SaBTO was, sadly, losing some members. Dr George Galea and Professor Marc Turner had both been co-opted to complete the work on Cell-based advanced therapies when their terms of appointment ended on 30th November 2013. The Chair noted their significant contribution to the work of the Committee over the last seven years, and undertook to write on behalf of the Committee to thank them when they left.

1.4 In addition, the Chair said that three further members would stand down from SaBTO when their terms of appointment ended on 30th November 2014: Dr Harpreet Kohli, Dr Eithne MacMahon and Professor Anthony Warrens. He mentioned their contribution to SaBTO, but noted it would be some months until they left the Committee. As the meeting scheduled for September had been cancelled, however, this was their final SaBTO meeting.

2 Item 2: Minutes of the meeting held on 3rd December 2013

2.1 The Chair noted that the publication of the minutes, and of the report on Pathogen inactivation of platelets, had been delayed by correspondence with the manufacturers of the pathogen inactivation systems concerned about how much information should be put into the public domain. Both the minutes and the report had been published on 28th April, however. The minutes had been approved via email in January.

3 Item 3: Action points and matters arising from the meeting on 3rd December 2013

Action 21.01: Dr MacLennan to ask EDQM whether bacterial screening had previously been in use in areas where PI had been adopted:
Dr MacLennan had added a question to the questionnaire, and hoped to have the information by the time of the next meeting.

Action 21.02: The Secretariat to amend the summary of measures to reduce the potential risk of vCJD transmission by blood to include immunoglobulin preparations, and arrange for its publication.
This had been done. The document was published in December 2013.

Action 21.03: The Secretariat to prepare a SaBTO response to the Commons Science & Technology Select Committee Inquiry into the screening of blood, tissues and organs for vCJD, and circulate it for Members' approval.
This had been done. The document was published on the Inquiry website on 27th January 2014.

The Authors to amend the DORA paper on use of organs from donors with a history of cancer:
Action 21.04: to clarify the difference between donor derived and donor transmitted cancer;
Action 21.05: to clarify that the retrieval team should only use the report of imaging, but could not review and interpret all imaging carried out on a patient:
This had been done. The document had been published on 22nd April.

Action 21.06: The Secretariat to send to the DORA working group the draft section on genetic risks from the draft Cell-based advanced therapies report, to avoid duplication and ensure consistency.

This had been done.

Action 21.07: Professor Tedder to pass information to Professor Turner on a discussion about antibiotics and bacterial contamination of stem cell lines, to check for relevance to the work of the Cell based advanced therapies working group. This had been done.

4 Item 4: Cell-based advanced therapies: Report and recommendations of the Working Group

4.1 The SaBTO Open Meeting had been held on Monday 28th April, and had been a successful event. A summary of the points raised and views expressed was tabled, for SaBTO to take into consideration before agreeing a final draft of the report.

4.2 The Chair thanked the members of the Working Group for the extensive work they had undertaken, over a relatively short period.

4.3 Professor Marc Turner, Chair of the Working Group, gave a presentation. The draft report had been circulated.

4.4 The Working Group was established to review the endogenous risks associated with cellular therapies, particularly with respect to donor selection, consenting and testing, and to make recommendations to SaBTO on how these could be optimised in order to support the development of cellular therapies in the UK while maximising donor and patient safety. Many aspects were covered by regulation, but open issues concerning donor screening for infectious agents or genetic abnormalities, and consent and traceability, fell within SaBTO's remit.

4.5 There was currently routine testing of donations for some infections, and selective screening of some donors, or donations for some recipients. However a number of infectious agents were not tested for, were of uncertain pathogenicity or were a threat only to some patients. The group considered issues such as how to manage tests introduced during the lifetime of a product, whether donors should be told the results of such tests, and the potential role of Whole Genome Sequencing.

4.6 Little or no genetic screening was carried out, but the group considered it likely that screening individuals for a propensity to develop certain diseases would become increasingly feasible.

4.7 Issues relating to consent were particularly challenging because of the potentially long period after donation for which a therapy derived from it could be used, with traceability to the donor remaining; and because of the number of potential recipients. Difficulties also arose from the areas which remained uncertain, so that no definite information could be given to the donor, such as the nature of potential future uses of their donation.

4.8 As this was such a fast-developing field, the Working Group had concluded that detailed and specific recommendations would quickly become out of date, and had sought instead to draw out guiding principles.

4.9 The Working Group's recommendations were as follows:

4.9.1 **Infectious risks: risk assessment:**

4.9.1.1 Follow existing SaBTO guidance on the selection and assessment of donors, and on risk assessment for infection, and apply it to tissues and cells; abide by legal requirements, and follow the best available professional guidance.
4.9.1.2 For live donors, risk assess to mitigate risk at the point of donation, and consider infections or agents that may not be cytopathic but could replicate *in vitro* or precipitate cell replication or transformation.
4.9.1.3 Maintain vigilance for new and emerging infections, and consider the potential for their transmission through a cell line.
4.9.1.4 Consider follow up of the donor.
4.9.1.5 When considering the safety of a product, take into account the effect of inactivation / decontamination strategies undertaken during processing, and their effect on the infection potential.
4.9.1.6 Consider assessment of the risk to the potential recipient, for example whether they are immunosuppressed or not.

4.9.2 **Infectious risks: Testing**
4.9.2.1 Follow existing SaBTO guidance on donor testing.
4.9.2.2 Test the end product for bacteria and fungi using assays such as the existing 16S and 18S PCRs.
4.9.2.3 Validate appropriately these and other tests required, including new tests, for use on each cell line or product.

4.9.3 **Genetic risks:** The recommendation is that no genetic screening should be carried out on donors and that relevant genetic tests should be done on the stem cell lines / derived product. These recommendations are based on the following considerations:
4.9.3.1 There is a significant genetic distance between the donor and the ATMP (advanced therapy medicinal product). Thus routine donor selection or screening (by history or testing) for genetic variation is unlikely to be relevant.
4.9.3.2 It would be commercially prudent to undertake selection and screening of the donor to avoid unnecessary expense in the production of a product that may subsequently have a limited market. This would be a commercial decision not a regulatory requirement.
4.9.3.3 Tests are recommended on the ATMP that would be determined by the required function of the product and the indications for use. Given the complexity of the options, this would have to be individually risk assessed by the producer and by the clinician / patient.
4.9.3.4 With the exception of a few specific cases, there is uncertainty about the relationship between genetics and disease.
4.9.3.5 If a decision is taken to regulate genetic testing prematurely, the recommendations are likely to become outdated / challenged in a rapidly moving complex field.
4.9.3.6 There is a further risk that over-regulation in this uncertain area may stifle a new technology that has significant therapeutic potential.

4.9.4 Informed Consent and Traceability: Background points:
4.9.4.1 The subject of cell-based advanced therapies should be discussed openly and transparently, in order to build growing and informed public awareness.
4.9.4.2 Consent should always be considered as a process, not an event.

4.9.5 Informed Consent and Traceability: Guiding principles:
4.9.5.1 *Capacity to consent* - the donation of cellular material should be assessed in the same way that it is for other forms of donation.
4.9.5.2 *Recording of consent*

- The consent must be recorded, together with the fact that clear, sufficient information has been given and explained.
- For donations of cells with potential for use in cellular therapies, consideration should be given to the establishment of a Cell Therapy History File.

4.9.5.3 *Communication of information*

- People being asked to consent should be given enough information on which to make an informed decision, and that information should be clearly presented – verbally or in written form or both - and understood.
- Staff giving the information should be adequately trained, and enough time should be allowed for the consenting process.
- In cellular therapies, there are limits to the extent to which risks and benefits can be identified and quantified; these limits of certainty should be communicated to the person consenting to donation or treatment.

4.9.5.4 *Scope of consent* - should be explicit, and take into account:

- Testing and screening - Donors need to understand that they will be consenting to various tests including: health and background checks; tests on their donation, or stem cell lines or products derived from it, for the presence of viruses or other diseases that may affect the safety of the products derived; and the provision of a blood sample which can be tested for infectious diseases should a stem cell line be derived. Consent should cover not only the tests available today, but also tests that may be available in the future. Donors should also be told the circumstances in which they could choose whether to receive feedback (e.g. information which has a direct consequence for their or their immediate family's health) and when they could not (e.g. information affecting public health).
- Traceability - Donors need to understand the need for traceability, and the implications of it, together with the circumstances in which they may or may not be alerted to an issue arising in relation to their traceable donation.
- Duration - In most cases of cellular therapies, consent should not be time-limited, but donors need to be aware of the consequences of this. It is important to be clear about the ability to withdraw consent, and the stages at which this can be done to the point at which it becomes impossible.
- Retention of samples - The donor should be asked explicitly to consent to this.

4.9.5.5 *Commercial Involvement and Overseas Domains* - Commercial involvement or implications should be openly disclosed, and explicitly covered by the consent; donors need to understand that their donations may be used to develop therapeutic products by commercial manufacturers, potentially for widespread use in the UK and overseas, but that their donation is a gift and they cannot themselves expect to benefit financially if this occurs.

4.9.5.6 *Validity of Consent* - Consent must remain valid at all stages of the development process. If the intended use of the donated material changes, and the existing consent does not cover the new use, additional consent from the donor should be obtained.

4.10 SaBTO was asked:

4.10.1 Does SaBTO endorse each of the recommendations made by the Cell-based advanced therapies working group?

4.10.2 If not, are there any amendments or alternative recommendations which SaBTO would make? If there are, on what evidence or grounds does SaBTO make any amendment or alternative recommendation?

4.11 The following points were raised in discussion:

4.11.1 Follow up of recipients was needed, and exchange and linkage of information eg on adverse outcomes, especially where therapies developed from the same cell line were marketed by different commercial companies. **It was agreed** this should be added;

4.11.2 The criteria for donor selection needed to be applied also to supporting and co-culture material, and the implications for consent and traceability considered. **It was agreed** this would be included in the report;

4.11.3 Re the elements to be included in a Cell Therapy History File, its ownership, responsibility for managing anonymisation/traceability etc, **it was agreed** the report could provide some indications, and possibly cross refer to work currently being done by the Cell Therapy Catapult and others, but detailed specification would not be appropriate;

4.11.4 Concern had been raised that commercial companies could be worried about a requirement to re-apply to the donor for further consent, especially as in practice this would sometimes not be possible if a donor could no longer be contacted. New consent would be needed if the original consent did not cover a proposed new use, but **it was agreed** the report could make clearer the need to get the initial consent right;

4.11.5 Enduring generic consent could be taken at the time of donation, but it was essential the donor should fully understand the limits of certainty. If a fundamentally new use arose, which was not covered by the consent, it might be necessary to derive a new cell line, with new starting material and new consent;

4.11.6 It would not be possible to specify, for example, that a future use would be reviewed by a UK Ethics Committee, as the cell line could be sent for use abroad;

4.11.7 The circumstances proposed in the report in which a donor could choose whether to be informed of incidental findings **were agreed,** but would be made clearer;

4.11.8 It was noted that the timelines concerned, and the probability of commercial involvement, represented a step change in the current position, and could have an impact on donors' perceptions of donation as a gift. This would need to be borne in mind when taking consent;

4.11.9 **It was agreed** the report would spell out more clearly the global nature of the CJD risk, including that vCJD cases had been found in other countries; and that it was a much lower risk than others highlighted;

4.11.10 **It was agreed** the report would highlight the value of samples for future-proofing / lookback exercises, but not recommend their collection and storage in light of the practical issues identified by the working group;

4.11.11 It was noted the authors would consider whether there was a need to review the period for which blood and tissue samples were kept;

4.11.12 If it was found that some required testing had not been carried out, eg in the case of supernumerary embryos originally donated for IVF treatment (for which different testing requirements apply), therapy developers should raise it with the regulator. **It was agreed** a reference would be added to the report.

4.12 Next steps:

4.12.1 It was noted that discussions with the MHRA were under way about the potential for the report to form part of an approach to the European Medicines Agency Committee for Advanced Therapies (EMA CAT), to influence the development of EU Regulations in this area. This was the reason for the late addition of Appendix 1 on the regulatory context;

4.12.2 It was agreed the Regenerative Medicine Expert Group (RMEG), of which Professor Turner was a member, should be asked to take note of the report, especially issues around consent and traceability, and support next steps. RMEG will report back to the House of Lords.

4.12.3 **SaBTO concluded** that, with the amendments to the report noted above, it agreed with the working group's recommendations. The revised draft report would be circulated for final approval via email before it was published, and widely promulgated.

5 Item 5: Paper on a recent incident

5.1 The Chair emphasised the confidential nature of this item, as the external review set up by the hospital concerned was still under way.

5.2 SaBTO had been notified of the incident because of the relevance of SaBTO *Guidance on the microbiological safety of human organs, tissues and cells used in transplantation*.

5.3 Members considered whether the guidance, published in 2011, was sufficiently clear and up to date; there was no suggestion that the guidance given was not appropriate. The question was also raised of whether it was sufficiently well-known to staff working in transplantation. It was noted that a small number of enquiries had been made, and had shown that while the guidance was well known to senior staff, more junior staff were less aware of it, possibly because of the time since it had been published and promulgated.

5.4 It was clarified that the implementation of SaBTO guidance was outside SaBTO's remit. SaBTO did, however, seek to ensure that when guidance was published, it was promulgated as widely as possible, and was drawn to the attention of a wide range of relevant professional and patient groups.

5.5 It was noted that a review of the guidance was already part of SaBTO's work programme for 2014/15. However, **SaBTO agreed** the prioritisation of the work would be reviewed in light of the findings of the external review of the incident.

6 Item 6: Presentation on the Alliance of Blood Operators "Risk-based decision making from donor to recipient" project

6.1 Dr Lorna Williamson spoke to this item.

6.2 The Alliance of Blood Operators (ABO) was seeking to develop a framework document which could be used in various jurisdictions, to improve services for blood recipients.

6.3 Volunteers were being sought to participate in a consultation exercise regarding the draft framework, by means of a Choicebook. Individuals were needed, especially

blood users, lay people and regulators.

6.4 Separately, groups were being sought who could test the feasibility of the draft framework, ideally in parallel with any 'live' issue under consideration. Dr Sheila MacLennan had kindly agreed that the review of HTLV testing being led by the Specialist Advisory Committee on Transfusion Transmitted Infections could be used for this purpose.

6.5 SaBTO was asked to agree that the working group which had been set up to consider Hepatitis E in the blood supply should use the ABO framework in parallel to its usual framework. The group would report back to SaBTO in the usual way, but would also report back to the ABO on the performance of the draft framework. **SaBTO agreed this,** with the proviso that if issues with the framework arose that could cause controversy, SaBTO would be informed at an early stage.

6.6 The following points were raised in discussion:

6.6.1 Feedback would be qualitative. The draft ABO framework was also being trialled by those who did not have an equivalent to SaBTO or SaBTO's current framework. SaBTO's participation would provide an indication of how far the ABO framework could be used to standardise the way problems are considered, though with some tailoring for individual cases.

6.6.2 It was suggested that it would be illuminating to 'post test' too, to see if the ABO framework would have helped deliver the solution arrived at in a particular case; for example, if it would have facilitated or delayed the introduction of leucodepletion to address the risk of variant Creutzfeldt Jakob disease (vCJD). It was agreed that the threat of vCJD would be an informative example to use.

Action 22.01: those willing to volunteer should contact Dr Williamson directly.

7 Item 7: SaBTO Work Programme for 2014-15

7.1 It was clarified that the Blood Services would report back to SaBTO when results were available from the work in hand on washing femoral heads and on testing deceased donors for abnormal prions using splenic / ocular tissue.

7.2 It was noted that the Regenerative Medicine Expert Group would consider issues relating to the use of non-human elements in the manufacturing of cellular therapies, and the issues relating to cellular therapies for bone and cartilage.

7.3 **SaBTO agreed** the Work Programme with the proviso at paragraph 5.5 above, that prioritisation of the review of *Guidance on the microbiological safety of human organs, tissues and cells used in transplantation* would be considered in light of the findings of the external review of the transplant-transmitted infection incident.

8 Item 8: Recruitment to SaBTO in 2014-15

8.1 A paper had been circulated for information, on the posts to which SaBTO would be seeking to recruit later in 2014. Members were encouraged to let the Secretariat know of individuals who might be suitable candidates, so they could be invited to apply when the vacancies were advertised; and to circulate the advertisement widely, and encourage suitable colleagues and contacts to apply.
Action 22.02: Members and Observers to notify the Secretariat of individuals suitable

to be invited to apply for vacant posts, and to circulate the advertisement in due course, and encourage suitable candidates to apply.

9 Item 9: Update: Donor/Organ Risk Assessment (DORA) Working Group

9.1 The Update was noted. The paper on transplantation of organs from donors with cancer or a history of cancer had been published on 22nd April, on the SaBTO page of the GOV.UK website.

10 Item 10: Update on deferral of MSM donors in Australia

10.1 The Update was noted.

11 Item 11: Any other business

11.1 There was no other business.

Date of the next SaBTO meeting:

Tuesday 9 December 2014