Introduction

This submission contains the response of the Steering Committee for the Centre for Cell and Gene Therapy (CCGT) at the Westmead Research Hub Campus in NSW to the Draft Standards for minimising infectious disease transmission vai the therapeutics goods that are human blood and blood components, human tissues and human cellular therapies.

Members of this Steering Committee represent research and clinical groups on the campus from the bone marrow transplantation, pancreatic islet transplantation and gene therapy fields. It contains representation from Westmead Hospital, Westmead Millenium Institute, The Children's Hospital at Westmead, the Kid's Research Institute and the Children's Medical Research Institute.

This committee is charged with the oversight of the development of a campus-wide GMP compliant quality system to provide the platform for the provision of cellular therapies to patients as an ARTG listed product where applicable, or in a GMP compliant manner where possible if the cellular product is considered as exempt, or under the provisions of "Exceptional Release".

General comment

This document largely describes processes which are already in place in clinical transplant practice, however, these processes are described in a complicated and inaccurate way. Many additional requirements to current practice, as presented in this document will result in increased complexity, not only in interpreting and complying with the standards, but in the day to day logistical completion of time critical testing regimens and donor evaluation. One major consequence for centres undertaking cellular therapies with be the additional costs in staffing, transporting and paying for tests to meet the standards.

In addition,

1. Most especially in relation to the area of HPC transplantation, this document duplicates what is in the NPAAC document. What purpose does this serve?
2. In relation to the ascertainment of cell products from overseas (as is common in the area of HPC transplantation) for use in the treatment of Australian patients, testing for overseas products will be done by overseas laboratories which are outside Australian jurisdiction.
3. These standards are of no value for international collections of cellular products, which account for almost 50% of HPC products for unrelated donors. HPC laboratories are thus better served by complying with an international standard, such as FACT, rather than a local one.

Specific Comments on Sections

Schedule 2 general comment

It is unclear which section of a centre or institution is going to accept the responsibility and associated expense of being labelled as the manufacturer of the multiple different products manufactured across an institution or campus.

Specific comments

(1) (b)

1. Requirement for "an approved quality system in place": This will be almost impossible for most centres to achieve as the availability of quality managers is very limited.
2. It appears that there was little consultation with experts in the field of human transplantation in relation to this requirement. In relation to HPC transplantation, this requirement is nonsensical. It is questionable which One would question which experts had been consulted if the ID standard immediately excludes one of our most important sources of HPC products – 10% of our overseas donors are from the UK.
   At times, patients with malignant diseases whose only opportunity for a related or unrelated donor stem cell transplant as a curative procedure may have as that donor a person who fulfils the criteria in part i or ii of the clauses. In such situations, the risk of infectious disease transmission is likely to be many fold lower than the risk of illness or death due to the underlying illness. An exception mechanism needs to be developed to account for these situations and to allow for use of these donors.

(4) It is not clear how the reference to "each human blood and blood component, human tissue or human cellular therapy product" relates to the product groupings referred to in the draft GMP code. The terminology is unclear and confusing.

Schedule 3

Part 1

- The following comment also applies to criteria applied to Table 2. Ineligibilities based on a, b, c, d, e, f, some sections of g, h, i, j, k, l, s, t are relative for patients with malignant diseases where the donor identified might be the only available stem cell source for a potentially life saving procedure. In particular, for hepatitis B and C infection, the absence of detectable virus in blood by qPCR testing could be used to identify donors at little or no risk of infectious disease transmission.

Part 2a

- The term "qualified interviewer" requires definition

- adoptive cell therapies in the context of stem cell transplantation using HPC-A or HPC-M most commonly use cells generated from peripheral blood and derived from haemopoietic stem cells. Examples include donor lymphocyte infusions and specific immunotherapy for infectious disease prophylaxis including amongst other cytomegalovirus and Epstein-Barr virus. Frequently, blood for cell generation is taken at the time the donor attends to commence the process of stem cell collection. In the setting of HPC-A or HPC-M, interview can take place within 30 days before collection of cells (see part b). However an HPC-A or HPC-M donor who is also donating blood for cell therapy for the same recipient as the stem cells and who has been interviewed between 7 and 30 days prior to donation, will have to be interviewed on a separate occasion in order to donate blood for generation of cells to be adoptively transferred. It would be most sensible to allow that in this situation where cells for adoptive therapy to a recipient of HPC-A and HPC-M are to be generated, the period between interview and donation should also be a maximum of 30 days.

Table 2

- It will be very difficult for assessors to confirm whether acupuncture in the period prior to donation was performed using non-reused needles or equipment. How is it proposed that confirmation be determined?
- For patients previously treated for hepatitis C and known to have cleared the virus how will clause g be applied?
- Clause i permanently bans stem cell transplant recipients as potential stem cell donors. There are several cases reported where a stem cell recipient has redonated stem cells after the original donor has fallen ill. These processes will now be prevented. Why?
- Under item j, including Hep C, the term ineligible suddenly appears, but is not defined anywhere in the document.
- Who is determined to be at risk of prion disease?
- Similarly to above, organ recipients or recipients of cell therapy products, many of whom are long term survivors, will now be excluded from the process of stem cell donation for potentially life saving transplants. This clause needs to have an exclusion mechanism after informed consent of the intended recipient.
- Item (q) relates to the exclusion for UK ACJD and is not a contraindication to BMT donation.

Table 3

- effective therapies are available for diseases for which some live viruses are given. For example, although varicella vaccine may result in low levels of viral load in the vaccine recipient, if these can be confirmed by viral quantitative polymerase chain reaction not to be excessive, it may be perfectly acceptable to use a donor within the exclusion period suggested, as long as appropriate therapy is also given to the recipient at the time of cell administration. This may be critical in a situation where time is of the essence in a transplant for a life threatening disease. As new therapies become available, these situations are likely to become more common. Thus an

exclusion criteria for Table 3 should be generated that permits the use of donors who have received live vaccines if low levels of virus can be documented and simultaneous effective anti-viral therapy can be given.

Schedule 4

In general, there is no appropriate Medicare rebate to cover the large number of tests that are required within a short period of time for HPC donation, Is this planned as part of this and/or the NPAAC process?

(6) (b)

The term regulatory approval requires definition. Do any PCR tests have regulatory approval?

Schedule 5

Part 1a

- NAAT testing for hepatitis B and C and for HIV infections has now been mandated for all donor products for autologous and allogeneic stem cell transplantation and blood derived products. The cost and logistic implications of these requirements and their introduction will need to be carefully negotiated between the regulatory, statutory and health administrative powers. Costs are not limited to the cost of the lab test but inlcude the procurement, transport, testing and rapid result return that is required for these time critical samples and scenarios. If the burden of funding for these tests is not negotiated between associated administrative powers, there is likely to be a politically unacceptable backlash resulting from curtailment of essential medical services should introduction be attempted in the absence of buy in and resourcing support at state health department and local hospital levels.

Part 1cii

- This requirement illustrates the lack of understanding of human transplantation in the construction of this document. In HPC transplantation, the critical point for donor evaluation is prior to the patient start to receive conditioning for the transplant. At Westmead, donors are evaluated 30 days prior to collection, to ensure they are medically fit, willing and safe to donate and then again within 7 days of the patient starting conditioning therapy, then again within 7 days of donation. It is of the utmost importance to ascertain fitness for donation at these time points. An examination within 5 days of donation which finds the donor unfit is too late.
- In addition, see comments on Schedule 3 Part 2a above in relation to adoptive cell therapies

Part 2

- the imposition of a necessity to retest donors of stored products will be logistically and financially extremely difficult to adhere to. With respect to HPC transplantation, in most cases that donor products are stored long term,

this storage is undertaken precisely for the reason that the donor is disabled mentally or physically, is inaccessible or geographically distant. These are the very cases that repeat testing will be difficult or impossible.

Part 5

Careful definition is required for what is approved, specified and acceptable.

Table 4

In relation to HPC transplantation, this table is incorrect - donors do not have to negative for Hep B and Hep C; they may be ineligible, but this does not mean that they may not be used.

Schedule 6

Part 2a, b

- There will be a problem in the insistence that all products that come in contact with blood, cells and tissues under manufacture be entered on the ARTG. A number of products currently used routinely in manufacture are not on the ARTG and there is little or no likelihood that the manufacturers of these products will make an application for these products to be entered on the ARTG on commercial grounds. This will leave manufacturing facilities without any options. If this issue is not resolved, it will become impossible to use an agent such as DMSO to freeze cells. Given that this agent is a worldwide standard, an exemption mechanism needs to be generated that will accommodate this situation. Further, the current use of peptides, tetramers and other agents that are now listed only for research purposes but are being used for the generation of cell therapy products will create exactly the same problem.

Incidental note:

On page 8 of the draft Therapeutic Goods Order at footnote b, is the word not at the end of the first line an error?