Response by Westmead Islet Program and Australian Islet Transplant Consortium to Draft Australian Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapies

This document is the response from the Westmead Hospital Islet Transplant Program and the Australian Islet Transplant Consortium. We are one of two islet isolation facilities providing clinical grade islets for transplantation. The consortium is currently undertaking a clinical trial of pancreatic islet transplantation in patients with type 1 diabetes and severe hypoglycemia unawareness.

Intro – overview of islet transplantation

Clinical islet transplantation involves the isolation of pancreatic islets of Langerhans from the whole pancreas of deceased organ donors. The isolation procedure occurs in specialized clean rooms conforming to GMP. The procedure takes about 6 to 8 hours, after which the isolated islets are placed in culture for approximately 24 to 48 hours before transplantation into a patient. The donor pancreas is collected by the organ donor team at a distant institution as part of a multiorgan donor procedure and transported to the isolation facility. There are very tight timelines between the removal of the pancreas and the commencement of the isolation process (less than 10 hours). Because the pancreas is taken from deceased organ donors which are in short supply there are limits on the information available, selection criteria and time available for decision making processes. Once islets are released from the isolation facility they are transplanted into the recipient by resuspending the islets in 150mls of media and infusing the islets into the liver via the portal vein. The islets from one isolation are only ever transplanted into one recipient. At the current state of technology islets from two to three donor pancreases are needed to achieve insulin independence ie the procedure is repeated two to three times. In Australia, donor pancreases processed in one of two physical locations (one in Melbourne and one in Sydney) as part of the Australian Islet Transplant Consortium.

Nature of Islet Transplantation-

- There are only 200-230 donor organs available in the whole of Australia each year. Currently up to 35 donor pancreases per year are used for whole organ pancreas transplantation. Other donors are deemed unsuitable for the islet isolation eg the pancreas was damaged by trauma or the donor had diabetes. Hence, the number of donor organs qualifying for use in the islet program less than 150 per year with the current organ donor rate. Last year 70 pancreases were used for islet isolation but a considerably smaller number reached release criteria. Hence this is a low

volume but complex procedure that requires staff to be on call 7 days a week 24hours a day. As a result the burden has a significant impact on the cost of the procedure. It has the potential to be a significant proportion of the overall cost of the procedure.

- We feel it is important for the TGA to distinguish between a complex, low volume procedure of less than 100 per year compared to high volume well established procedures such as the. Blood transfusion service where the cost impost of regulation per unit of product is much less. Regulation has the potential to be a major cost factor for what is already an expensive procedure. The TGA needs to realize that:
    - islet isolation is relatively new experimental procedure that is undergoing constant change refinement
    - It is a low volume procedure that is being undertaken by public hospital and is funded by state and federal government
    - Any additional costs of regulation will ultimately have to be borne by the tax payer and cannot be passed onto third parties
    - The TGA needs to advise how they propose to regulate experimental and evolving cellular therapies as distinct from well established procedures such blood transfusion.
- An important point to emphasise is that islet isolation and transplantation is not another version of blood transfusion or bone marrow transplantation. It is not possible for it to comply with FACT or regulations for blood products. Islets are sourced from deceased donors and hence need to be regulated differently from blood donors and bone marrow donors. The procedure from isolation to transplantation is under control of medical staff that have a specialist interest in this area. Patients are seriously ill and are at risk of significant morbidity and death from their underlying condition. The risk benefit analysis that defines the regulatory process for islet transplantation needs to reflect this fact. For these reasons islet transplantation is more like solid organ transplantation than blood transfusion and this should be reflected in the regulation.

Donation and Collection of donor organs for islet transplant Section 8, 800 to 820

- We are unable to control the process at point of collection due to the nature of donor organ retrieval. This area is already the responsibility of the Australian Organ and Tissue Authority (AOTA), created by the Federal Government in January 2009.
- Multiple surgical teams in different states across Australia retrieve organs with very diverse staff. Regulations by two different authorities (TGA and AOTA) in this area may alienate surgical doctors. The refusal by surgeons to retrieve for the islet program is a very real scenario with increased regulation. Without donor organs, we will no longer operate, shutting down islet transplantation in Australia. This will close one avenue of treatment for the ever-increasing numbers of Type 1 diabetics with hypoglycemia unawareness.

- ***The audit trail should start at the point of receipt of the donor organ by the processing laboratory.***

- It should also be pointed out that some donor data cannot legally be given to the processing facility due to privacy stipulations within state based Organ Donor Acts. The organ arrives at the facility de-identified. However if it was necessary to trace donor data this can be done via the state based organ procurement organizations.

- Because islets are retrieved from deceased donors some health, social and travel data will be unavailable.

- **Autologous Donation**
  - The criteria for acceptance of a donor for an autologous islet transplant needs, by definition, to be different from that of a cadaveric donor. If there is a medical rationale for an autologous islet transplant for a patient, the procedure should take place. In other words, factors such as hepatitis viral status of the recipient may not be relevant based on specific medical information.

Control of material **Section 5, 500 to 511**

- There are a large number of media and additives used in the manufacturing process. These have been developed specifically for islet isolation and culture. We access this material from US manufacturers that supply US islet facilities and comply with FDA guidelines for Class I Medical Devices. Solutions are manufactured to ISO 13485:2003. They are not licensed for human use in Australia (and may not be licensed in the US or Europe) and economies of scale mean that the manufacturer would not submit for licensing in Australia. The wording of any regulations should be such that the use of licensed products should not be mandated as it well impede the development of small scale procedures such as islet transplantation

Processing of donor organs **Section 8, 821 to 841**

Validation **Section 8, 835 to 841**

- Any change in equipment or materials cannot be validated prior to processing a donor organ. All validations will be during routine processing (concurrent validation). Due to the nature of the starting material, the donor organ, validations on processes and material would mean utilizing a human organ of quality control purposes. This has ethical and legal and resource implications.

Quality Control Section 9, 900 to 913

Product Release Section 9, 914 to 918

- Because of intrinsic human variability in the quality of the donors, it is impossible to produce a standardized product. The important issue is to have a clear standard for an acceptable product for transplant rather than a standardized product.
- Quarantine of product is not possible. There is a biological timeline, which is limited making quarantine of the product unfeasible.
- Due to the fragility of the cells transplanted, and the urgent nature of the procedure, there is only a limited time for product validation. This places limitations on what tests can be carried in the limited time available before release of product.

Informed consent by patients

- The above points highlight the difficulties of regulatory compliance with low volume procedures such as islet transplantation. Because all of one islet isolation goes only to one patient it is possible to overcome these problems with individual patient consent prior to transplantation.
- Individual informed patient consent occurs with patient recipients signing a six-page information sheet identifying the risks of their procedure. Among other features it highlights the potential infective risks and the fact that cells are cultured and delivered in media that is not a licensed product for human use. There is scope to further extend this document if need be. There is total clinical control over the whole process because of the one-to-one aspect of this procedure.
- It must be noted that only one donor organ is transplanted into only one recipient. This is not a multi recipient procedure from a single source.
- Westmead transplanted **5** pancreases last year while a unit in Melbourne transplanted **5.** A large proportion of donor organs do not proceed to transplantation due to the nature of the biological starting material.

Implementation of these regulations has the potential to set back islet transplantation in this country. The size of our market means that it will never meet the economies of scale of other procedures or indeed other jurisdictions eg US and Europe.

Cost implications –

- There will be both capital costs and ongoing costs. The capital costs include a compliant GMP facility and additional personnel for preparation and implementation of the documentation required. The ongoing costs will include doubling the number of personnel for compliance with regulations on an ongoing basis, quality control through all processes as well as increased ongoing costs for facility maintenance.

- The additional burden of regulatory compliance will be borne by the government and the public health system and thus, ultimately the taxpayer.
- The implications of these regulations for islet transplantation are foreboding. Development of this therapy in Australia would not have happened without the support of large charities such as the Juvenile Diabetes Research Foundation that have been working tirelessly for many years to support research for a cellular treatment for Type 1 diabetes in this country. The regulatory infrastructure has the potential to add substantially to the cost of initiating such trials of cell based transplantation in this country. There needs to be a clear pathway to develop such trials not impede them.
- The change of direction that the transition from research to experimental clinical procedure is taking will dry up funding for these types of translational research projects. Regulation of these procedures must be mindful of what is achievable with a small volume rapidly developing field. These regulations have to potential to a have a major negative impact on cost, staffing, productivity and ongoing development. The aim should not be prevent essential clinical research in this area from happening.

- **It is important to realize that these procedures are carried out within the public health system and not by pharmaceutical companies.** The substantial costs of any regulatory process will be borne by state health departments which are already under enormous cost pressures. A situation should not exist where emerging therapies are denied to the Australian public because of the cost of regulating them. Regulation should be subject to risk benefit and cost benefit analyses that are relevant to the procedure.