LANDMark Biobank

Manual of Operations

(Incorporating Standard Operating Procedures)

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Sponsor: JDRFI*

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1 Overview

This tissue banking initiative is an adjunct to the JDRFI and NHMRC funded 5-year clinical study entitled "Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic Diabetic Markers", also referred to as LANDMark Study (the full title of this study as originally submitted to JDRFI in Sept 2007 is "A longitudinal study of ophthalmic markers of neuropathy in type 1 diabetes"). Specifically, the LANDMark Biobank is a JDRFI initiative located at the Institute of Health & Biomedical Innovation at Queensland University of Technology (QUT), Australia, and the University of Manchester, United Kingdom. The purpose of the facilities is storing and managing ethically consented blood, other tissues and matching longitudinal clinical data. The Biobank is a resource that will become available in the future to researchers throughout the world to support research investigating biomarkers of diabetes and its complications, improving or creating diagnostic tests and identifying potential new treatments for diabetes and diabetic neuropathy. The JDRFI has funded and equipped a dedicated laboratory with high-precision equipment for preparation of specimens. This equipment includes a -80ºC freezer and may include a vapour phase liquid nitrogen storage vessel (-196ºC) and which have the capacity to house in excess of 50 000 tissue and blood samples. The samples collected from study participants will be stored in cryogenic vials that help preserve the tissue's proteins and genetic material almost indefinitely.

The specimens, with matching clinical data, will be donated by consenting participants while enrolled in the LANDMark Study. Participants will have the option of consenting to the research team collecting a small additional sample of blood and/or skin tissue. These specimens are processed and stored at the LANDMark Biobank, initially located at two sites: Brisbane, Australia and Manchester, UK. These samples are stored under a unique code without the participants' identity.

Potential outcomes from tissue research include finding potential causes of type 1 diabetes or identifying factors predisposing the development of diabetes and its complications, and developing vaccines, drugs or other treatments for diabetes and its complications. New methods for screening, diagnosis and evaluation of diabetes are likely to make a significant impact on patient care in the future. Researchers who are part of an ethically and scientifically approved research project will be able to apply to access samples from the LANDMark Biobank.

2 Introduction

Blood and other tissue-based biomarkers are emerging as one of medicine's significant clinical research tools, resulting in enhanced development of pharmaceuticals and improved diagnosis of individual health conditions. Biomarkers are substances, structures or processes that can be measured in biological samples (such as urine, skin, blood, or saliva) that indicate, in the case of diabetes and its complications, susceptibility, or predict the onset and progression of disease. They help us to understand how chemicals move through the body and cause biological changes that can lead to illness and disease.

The overall goal of the LANDMark Biobank is to establish a repository of blood and skin biopsy specimens with detailed clinical information from a large number of unrelated

patients with type 1 diabetes and Latent Autoimmune Diabetes in Adults (LADA) in order to facilitate studies into biomarkers of diabetes and diabetic neuropathy. The specific goals are to:

- Recruit and examine 288 type 1 and LADA diabetic patients with and without diabetic neuropathy.
- Recruit and examine 116 non-diabetic participants without neuropathy.
- Collect baseline and longitudinal information on other markers through the LANDMark study.
- Maintain an inventory of the samples and clinical data for individuals included in the JDRFI funded LANDMark Biobank collection.
- Develop shared databases.

This set of LANDMark Biobank Standard Operating Procedures has been developed according to best practice and other guidelines as follows:

- International Society for Biological and Environmental Repositories (ISBER) Best Practices for Repositories: Collection, Storage and Retrieval of Biological Materials for Research (2008)
- NHMRC. Organ and Tissue Donation by Living Donors - Guidelines for Ethical Practice for Health Professionals (2007)
- Human Tissue Act 2004 (England, Wales, Northern Ireland)
- Transplantation and Anatomy Act 1979
- Australasian Biospecimen Network Biorepository Protocols (March 2006)
- Eiseman E et al. Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era. Rand Science and Technology's (2003)
- Australian Privacy Act 1988 (Sections 95 and 95A)
- UK Data Protection Act 1998
- National Health and Medical Research Council of Australia (NH&MRC) National Statement on Ethical Conduct in Research Involving Humans (2007)
- NIDDK Central Repository for the "The Genetics of Kidneys in Diabetes (GoKinD) Study" Manual of Operations (GoKinD MOOP). See:
    - https://www.niddkrepository.org/niddk/jsp/public/GOKIND/MOOP.jsp

The LANDMark Biobank acknowledges the substantial assistance of staff of the Australian Prostate Cancer Collaboration BioResource in the development of these Standard Operating Procedures (SOPs).

2.1 Scope

The procedures within this document are for the practical guidance of all authorized personnel involved in the biological sample procurement and data collection of the LANDMark Study, housed at IHBI, Queensland University Technology, 60 Musk Avenue, Kelvin Grove, Australia and Core Technology Facility, University of Manchester, United Kingdom.

2.2 LANDMark Biobank Management Committee

The LANDMark Biobank Management Committee (LBMC) should meet at least once per year (or more if needed) to monitor, on a regular basis, the progress of the Biobank, its procedures, records, efficacy and quality of operations and any positive and negative feedback received from participants, staff or other stakeholders. Adverse outcomes and major procedural changes may be reported the ethics committees and the JDRFI.

The LBMC accepts applications from researchers who wish to use biospecimens from the Biobank. The LBMC will have policies and procedures relevant to the Biobank and will endeavour to ensure they are adhered to. The Committee will also oversee the appropriate use of biospecimens and administer over any conflicts of interest or complaints.

After a two-year moratorium on access, the LBMC will consider proposals as they are presented. This committee should communicate at least annually to review the progress of the LANDMark Biobank. In the unlikely occurrence of a serious event, an urgent meeting will be arranged.

The LANDMark Biobank Management Committee (LBMC) will comprise of Nathan Efron (Chief Investigator of the LANDMark Study, IHBI), Nicola Pritchard (IHBI), Katie Edwards (IHBI), and Rayaz Malik (University of Manchester). The Committee may also invite the participation of a consumer representative, typically appointed by the chair of a human research ethics committee, as a member. Nicola Pritchard will act as LANDMark Biobank Manager.

2.3 Responsibilities

The Manager or delegate is responsible for all operations including compliance with current national, state and local regulations. The Manager will also ensure the Biobank operates within budget (in Brisbane only), and serve as a liaison to key users.

Personnel authorized and supervised by LANDMark Biobank Manager (Brisbane site) for biological sample procurement and processing, and data collection must familiarize themselves with these SOPs. Each person is responsible for ensuring that all procedures are performed as defined in the individual SOPs. The order for execution of the various procedures is indicated in the flow diagram in SOP 1:

The Manager shall arrange internal review and audits to ensure compliance with the SOPs and regulations (Brisbane only).

2.4 Safety

Safety plans are used to prevent or to minimize injuries to employees. LANDMark Biobank personnel will adhere to the Health and Safety guidelines of the host Institution in the areas of biological, chemical, electrical, radiational, physical and fire safety. Staff shall undergo training (or induction) in possible hazards and precautionary measures e.g. staff members working with human research participants are encouraged to be vaccinated against hepatitis.

Personnel and visitors should wear appropriate personal protection wear (lab coats, long pants, covered shoes) and eye protection. Appropriate gloves are recommended in handling specimens.

2.5 Facilities and Equipment

Facilities including air conditioning, lighting, flooring, backup power, access, security systems, fire prevention systems and emergency preparedness are maintained by the host institution.

Equipment, including liquid nitrogen freezers, mechanical freezers and refrigerators are maintained and will typically be monitored by the Biobank staff. Where dry ice is employed, there should be adequate ventilation to ensure sufficient air or oxygen levels exist. A temperature log of the freezers will be maintained and recorded at least 3 working days per week. At QUT an alarm will be triggered at QUT Security if the temperature goes above -70ºC.

Operation of equipment by Biobank personnel will be strictly according to the operation manual specified by the manufacturer and the Standard Operating Procedures (SOP) specified by the LANDMark Biobank. All equipment is to be set up, used, maintained, calibrated, and serviced according to the manufacturer's instructions, the LANDMark SOP and the preventative maintenance schedules of the host Institution.

2.6 Training

All LANDMark staff are properly trained to perform the task required. Training associated with safety and SOPs will be recorded in the training record.

2.7 Standard Operating Procedures (SOP) Format

The SOP must include title, number, date, staff covered, protective wear, equipment, supplies, and step-by-step guidance.

The primary format of the SOPs is as follows:

- PURPOSE – This will expand on the title to briefly outline the purpose/objective of the SOP

- SCOPE – This will outline the staff covered by the SOP

- RESPONSIBILITIES – This will outline the responsibilities of individual personnel involved in the procedure

- PROCEDURE – This section will detail all the steps necessary to carry out the procedure. Reference to other related Biobank SOPs should be made in this section as necessary.

Date format on hardcopy documents for all Biobank forms or SOPs requiring a date will be made on the form as follows: ……-…….-….. [dd - mmm - yyyy].

The Distiller database will automatically request, by dropdown multiple choice menus, that the date be entered in the form of day, the month and the year, e.g. 23-DEC-2007 i.e. 23rd December 2007.

2.8 Records Management

Records are maintained securely and confidentially. Records associated with the LANDMark Biobank include training documents, SOPs, equipment maintenance records, audit documents, informed consent documentation, collection and processing records, specimen storage location, sample distribution and quality control activities. Paper files containing confidential participant information are locked in records cabinets and access is limited to LANDMark team members. Electronic records are backed up daily on the QUT remote servers (Brisbane). All computer access is password protected and uses automatic timeout mechanisms (e.g. screensavers). Multi-level permission levels are determined by the Manager.

Documents have unique titles, dates and version numbers i.e. version tracking. Dates have an unambiguous format where d stands for day, m for month and y for year. SOPs should be reviewed annually.

Corrections in paper records are initialed and dated; changes in electronic records are noted and tracked with name, date and reason for change.

Records will be accessible for inspection by authorized regulatory or sponsor personnel. The Manager or delegate staff will oversee access of confidential participant information by regulatory agencies and other auditing groups.

2.8.1 Document Review

The Manager is responsible for overview of writing, for review and approval, and for maintenance of the master copies of all SOPs. The Manager will maintain a historical file of rewritten SOPs for audit purposes, and will ensure that all SOPs are reviewed annually, on the anniversary of their initial acceptance.

The author(s) of an SOP is (are) responsible for the preparation of clear and concise practice guidelines for the procedure, which comply with the requirements of the current scientific, technical, safety and regulatory standards. Detail should be sufficient to guide a trained operator to perform the procedure, ensuring uniformity in the conduct of the activity.

Authorized personnel performing the duties are required to inform the Manager when alteration to a procedure is required, in order that a review of the SOP can be conducted and the procedure amended accordingly. SOP documents must be reviewed at 12 months after previous review to maintain contemporary content.

2.9 LANDMark Study Database (via Slidepath Distiller™)

Distiller™, is manufactured by Slidepath (Ireland, UK). The LANDMark Study database can be populated and managed by the investigator's site using the Distiller application through a web interface, facilitating international collaboration. The database platform will be hosted by QUT and University of Manchester.

2.10 Quality Standards

The LANDMark Biobank has a system to ensure that current good practice is in place with documentation and traceability. These quality standards include a secure, limited-access facility where personnel are trained in all procedures which are documented. Internal audits are conducted; policies and procedures are documented in SOPs approved by the Manager and updated using strict document control rules. Records are maintained with the respect to purchase of new equipment, maintenance and repair activities and equipment disposal. Records are maintained for critical materials such as item purchased, date of purchase, expiration date and material safety datasheets (MSDs) where appropriate. Deviations to SOPs are recorded.

2.11 Identifiable and De-Identified Data

The LANDMark Biobank samples will have identifiers removed and replaced by a code. Each sample will have a participant and sample ID; however, a link between the sample and the participant's identity will be retained (primarily due to the likelihood of ongoing involvement of this cohort). It will be possible to use the code to re-identify the person who donated the sample. The samples are therefore referred to as re-identifiable (see below). A sample will only be re-identified in the instance a participant wishes to have their sample destroyed. Also, participant can indicate on the consent form if they wish to be contacted in future if a new finding is made from their sample that may have implications to their wellbeing or that of their family.

For the purpose of these SOPs, the following definitions are applied per the National Statement on Ethical Conduct in Research Involving Humans (2007, updated in 2015) (NS):

- individually identifiable data, where the identity of a special individual can reasonably be ascertained. Examples of identifiers include the individual's name, image, date of birth or address;

- re-identifiable data, from which identifiers have been removed and replaced by a code, but it remains possible to re-identify a special individual by, for example, using the code or linking different data sets;

- non-identifiable data, which have never been labelled with individual identifiers or from which identifiers have been permanently removed, and by means of which no special individual can be identified. A subset of non-identifiable data

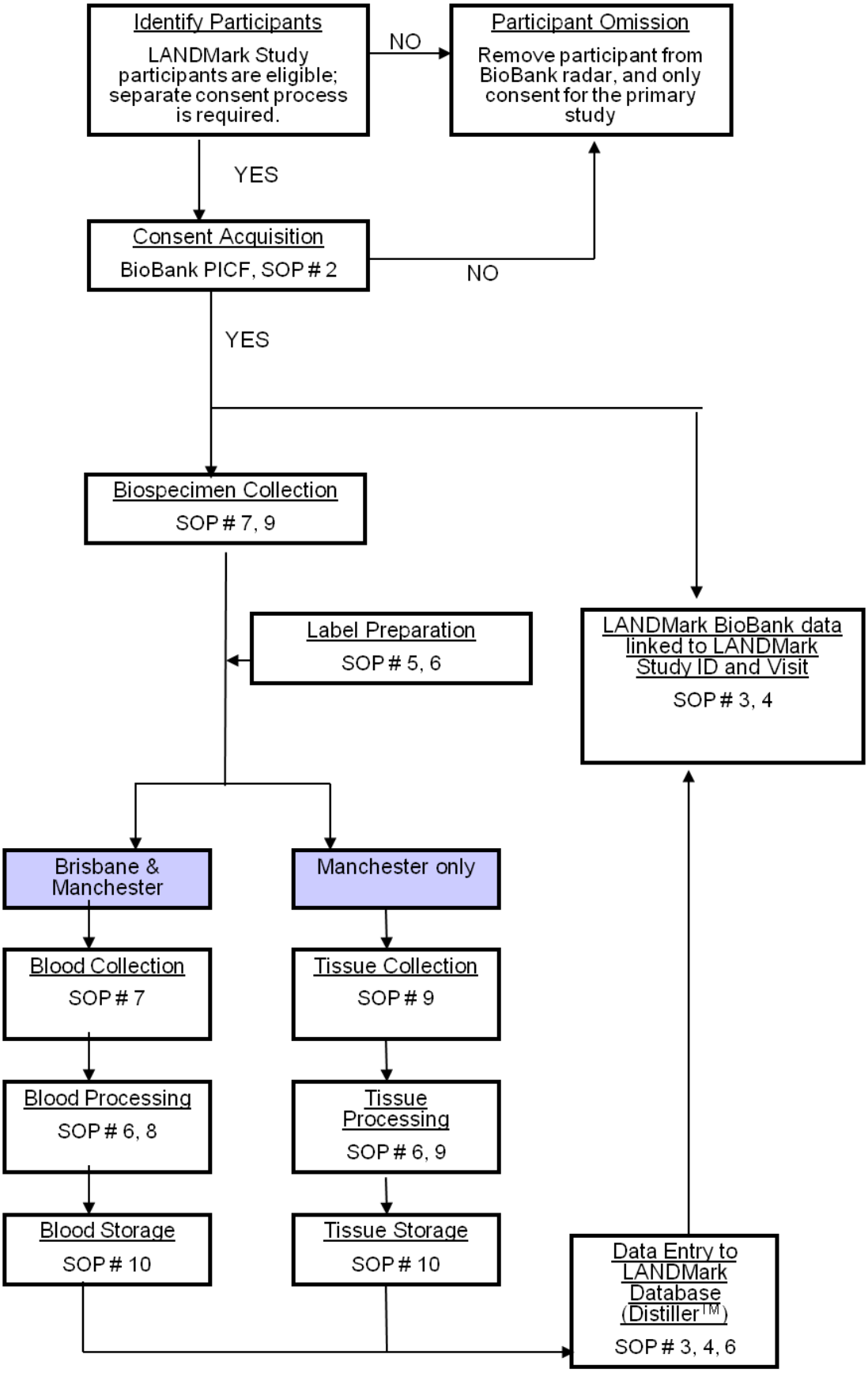
are those that can be linked with other data so it can be known that they are about the same data subject, although the person's identity remains unknown.

The LANDMark Biobank Withdrawal of Consent Form (Appendix 10) also includes an option for participants to leave their biological samples in the Biobank, but to remove their obvious identifiers from their samples ie be recoded so that there is no link to their name, dob etc. However, human biosamples should always be regarded as, in principle, re-identifiable (NS 3.2) due to advances in genetic testing.

3 Standard Operating Procedures

Standard Operating Procedures (SOPs) include all the processes and procedures for the LANDMark Biobank for both the Brisbane and Manchester sites, however the Manchester site may have some site-specific requirements.

SOP 1: Flow Chart



SOP 2: Obtaining Informed Consent

1. PURPOSE

To describe the procedures required to obtain informed consent from participants for:

- procurement and storage of biological samples
- procurement and storage of linked demographic, clinical, pathological and epidemiological data (also described in primary consent for study).

2. SCOPE

This procedure is applicable to research team members authorized to obtain informed consent from participants for the LANDMark Biobank.

3. RESPONSIBILITIES

Research team members must ensure that fully informed consent is obtained from the participant prior to procurement of any biological samples or required data, and that all documentation is completed.

4. PROCEDURES

4.1 Identification of willing participants will be performed by the research team members.

4.2 An invitation is to be extended for participation in the Biobank project and further information provided. The objectives of the Biobank, and the process and procedures are to be explained, and informed written consent obtained from the participant by the research team member.

4.3 The participant must be provided with a copy of the current version of the LANDMark Biobank Participant Information and Consent Form (LB PICF). A copy of the LANDMark Biobank Withdrawal of Consent Form will be provided to participants on request.

4.4 The research team member must ensure that all information and signatures required on the forms are complete.

SOP 3: Allocation of Participant and Sample ID Numbers

1. PURPOSE

To describe the participant and sample identification numbers for both Brisbane and Manchester sites of the LANDMark Biobank.

2. RESPONSIBILITIES

The LANDMark Project Manager is responsible for ensuring the sample identification numbers determined by the site can be accommodated in the database.

It is the responsibility of the site to communicate the nature of the sample identifiers used for the Biobank to the Project Manager via the LANDMark Study database (Distiller).

Authorized personnel acting for the LANDMark Biobank must ensure that all procedures for allocation of participant and sample ID numbers are correctly followed.

3. PROCEDURES

The participant ID is a three number and two or three letter identifier e.g 134 FGH or 268 LJ. In Brisbane the sample IDs are predetermined by the Nunc BankIt cryovials.

3.1 ALLOCATION OF PARTICIPANT AND SAMPLE ID NUMBERS

The numeric parts of the Participant ID are automatically assigned by the LANDMark database and the alphabetic part, from the participant initials.

In Brisbane the sample ID numbers are predetermined by the Nunc BankIt cryovials. The Guthrie card IDs are assigned as a two letter four number ID, sequentially incremented eg. GC 0001, GC 0002 etc.

The ID numbers are unique to the participant sample, and must never be reissued if a sample is withdrawn or distributed.

SOP 4: Storage of Participant Information

1. PURPOSE

To describe the procedures required to store participant information for the sites of the LANDMark Biobank. Participant information is that recorded for the LANDMark Study.

2. RESPONSIBILITIES

The on-site Manager/Coordinators will ensure that all security systems are in place to guarantee confidentiality of participant information.

Authorized personnel will ensure that all personal, clinical, pathological and demographic information obtained from the participant is securely stored to preserve the confidentiality of all gathered information. Information on biological sample type, storage location and storage coordinates will also be securely stored.

3. PROCEDURES

Hardcopy documents:

Paper records are stored in a locked cupboard or filing cabinet [preferably fireproof] within a secure access area [preferably with a smoke detector and sprinkler system].

Note: Authorized persons should ensure that all LANDMark Biobank forms for the collection of clinical and pathological information required for entry into the database are retrieved from the participant, investigator and pathologist.

Distiller™ Database:

Both the computer and the database used to enter and store participant information must be accessible only with the knowledge of independent security passwords. This knowledge must be restricted to authorized personnel.

The authorized personnel will enter all relevant information from the hard copy documentation onto the Distiller database maintained for the site.

Where researchers outside the team are allowed access to the Distiller database for data analyses, they will be issued a lower level of access, and only be permitted to view de-identified information.

Note: Regular back-up copies of the Distiller database for each site are the responsibility of the on-site Managers/Coordinators.

SOP 5: Preparation of Labels

1. PURPOSE

To describe the procedure for preparation of:

- specimen labels
- documentation labels

2. SCOPE

To ensure the format for labels is standardized across the Biobank sites, the actual procedure for printing labels within this SOP utilizing a Brady printer pertains only to the Brisbane site. Both sites will use Distiller allocation of Participant ID numbers.

Note: It is possible in the future that the Manchester site may print labels using alternate printing system e.g. Zebra label printers.

3. EQUIPMENT AND MATERIALS

EQUIPMENT	MATERIALS
Computer with installed Brady® Identilab software	Brady IP Printer Ribbon R4300
Brady IP® 3000 Printer	Brady Thermatab™ Markers THT-133-461 (Wrap around labels)
Brady® IdentiLab™ Laboratory Labelling System software	
Brady® Data cable with USB adapter	
Printer Cleaning Kit for TLS2200™ Thermal Labelling System	

4. PROCEDURES

4.1 Preparation of Specimen Labels

In Brisbane, this will be done using the Brady® IdentiLab™ Laboratory Labelling System software.

For all biological samples wrap around labels e.g. Brady Thermatab™ Markers THT-133-461 are to be used.

Note: Choice of this label type is dictated by suitability for long-term storage in vapour phase of liquid nitrogen (LN), and resistance to numerous laboratory chemicals.

Follow software instructions to print labels for cryovials similar to shown in Figure 1.

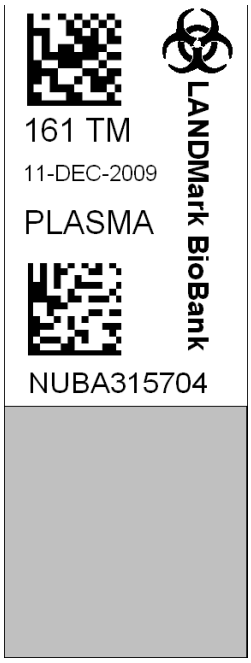


Figure 1. LANDMark Biobank cryovial label from Brisbane site showing printable area and wrap around area of label (in grey).

Item 1: Bar code / data matrix of Participant ID

Item 2: Participant ID (human readable format)

Item 3: Date of collection (tissue) or processing (blood products) of specimen date in format DD-MMM-YYYY

Item 4: Specimen Type e.g. PLASMA, SERUM), BUFFY C (buffy coat, Guthrie card (GUTHRIE), skin tissue

Item 3: Bar code / data matrix of Sample ID (human readable format)

Item 6: Sample ID (human readable format)

Item 7. Biohazard symbol

Item 8: LANDMark Biobank

Note: The appropriate number of specimen labels should be prepared as per:

LB SOP 8: Processing Whole Blood to Blood Products, and

LB SOP 9: Collection of Skin Punch Biopsy

See also: LB SOP 3: Allocation of Participant and Sample ID Numbers

4.2 Preparation of Labels for Storage Boxes (where appropriate)

If storage boxes are to be used, this will be done using the Brady® IdentiLab™ Laboratory Labelling System software, or equivalent.

If the Brady system is used for storage box identification, the Brady Thermatab™ Markers THT-133-461 should be used.

Follow software instructions to print labels for storage boxes with barcode or data matrix and human readable format for box number and storage site.

4.3 Preparation of Labels for Documentation

Avery labels (e.g. Avery™ L7656) or Brady labels can be used for labels of documentation.

SOP 6: Labelling Biospecimens and Documentation

1. PURPOSE

To describe the procedure for the labelling of biospecimen samples, sample storage boxes (where appropriate) and documentation for the Brisbane and Manchester sites of the LANDMark Biobank.

2. RESPONSIBILITIES

Authorized personnel labelling biospecimen samples and other materials at the sites of the LANDMark Biobank must ensure that the appropriate label is used for each application, and that the Sample ID label numbers comply with the standard format.

3. PROCEDURES

All labels must be prepared as per SOP 5: Preparation of Labels using the Brady printer system (or equivalent) in combination with Distiller allocation of ID numbers.

Note: When labelling biospecimen samples avoid touching the adhesive area of the label whilst attaching to the container.

3.1 Labelling of Whole Blood Collection Tubes

The minimum information on blood collection tubes is: participant ID, date of collection, time of collection, initials of collector.

3.2 Labelling of Guthrie Cards

The Brady Thermatab™ Markers THT-133-461 are used at the Brisbane site.

Apply label to “label area” on Guthrie card.

3.3 Labelling of Cryovials

The Brady Thermatab™ Markers THT-133-461 are used at the Brisbane site.

Labels should be attached to the cryovials prior to conducting sample processing. Contents should be visible.

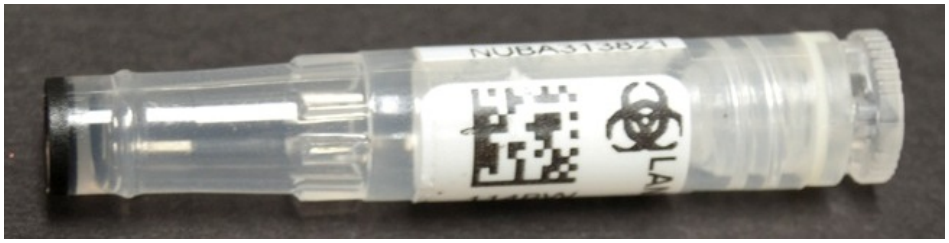


Figure 2. Nunc BankIt cryovial with label.

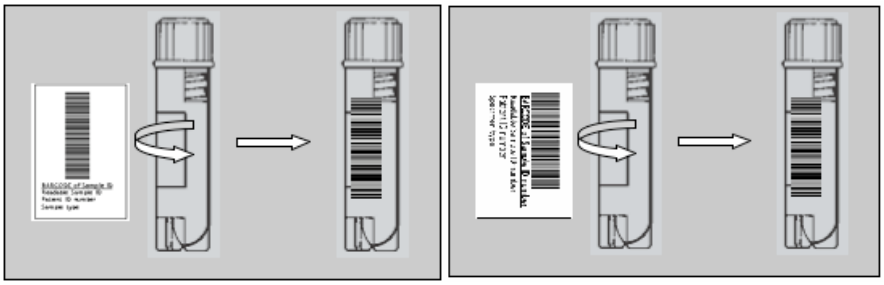


Figure 3. Labelling containers of participant blood or cryovials of blood products with alternative format labels.

3.4 Labelling of Histology Cassettes for Skin Tissue Cryovials (alternate)

Labels should be attached to histology cassettes prior to conducting sample processing.

Labels are attached to the histology cassettes with the barcode parallel to the ramped edge. Refer to Figure 2.

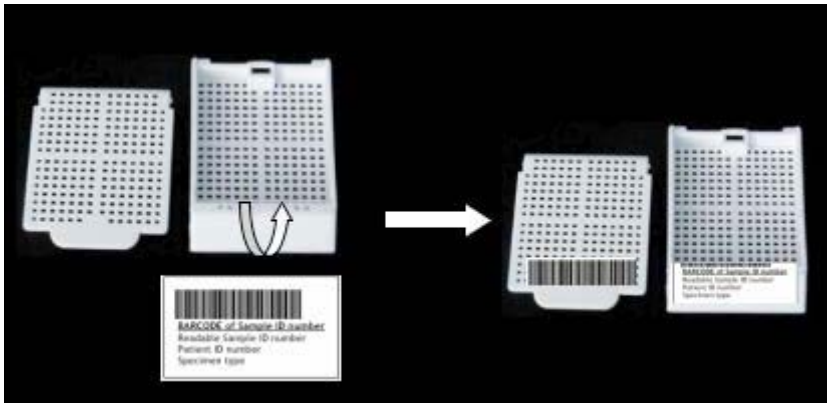


Figure 4.: Alternative labelling of histocassettes containing participant skin tissue samples.

3.5 Labelling of Storage Boxes

Placement of labels on storage boxes is dependent on the storage system employed. One Box Identification Label could be placed on the middle of the lower portion of the front side of the box, and a second containing the same box number could be placed on the lid of the box, if required.

Supplementary identification of boxes by permanent marker is recommended.

3.6 Labelling of Documentation

Where appropriate, Participant ID label in top right hand corner of each document can be used. Labels such as L7656™ labels (Avery™ labels) can be used for this purpose.

SOP 7: Collection of Whole Blood Samples

1. PURPOSE

To describe the procedures required for the collection of whole blood samples from participants in the LANDMark Biobank.

2. RESPONSIBILITIES

Authorized personnel must:

- ensure informed consent has been obtained prior to blood collection. Refer to LB SOP 2: Obtaining Informed Consent
- collect or arrange collection of whole blood samples for the LANDMark Biobank
- ensure this SOP and relevant safety practices are followed
- ensure all blood samples are adequately de-identified
- ensure accurate records are kept and maintained on all samples processed
- ensure (where appropriate) the research nurse/phlebotomist has sufficient number of appropriate blood collection tube types (see Item 4 MATERIALS below)
- ensure (where appropriate) the research nurse/phlebotomist is aware of the volumes of blood to be drawn (8-9ml per tube).

3. HEALTH AND SAFETY

Authorized personnel carrying out this procedure must maintain safe working practices and observe all relevant Health & Safety guidelines of their respective institutions pertaining to the collection, transportation and handling of human blood.

This includes the appropriate use of Personal Protective Equipment (PPE), disposal of waste, disinfection & clean-up of spills, and personal hygiene.

4. MATERIALS

2 x 9mL K_2/K_3 EDTA (di- or tri-potassium ethyldiamino-tetra-acetic acid) or ACD-A (Acid Citrate Dextrose) additive blood collection tubes.

1 x 8mL SST (Serum Separator Tube) gel separator/clot activator blood tube

Blood collection set

Transport container for human blood specimens (e.g. biospecimen bags).

5. PROCEDURES

Blood may be drawn by either Research Nurse or Phlebotomist.

Up to 30ml total blood sample should be collected from the participant as:

1 x 8mL SST clot activator blood collection tube

2 x 9mL K_2EDTA or K_3EDTA or ACD-A additive tubes

Blood should be transferred to the Biobank laboratory, preferably in a biospecimen bag, at ambient temperature (i.e. not on ice) as soon as possible. A record of the sample arriving in the lab shall be noted, including lot numbers and expiry dates of collection tubes and cryovials (Appendix 1). The 3 tubes destined for the Biobank laboratory are to be inverted 6 times before being left to rest for at least 30 mins before spinning.

Under normal circumstances blood should be processed immediately upon receipt in the laboratory. Where blood has to be stored overnight in the laboratory before processing, the tubes should be refrigerated (4°C) upon receipt in the laboratory.

Irrespective of mode of collection, blood tubes should be adequately labelled with participant ID, date of collection and time of collection as minimum.

SOP 8: Processing Whole Blood to Blood Products

1. PURPOSE

To describe the procedures for the processing of participant blood samples into the following blood products:

- Guthrie card spots
- Plasma
- Buffy coat cells
- Serum

2. RESPONSIBILITIES

Authorized personnel processing whole blood samples must ensure that the procedures are followed correctly, and all documentation is completed.

3. HEALTH AND SAFETY

Personnel carrying out this procedure must maintain safe working practices and observe all relevant Health & Safety guidelines of their respective institutions pertaining to the collection, transportation and handling of human blood, according to universal precautions.

This includes the appropriate use of Personal Protective Equipment (PPE), Class II BioHazard Cabinets, and procedures for waste disposal, disinfection and spill clean-up, handling and transport of dry ice and liquid nitrogen, and personal hygiene.

4. EQUIPMENT AND MATERIALS

EQUIPMENT	MATERIALS
PPE	Sterile cryovials, 1.8 ml, Nunc®
Sterile plastic Pasteur pipettes	Blue cryovial cap inserts, Nunc®
Calibrated P1000 and P200 pipettes	Green cryovial cap inserts, Nunc®
Sterile P1000 and P200 aerosol pipette tips	Red cryovial cap inserts, Nunc®
Cryovial racks	Guthrie cards
Centrifuge	Ethanol or alcohol wipes
Counter-balance tubes	Liquid nitrogen
Dewar flask	Sterile syringe and needle (21g)

5. PROCEDURES

5.1 Processing of Guthrie Cards

Guthrie spots are produced from K_2EDTA / K_3EDTA or ACD-A tubes only.

Prepare labels and label Guthrie card(s) according to LB SOP 5: Preparation of Labels and LB SOP 6: Labelling Biospecimens and Documentation.

Each whole blood sample should be mixed by gently inverting the tube 6 times.

The top and outside of the blood tube should be alcohol wiped before opening.

Using a sterile disposable pipette, aspirate approximately 500µl whole blood from the tube, gently place 40-50µl of the whole blood (one drop at a time) in centre of first circle of labelled Guthrie card until the circle is filled. Ensure each drop is completely absorbed through Guthrie card, before adding additional drops.

Replace cap on collection tubes and set aside.

Avoid touching the surface of the Guthrie card, or allowing it to contact any unclean surface.

Repeat procedure on remaining circles of the Guthrie card.

Do not apply blood to both sides of a Guthrie card.

Allow card(s) to air dry in back of BioHazard cabinet, or equivalent.

Place Guthrie card(s) into labelled paper envelopes for storage.

Store Guthrie card(s) according to LB SOP 10: Storage of Biological Samples.

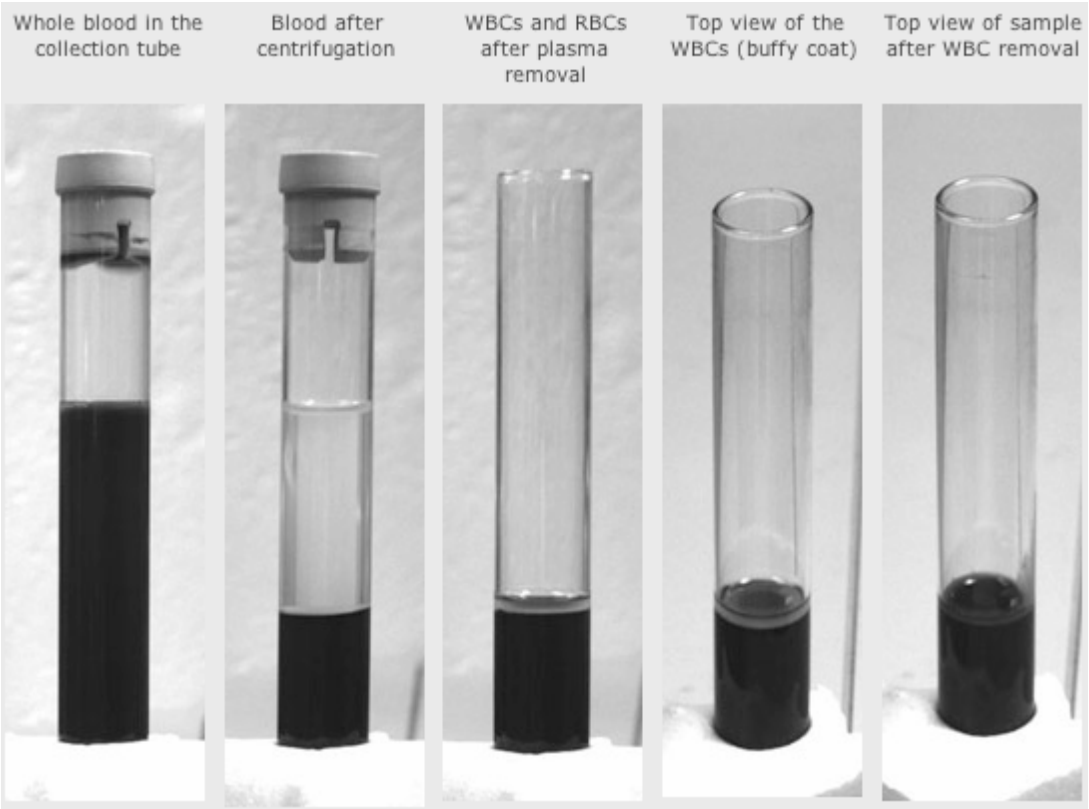


Figure 5: Blood processing for plasma and buffy coat cells, layers of blood products in EDTA blood tube after centrifugation at 2500 rpm for 10 minutes.

5.2 Processing of Plasma

Plasma is harvested from K_2EDTA / K_3EDTA or ACD-A tubes only (Figure 4).

Prepare labels and label storage cryovials according to LB SOP 5: Preparation of Labels and LB SOP 6: Labelling Biospecimens and Documentation.

Centrifuge each whole blood sample at 4000 rpm for 10 minutes. Ensure centrifuge rotor is balanced, and that the procedure follows that outlined in the respective manufacturer's instrumentation manual.

The top and outside of the blood tube should be alcohol wiped before opening

Using a calibrated / P1000 pipette with sterile aerosol tip or sterile disposable plastic Pasteur pipette, gently aspirate plasma without disturbing the buffy coat layer, leaving a small amount of plasma above the buffy coat layer for aliquotting directly into the cryovials. The aspirates from an individual participant can be combined in a separate tube.

Retain blood tube for buffy coat collection.

Using a calibrated / P1000 pipette with sterile aerosol tip or sterile disposable plastic Pasteur pipette, dispense 500µl aliquots of plasma into labelled 1.8 ml cryovials, without wetting the rim. Up to 16 aliquots should be collected.

Inset a red cryovial cap into each cryovial.

Place each cryovial into liquid nitrogen to snap freeze (where appropriate).

Transfer specimens into storage tray/box and store according to LB SOP 10: Storage of Biological Samples.

5.3 Processing of Buffy Coat Layer

The buffy coat, a thin, greyish-white layer of white blood cells (leukocytes) and platelets covers the top of the packed red cells, following centrifugation at 4000 rpm for 10 minutes.

Buffy coat cells are harvested from K_2EDTA / K_3EDTA or ACD-A tubes, usually following harvest of the plasma fraction (see Figure 4 and section 5.2: Processing of Plasma).

Prepare and label storage cryovials according to LB SOP 5:Preparation of Labels and LB SOP 6: Labelling Biospecimens and Documentation.

Using a sterile 2ml syringe and 21G needle or sterile disposable plastic Pasteur pipette in a circular motion, gently aspirate the buffy coat layer. Of necessity, passenger red blood cells will be included. The aspirates from an individual participant can be mixed, or kept separate according to individual site practice.

Using a calibrated / P200 pipette with sterile aerosol tip or sterile disposable plastic Pasteur pipette, dispense buffy coat cells in approximately 200µl aliquots into labelled 1.8mL cryovials, without wetting the rim. Up to 2 aliquots from each K_2EDTA / K_3EDTA or ACD-A tube should be collected.

Inset a blue cryovial cap into each cryovial.

Place each cryovial into liquid nitrogen to snap freeze, where appropriate.

Transfer specimens into storage tray/box and store according to LB SOP 10:Storage of Biological Samples

5.4 Processing of Serum

Serum is harvested from SST tubes only. Ensure blood is clotted before proceeding. (See Figure 6).

Prepare labels and label storage cryovials according to LB SOP 5: Preparation of Labels and LB SOP 6:Labelling Biospecimens and Documentation.

Centrifuge the SST tube at 4000 rpm for 10 minutes. Ensure centrifuge rotor is balanced, and that the procedure follows that outlined in the respective manufacturer's instrumentation manual.

The top and outside of the blood tube should be alcohol wiped before opening.

Using a calibrated pipette with sterile aerosol tip or sterile disposable plastic Pasteur pipette, gently aspirate serum avoiding contact with the gel layer.

Pipette serum in 500µl aliquots into labelled 1.8 ml cryovials, (collect up to 8).

Insert a green cryovial cap into each cryovial.

Place each cryovial into liquid nitrogen to snap freeze, where appropriate.

Transfer specimens into appropriate tray/box and store according to LB SOP 10:Storage of Biological Samples.

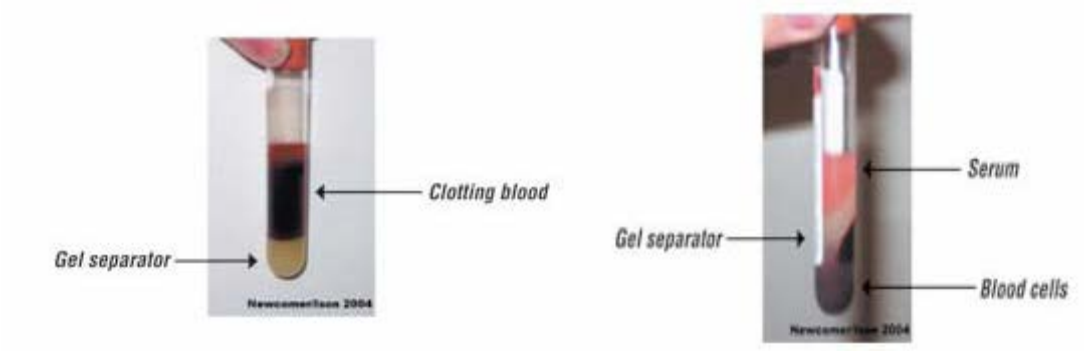


Figure 6: Blood processing for serum: layers of blood products in Serum Gel Separating blood tube before and after centrifugation at 2,500g for 10 minutes.

Wipe down the Bench, tube racks and equipment with 70% ethanol.5.5 Completion of Forms for All Blood Products:

Record all sample details into the LANDMark Study database.

SOP 9: Collection of Skin Punch Biopsy

1. PURPOSE

To describe the procedure for the collection, sampling and processing of skin punch biopsy tissue and transfer of tissue samples to the LANDMark Biobank (Manchester site).

2. RESPONSIBILITIES

Authorized personnel collecting and sampling skin punch biopsy tissue must ensure that:

- full informed consent is obtained prior to skin biopsy, according to LB SOP 2:Obtaining Informed Consent
- all tissue sampling procedures are followed correctly
- all tissue samples are adequately de-identified
- all documentation is completed, and accurate records maintained on all samples
- sufficient quantities of appropriate forms are available for providing minimum operative information (where applicable).

3. HEALTH AND SAFETY

Personnel carrying out this procedure must maintain safe working practices and observe all relevant OHS guidelines of their respective institutions pertaining to the collection, transportation and handling of human tissues, according to universal precautions.

This includes the appropriate use of Personal Protective Equipment (PPE), and procedures for waste disposal, disinfection and spill clean-up, handling and transport of dry ice, Techni-Ice®, or liquid nitrogen, and personal hygiene.

4. EQUIPMENT AND MATERIALS

EQUIPMENT	MATERIALS
Protective glasses	Copy of signed participant consent
Surgical gloves	Relevant documentation (see 7.6)
Biopsy punch, 3mm	Liquid nitrogen
Sterile surgical blade and handle	Dry Ice, or Techni-Ice®
Sterile straight forceps	Cryovials, 1.8 ml, Nunc®
Gauze squares	Green cryovial cap inserts, Nunc®

Labels for specimen containers and tubes	O.C.T. compound
Absorbent underpad (Bluey)	No.22 Surgical blades
Paint brush	Aluminium foil squares (10cm x 6cm)
Cutting block	All purpose towels
Histology cassettes	Gelatine capsules, size 00
Approved LN transport container for biological specimens (Dry shipper)	Two pots with PBS-buffered 4% paraformaldehyde (PFA).

5. PROCEDURES

5.1 Collection of Skin Biopsy Tissue

Irrespective of the procedure, care must be taken to ensure that the tissue is collected and stored using aseptic techniques.

The patient will rest in semi-reclining position on the couch.

Inspect the foot dorsum and choose 2 points approximately 2 cm proximal to the metatarsal bone.

Clean the skin with betadine and inject 1% lignocaine. Wait 3-5 minutes and check the skin is insensitive to pinprick.

Incise the skin with 3 mm punch biopsy device X2, lift the skin with forceps and cut the bottom with scissors.

Stop the bleeding by pressing with gauze and close the wounds with steri-strips.

Cut 1 biopsy specimen immediately into 2 halves (1/2 biopsy to be fresh frozen (remaining 1/2 into 4% PFA for immunohistology).

The 2nd half biopsy goes straight into 4% PFA for immunohistology.

Bring frozen piece to CTF Building (3rd floor) in box filled with dry ice (Manchester Royal Infirmary).

Fix samples immediately in PBS-buffered 4% paraformaldehyde for 18-24 hours, rinse in Tris-buiffered saline and soak in 33% sucrose (2-4 hours) for cryo-protection.

Embed in OCT (Optimum Cutting Temperature embedding compound), rapidly freeze in liquid nitrogen and store in -80C.

Place each biopsy into a 1.8ml cryovial.

Insert a coloured cryovial cap into each cryovial.

Label cryovials according to SOP 5: Preparation of Labels and SOP 6: Labelling Biospecimens and Documentation

Complete forms:

LANDMark Biobank Tissue Collection Form

Record the relevant sample ID number on form: LB Tissue Collection Form.

Transfer skin biopsy samples to LANDMark Biobank (Manchester) in dry shipper /Dewar flask (To prevent degradation of the sample, a Nalgene Mr Frosty or equivalent may be required to reduce the temperature of the tissue by 1°C per minute to the desired temperature)

Transfer specimens into appropriate storage container and store according to LB SOP 10: Storage of Biological Samples

Record all sample details into the LANDMark Study database.

SOP 10: Storage of Biological Samples

1. PURPOSE

To describe the procedures for storage of biological samples after processing.

2. RESPONSIBILITIES

Authorized personnel storing biological samples must ensure:

- storage procedures are carried out as directed
- all documentation is completed, and accurate records maintained on all samples.

3. HEALTH AND SAFETY

Personnel carrying out this procedure must maintain safe working practices and observe all relevant Health & Safety guidelines of their respective institutions pertaining to the collection, transportation and handling of human tissues, according to universal precautions.

This includes the appropriate use of Personal Protective Equipment (PPE), procedures for waste disposal, disinfection and spill clean-up, handling and transport of samples in dry ice, liquid nitrogen and at -80C, and personal hygiene.

4. EQUIPMENT AND MATERIALS

EQUIPMENT	MATERIALS
Ultracold -80C freezers	Storage boxes, with grid
Liquid nitrogen storage tanks	Storage box identification labels
Aluminium freezer racks	PPE
Block filing cabinets	
Slide Filing cabinets	

5. PROCEDURES

STORAGE OF TISSUE SAMPLES

All samples and sample boxes must be labelled according to SOP 6: Labelling Biospecimens and Documentation before storage.

Guthrie cards:

Guthrie cards should be stored in labelled paper envelopes in a cool dry place at room temperature preferably within a [fireproof] locked cupboard. In humid atmospheres, desiccant should be use to control moisture levels.

Guthrie cards must not be stored in plastic bags or plastic wrapping.

Plasma, buffy coat cells, serum:

- Cryovials containing the above products are stored in sample boxes or trays at -80C in an Ultracold freezer.

Skin biopsy samples:

- Cryovials containing skin biopsy tissue samples (with and without OCT) are stored in sample boxes at -80C in an Ultracold freezer.

Paraffin-embedded tissue:

- Paraffin blocked tissues are stored in a lockable room, which is temperature controlled and has a sprinkler system installed.

STORAGE PROCEDURE:

When transferring samples to storage boxes/racks, place the cryovials sequentially in the next available slot beginning in the top left hand corner.

Blood Products:

- Transport the processed blood products in the cryobox immersed in liquid nitrogen to the –80C freezer or liquid nitrogen tank in which they are to be stored.
- Complete the sample record forms.
- Lock the –80C freezer or liquid nitrogen tank.
- Record all sample details in the LANDMark Study database.

Fresh-Frozen Skin Biopsy Storage:

- Using long forceps and cryogenic gloves, transfer the fresh-frozen cores (in cryovials or histocassettes) from the liquid nitrogen dewar into the next sequential CryoBox designated for tissue storage in the –80C freezer or liquid nitrogen tank.
- Complete form: LB Tissue Collection Form.
- Return the CryoBoxes to the designated location in the –80C freezer / LN tank.
- Lock the –80C freezer / LN tank.
- Record all sample details in LANDMark Study database.

Short-Term Formalin-Fixed Paraffin-Embedded (FFPE) Tissue Storage:

- Ensure all blocks received are present. Query any missing blocks.
- Transfer the transportation container(s) holding FFPE tissue for short-term storage to the designated block storage area.
- Lock the block storage room.
- Record all sample details in LANDMark Study database.

Long-Term Formalin-Fixed Paraffin-Embedded Tissue Storage:

- Transfer the FFPE skin biopsy tissue for long-term storage to the designated storage area.
- Label each block with the Participant ID number.
- Transfer each FFPE tissue block(s) per participant into the block filing cabinets in order of Participant ID number. The blocks should be stored upside down in the storage racks, i.e. with the LB Participant ID number uppermost.
- Lock the block storage room.
- Record all sample details in LANDMark Study database.

RECORDING LOCATION AND RELOCATION OF SAMPLES:

For each new storage box/tray and any subsequent movement of each storage box/tray complete a new form: LB Tissue Collection Form, and enter details to database (Distiller will subsequently flag all changes in storage location).

Note: LB Biological Specimen Transfer Form.

SOP 11: Transfer to Secondary Storage

1. PURPOSE

To describe the procedures for transfer of biological samples to secondary storage.

2. SCOPE

These procedures pertain to the practice of transferring stored frozen samples to an alternate or secondary location, i.e. freezer to freezer or LN tank at the same location, or at a separate location at the same Institution, or a at a separate Institution.

These procedures apply to Brisbane and Manchester sites.

NB. For sample distribution to requesting researchers see: LB SOP Researcher Specimen Distribution Form.

3. RESPONSIBILITIES

Authorized personnel storing biological samples must ensure:

- Preparation and storage procedures are carried out as directed
- All documentation is completed, and accurate records maintained on all samples.

4. HEALTH AND SAFETY

Personnel carrying out this procedure must maintain safe working practices and observe all relevant Health & Safety guidelines of their respective institutions pertaining to the collection, transportation and handling of human tissues, according to universal precautions.

This includes the appropriate use of Personal Protective Equipment (PPE), procedures for waste disposal, disinfection and spill clean-up, handling and transport of samples in dry ice, liquid nitrogen and at -80°C, and personal hygiene.

5. MATERIALS

Storage boxes/trays, with grid

Storage box ID labels

PPE

Institution Shippers Declaration for Dangerous Goods by Road

Outer packaging materials

Dry Ice, Techni-Ice or -80°C ice blocks

Biohazard Spill Clean Up Kit

6. PROCEDURES

6.1 Preparation of Stored Frozen Samples for Transfer to Secondary Storage

Notes: All sample and sample boxes will have been previously labelled according to LB SOP 6: Labelling Biospecimens and Documentation before initial storage.

The procedures for transferring cryovials containing skin tissue, plasma, buffy coat cells or serum are identical.

Pre-identify the samples for transfer to minimize the actual transfer procedure time.

Label new storage boxes/trays for transfer to alternate site. The storage box ID number should bear the prefix 'TF" to denote its transfer purpose.

For each new storage box and subsequent movement of a storage box, complete form: LB Biological Sample Transfer Form, identifying in the table for each sample to be transferred, its original location and final destination.

Remove original storage box from -80°C freezer to LN tank, and place onto Dry Ice, Techni-Ice or ice blocks at -80°C to maintain temperature as low as possible during sample transfer procedure.

Using forceps (where applicable), transfer designated samples into new transfer box/tray.

Return the original storage boxes to designated location in -80°C freezer/LN tank.

Lock the -80°C freezer / LN tank.

Complete and sign LB Biological Specimen Transfer Form.

Photocopy form, temporarily retain copy, original to be forwarded with consignment of sample for recipient signature

6.1.1 Transfer to Intact Boxes of Samples From -80°C to Liquid Nitrogen Storage

Identify the storage boxes to be transferred to the liquid nitrogen storage facility.

Place boxes in a suitable container of dry ice.

Transfer to liquid nitrogen.

Record new storage details on LB Biological Specimen Transfer Form.

6.2 Packaging of Sample For Shipment To Separate Institution

Pre-arrange adequate dry ice to maintain frozen state during transport of samples to secondary storage.

Package samples according to Institutional guidelines, completing form: Institution Shippers Declaration for Dangerous Goods by Road. One copy to be filed at primary site, 2 copies to accompany shipment.

Ship samples immediately after packaging.

Upon receipt at secondary site, store samples at designated location

Recipient to complete and sign front page of original LB Biological Specimen Transfer Form.

Photocopy form, original to return to primary storage site, copy to be retained by secondary site.

6.3 Recording Transfer of Samples to Secondary Location

Record all details in database (Distiller will flag all changes in storage location).

SOP 12: Distribution to Researchers

1. PURPOSE

To describe the procedures for distribution of biological samples to researchers.

2. RESPONSIBILITIES

Authorized personnel distributing biological samples to researchers must ensure:

- Preparation and distribution procedures are carried out as directed
- All documentation is completed, and accurate distribution records maintained.

3. HEALTH AND SAFETY

Personnel carrying out this procedure must maintain safe working practices and observe all relevant Health & Safety guidelines of their respective institutions pertaining to the collection, transportation and handling of human tissues, according to universal precautions. This includes the appropriate use of Personal Protective Equipment (PPE), procedures for waste disposal, disinfection & spill clean-up, handling and transport of samples in dry ice, liquid nitrogen and at -80C, and personal hygiene.

4. MATERIALS

MATERIALS	PPE
Storage boxes/trays, with grid	Glass microscope slides
Storage box/tray identification labels	Outer packaging materials
	Dry Ice, Techi-Ice, or -80C ice blocks
	Biohazard Spill Clean Up Kit
	Institution Shippers Declaration for Dangerous Goods by Road

5. PROCEDURES

5.1 Preparation of Stored Tissue Samples for Distribution to Researchers

Notes: A list of samples for distribution to a researcher approved by the Biobank Committee will be received at each node from the Manager/Project Manager.

Pre-identify frozen samples for transfer to minimize the actual transfer procedure time; this can be achieved by completing LB Researcher Specimen Distribution Form, prior to sample retrieval.

The procedures for transferring cryovials containing skin tissue, plasma, buffy coat cells, or serum, or histocassettes of skin tissue are identical.

All samples and sample boxes will have been previously labelled according to LB SOP 6: Labelling Biospecimens and Documentation before initial storage.

Sections cut from tissue biopsies can also be entered into Researcher Specimen Distribution Form.

5.1.1 Guthrie Cards

Label empty recipient paper envelopes with Participant ID numbers for Guthrie blot distribution.

Remove individual patient master Guthrie Card from original paper envelope, and cut a square containing one circle of blood from the sheet.

Grip the cut square with forceps well clear of the blood spot and place the square into the appropriate ID-labelled envelope for distribution.

Return the master Guthrie card to its original envelope and return to storage.

Should the forceps (or scissors) become accidentally contaminated with dried blood during the above procedure, the instruments must be decontaminated by wiping with Nucleoclean Decon Wipes (Chemicon #3097) or equivalent before proceeding to the next sample.

Complete for all participants blots for distribution.

5.1.2 Frozen skin tissue, plasma, serum and buffy coat cells

Label new storage box(es) for transfer to researcher. The storage box should bear the 'Principal researcher's name' to denote its distribution purpose

Remove original storage boxes individually from -80C freezer or LN tank, and place onto dry ice, Techni Ice, or ice blocks at -80C to maintain temperature as low as possible during sample transfer procedure.

Using forceps, transfer designated samples into researcher distribution box.

Return the original storage boxes to designated location in -80°C freezer / LN tank.

Lock the -80°C freezer / LN tank.

Keep all tissue samples for distribution on dry ice while paperwork is completed.

5.1.3 Tissue Sections

Cut requisite number of sections off each block for the appropriate number of blocks requested for each analysis, and mount on labelled glass microscope slides [For

example: a request may be made for approx 90 patients, i.e. 3 blocks from a 150 patient 5-block array].

Pack slides into slide box for dispatch.

Keep slides cool while paperwork is completed.

5.2 Sample Distribution Paperwork

Complete and sign form: LB Researcher Specimen Distribution Form, identifying in the table each sample to be distributed by its participant ID, sample ID and sample type, or the details of any tissue microarray sections cut.

The upper table has provision to record details of 30 samples. Should additional samples be scheduled for distribution, additional lines can be added to the table if provision for the dispatch and receipt signatures is retained.

Photocopy form [LB Researcher Specimen Distribution Form] twice, the original is to be kept at the site distributing the samples; both copies are to accompany the shipment of samples.

Tick 'Original Copy' box on original, and retain.

Tick 'Researcher Copy' box on one of the copies, and tick 'Signed Copy for Return to Project Manager' box on the other copy.

Attach form LB Researcher Specimen Receipt Form to the copy of LB Researcher Specimen Distribution Form designated to be returned to the LANDMark Biobank Project Manager.

On LB Researcher Specimen Receipt Form, complete the sections:

i) Site Distributing Biological Samples

ii) Date Samples Dispatched

5.3 Packaging of Samples for Shipment to Researcher at Separate Institution

For frozen samples, pre-arrange adequate dry ice to maintain frozen state during transport of samples to researcher storage facility.

Package samples according to Institutional guidelines, completing Form: Institution Shippers Declaration for Dangerous Goods by Road. One copy to be filed at primary site, 2 copies to accompany shipment.

Enclose the 2 copies of the completed LB Researcher Specimen Distribution Form, including attached LB Researcher Specimen Receipt Form in a plastic sleeve, seal with tape, and enclose in package with samples.

Ship samples immediately after packaging.

5.4 Recording Transfer of Samples to Researcher

Record all details in database (Distiller will flag all samples distributed).

SOP 13: Researcher Access to Biological Samples

1. PURPOSE

To describe the procedures for assessment of applications by diabetes researchers to the LB Tissue Access Committee and to give access to the Biobank tissue collection.

2. RESPONSIBILITIES

Only the Project Manager, Chief Investigator, JDRFI personnel or delegated authority will engage in processing applications for researcher access to the Biobank tissue collection via the LANDMark Biobank Tissue Access Committee (LBTAC).

3. HEALTH AND SAFETY

Not applicable

4. MATERIALS

Not applicable.

5. PROCEDURES

5.1 Handling of Requests for Access to Biobank Tissue

Details of the overall application procedure are outlined in the Biobank Tissue Access Policy.

5.5.1 Letter of Intent (L0I) and Full Application

Researchers may be required to complete an LOI. LOI can be forwarded to the Project Manager or delegated authority at any time.

If the LOI is complete and acceptable, the Manager may consult with members of the LBMC prior to review. A reply email should be sent to the applicant (chief investigator) indicating the LOI has been received.

Review of applications should be arranged for the LBTAC to deliberate any LOIs or Full Applications, with the Project Manager or authorized delegate as Coordinator.

If the LOI is approved, the applicant will be asked to make a Full Application. These will go out to peer review unless a review from the NHMRC or other appropriatel body is provided.

The Project Manager or authorized delegate will convey to the intending applicant in writing the outcome of the LBTAC deliberations.

If the application is approved, the Project Manager or authorized delegate will determine with the researcher a timeline for supply of the required tissue (and data if requested), provide an acceptance letter outlining the conditions on tissue provision as

per the Tissue Access Policy, and obtain a signed Material Transfer Agreement (MTA) document from the researcher.

The Project Manager or authorized delegate will calculate the cost recovery fee (NB in Queensland a permit is currently required from the Chief Health Officer for cost recovery to be received).

The Project Manager or authorized delegate may request progress reports from the researchers. At the conclusion of the project the Project Manager or authorized delegate will obtain a formal report and arrange for any residual materials to be returned to the Biobank or destroyed.

SOP 14: LANDMark Biobank Management Committee

1. PURPOSE

To describe the procedures for the conduct of the LANDMark Biobank Management Committee.

2. RESPONSIBILITIES

Oversee the use of biospecimens and administer over any conflicts of interest or complaints.

Observe a two-year moratorium on access to biospecimens.

Monitor the progress of the Biobank and positive and negative feedback from all stakeholders, including participants about their participation.

Ensure all protocol changes are reported to the ethics committees.

Ensure all procedures are performed as defined in the individual SOPs.

3. HEALTH AND SAFETY

Not applicable

4. MATERIALS

Not applicable.

5. PROCEDURES

5.1 Membership

Table 1. The expected members and role in project. The role in the project serves to indicate the potential conflicts of interest where appropriate.

Member	Role in Committee
Nathan Efron, IHBI @ QUT n.efron@qut.edu.au	Principal Investigator and Chair
Nicola Pritchard, IHBI @ QUT n.pritchard@qut.edu.au	Project Manager
Rayaz Malik, University of Manchester Rayaz.A.Malik@manchester.ac.uk	Co-Principal Investigator
Consumer representative (where available)	Independent Typically appointed by the chair of an HREC

5.2 Frequency and Format of Meetings

The Management Committee will confer annually, or as needed.

An urgent meeting would be arranged in the unlikely event of any serious event.

The Project Manager will submit (usually) a one-page report by the due date to the Committee members by email. The due date will be the anniversary of the biobank commencement (20-Aug-2009 first donation).

Members will respond accordingly by email with their acceptance, or recommendation for further evaluation or intervention.

5.3 Communication Procedures, Timelines and Documentation

The one-page report and summary email to members will serve as documentation for each virtual meeting.

The Project Manager will prepare the summary and members will acknowledge (or otherwise) this summary as being a true and accurate record of the virtual meeting within 30 days of the anniversary/due date.

4 Abbreviations

°C	Degrees Celsius
Distiller™	Slidepath web-based inventory and data platform
DOB	Date of birth
EDTA	Ethylenediamine tetra-acetic acid
g	Gravity
G	Gauge, as per hypodermic needle size
ID	Identification number
IRB	Institutional review board
ISBER	International Society for Biological and Environmental Repositories
JDRFI	Juvenile Diabetes Research Foundation
K_2EDTA	Dipotassium salt of EDTA
K_3EDTA	Tripotassium salt of EDTA
LB	LANDMark Biobank
ml	Millilitres
NIDDK	National Institute of Diabetes & Digestive & Kidney Diseases
NIH	National Institutes of Health
OCT	Optimal cutting temperature (compound)
OHS	Occupational health and safety
PICF	Participant information and consent form
PPE	Personal protective equipment
HREC	Human research ethics committee
rpm	Revolutions per minute
SOP	Standard operating procedure
SST	Serum separator clot activator blood collection tube
TLS	Thermal labelling system
UR#	Unit record number
x	Multiplication factor
µl	Microlitre

5 References

1. International Society for Biological and Environmental Repositories (ISBER). 2008 Best Practice for Repositories: Collection, storage, retrieval and distribution of biological materials for research.2nd Ed.

2. Eiseman E, Bloom G, Brower J, Clancy N, Olmsted SS. Case Studies of Existing Human Tissue Repositories: “Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era. RAND 2003. Santa Monica CA.

6 Appendices

Appendix 1 LANDMark Biobank Sample Record

Appendix 2 LANDMark Biobank Tissue Collection Form

Appendix 3 LANDMark Biobank Equipment Record Log

Appendix 4 LANDMark Biobank Specimen Transfer Form

Appendix 5 LANDMark Biobank Specimen Destruction Form

Appendix 6 LANDMark Biobank Researcher Specimen Distribution Form

Appendix 7 LANDMark Biobank Researcher Specimen Receipt Form

Appendix 8 LANDMark Biobank Participant Information and Consent Form

Appendix 9 LANDMark Biobank Withdrawal of Consent Form

Appendix 10 LANDMark Biobank Tissue Access Policy

History

Version	Changes	Initials/Year
V2.1	Management committee roles updates, added history tabel	NP 2009
V3	Management committee updates, editorial changes.	NP 2015

Institute of Health and Biomedical Innovation

LANDMARK BioBank Sample Record

Lot Numbers & Expiry Dates:

EDTA:_____

_____

SST: _____

_____

BankIt: _____

_____

Week Beginning:_____

Date of Collection	Participant ID	Collection Time	Collector Initials	Guthrie Card Time	Time of Spin	Time of Aliquot	Time in Freezer	# Aliquots Plasma	# Aliquots Serum	# Aliquots Buffy Coat	SOP Deviations	Signature

Institute of Health and Biomedical Innovation

LANDMARK BioBank Sample Record

Lot Numbers & Expiry Dates:

EDTA:_____

_____

SST: _____

_____

BankIt: _____

_____

Week Beginning:_____

Date of Collection	Participant ID	Collection Time	Collector Initials	Guthrie Card Time	Time of Spin	Time of Aliquot	Time in Freezer	# Aliquots Plasma	# Aliquots Serum	# Aliquots Buffy Coat	SOP Deviations	Signature

QUT ihbi Institute of Health and Biomedical Innovation	**LANDMARK BioBank**
Tissue Collection Form	Version 2 (December 2009)
Participant ID	Collector
Skin biopsy collection complete Y / N	Date ___/___/___ Time:__ __ __ __ DD/MMM/YYYY 24 hr clock
Initial freeze Date ___/___/___ Time:__ __ __ __ DD/MMM/YYYY 24 hr clock	Initial freeze ☐ LN2 ☐Dry Ice ☐-80°C ☐Techni Ice
Transfer to main storage Date ___/___/___ Time:__ __ __ __ DD/MMM/YYYY 24 hr clock	

Tissue Sample			Storage Site:_____		
Specimen ID	Tissue preparation	Notes	Box	Grid H/V	Freezer/type

Comments:

Deviations from SOPs if any:

Collectors Signature _____ Date:___/___/___
DD/MMM/YYYY

LANDMARK BioBank Equipment Record

Date dd/mm/yyyy	Equipment Item# & Site	Asset #	Details$	Date Resolved	Signature

#Equipment item may include name, model, manufacturer, contact info, serial number. $Details may include date of purchase, maintenance, repair etc.

LANDMARK BioBank Equipment Record

Date dd/mm/yyyy	Equipment Item# & Site	Asset #	Details$	Date Resolved	Signature

#Equipment item may include name, model, manufacturer, contact info, serial number. $Details may include date of purchase, maintenance, repair etc.

QUT ihbi Institute of Health and Biomedical Innovation	**LANDMARK BioBank**
Specimen Transfer Form	Version 2 (December 209)
Participant ID	Person Transferring:
Original storage freezer Signature:_____ Date ___/___/___ Signature of person transferring specimens	Location:_____ Type:_____ Shelf:_____ Rack #:_____ Removal from original storage Date ___/___/___ Time:__ __ __ __ DD/MMM/YYYY 24 hr clock Transfer medium:_____
Completion of transfer Signature:_____ Date ___/___/___ Signature of person accepting specimens	Date ___/___/___ Time:__ __ __ __ DD/MMM/YYYY 24 hr clock

Comments

QUT ihbi Institute of Health and Biomedical Innovation	**LANDMARK BioBank**
Specimen Destruction Form	Version 2 (December 2009)
Participant ID:	Destruction requested by:
Reason for destruction:	
Destruction authorization attached Y / N	Comments:
Request date	Date ___/___/___ DD/MMM/YYYY
Destruction date	Date ___/___/___ DD/MMM/YYYY

Blood Processing			Freezer Site: _____		
Specimen ID	Box number	Box position	Type/Location	Shelf	Rack

Method of destruction:	
Participant notification Y / N Phone / mail Date ___/___/___ DD/MMM/YYYY	Comments:

Signature (person retrieving specimen)_____ Date:___/___/___
DD/MMM/YYYY

Signature (witness to destruction of specimen)_____ Date:___/___/___

QUT ihbi Institute of Health and Biomedical Innovation	**LANDMARK BioBank**
Researcher Specimen Distribution Form	Version 2
Approved researcher	Date of distribution ___-___-___ DD-MMM-YYYY
Time specimen removed from storage	Date ___-___-___ Time:__ __ __ __ DD-MMM-YYYY 24 hr clock
Time dispatched	Date ___-___-___ Time:__ __ __ __ DD-MMM-YYYY 24 hr clock

Enter details of specimens provided below:

Sample #	Participant ID	Sample Type	Sample ID		Sample #	Participant ID	Sample Type	Sample ID
1					21			
2					22			
3					23			
4					24			
5					25			
6					26			
7					27			
8					28			
9					29			
10					30			
11					31			
12					32			
13					33			
14					34			
15					35			
16					36			
17					37			
18					38			
19					39			
20					40			

Signature (person retrieving & dispatching specimen) _____ Date:___/___/___
DD/MMM/YYYY

Signature (researcher receiving specimen)_____ Date:___/___/___
DD/MMM/YYYY

Note to researcher: Complete form LLB Biological Specimen Receipt Form, attach to the copy of this sheet designate to be returned to BioBank Project Manager.

QUT ihbi Institute of Health and Biomedical Innovation	**LANDMARK BioBank**
Researcher Specimen Receipt Form	Version 2

To researcher receiving tissue samples from the LANDMARK BioBank:

Please keep this form attached to the 'Signed Copy of Researcher Specimen Distribution Form for return to Project Manager'

Once Researcher Distribution Form has been signed, complete this Researcher Specimen Receipt Form, and return both ASAP to:
Nicola Pritchard, Project Manager
IHBI/Queensland University of Technology
60 Musk Ave
Kelvin Grove Q 4059
Australia

Site distributing sample:	Date sample dispatched ___-___-___ DD-MMM-YYYY
Time specimen removed from storage	Date ___-___-_____ Time:__ __ __ __ DD-MMM-YYYY 24 hr clock
Time dispatched	Date ___-___-_____ Time:__ __ __ __ DD-MMM-YYYY 24 hr clock

To be completed by recipient:

Name & address of researcher receiving samples:	
Date and time samples received	Date ___-___-_____ Local Time:__ __ __ __ DD-MMM-YYYY 24 hr clock
Date and time samples placed into researcher storage:	Date ___-___-_____ Local Time:__ __ __ __ DD-MMM-YYYY 24 hr clock
Temperature at which samples will be held until use:	

Please note: You may receive deliveries from two sites (Brisbane and Manchester) to complete the cohort you requested.

Please answer the following questions for the LANDMARK BioBank Quality Assurance Program:

1. Was the delivery time for receipt of this batch of samples within normal expectation?	
2. Has the delivery carton and the samples inside, sustained visible damage on receipt?	
3. Was sufficient Dry Ice remaining in the carton? (Not applicable for Guthrie blots)	
4. Were the samples still frozen? (Not applicable for Guthrie blots)	
5. Were all the samples listed on Researcher Specimen Distribution Form present in the carton?	
6. Do you have any criticisms of the overall procedures for application and supply of tissues by the LANDMARK BioBank?	

Name (researcher receiving specimen)_____

Signature (researcher receiving specimen)_____ Date:___ -___-_____
DD-MMM-YYYY

Princess Alexandra Hospital
Health Service District

LANDMARK BioBank
Withdrawal of Consent Form

for a joint project by Princess Alexandra Hospital and Queensland University of Technology

Project Title: LANDMARK BioBank

Principal Researcher: Prof Nathan Efron[1]

Associates: Prof Andrew Boulton[2], Prof Rayaz Malik[2], Prof John Prins[3], Dr Anthony Russell[3], Ms Nicola Pritchard[1] , Dr Katie Edwards[1]

1 Queensland University of Technology, 2 University of Manchester, 3 Princess Alexandra Hospital

Participant ID ____

I hereby wish to WITHDRAW my consent to further participation in the LANDMARK BioBank.

I request that the following ACTION is taken on my behalf. (Please tick one box only☑)

☐ I wish to leave my biological samples in the tissue bank, but request their anonymization, so no further personal data will be acquired.

☐ I wish to have my biological samples destroyed, and no further personal data will be acquired.

Please be assured that whatever your request, your wishes will be carried out in the presence of a witness, and will not jeopardise your treatment by, or your relationship with, your endocrinologist or other health professionals.

Witness Name____

Signature____

Date ____

✂ ....

[To anonymize this form after completion of participant request cut where indicated and destroy]

Participant Name or Relative Name, if Participant Deceased ____________________

Signature____

Date ____

Princess Alexandra Hospital
Health Service District

Participant Information and Consent Form

for a joint project by Princess Alexandra Hospital

and Queensland University of Technology

Project Title (official): Ophthalmic Markers of Diabetic Neuropathy

Project Title (simplified): Examining the eyes to diagnose nerve problems in patients with diabetes.

Principal Researcher: Prof Nathan Efron[1]

Associates: Prof Andrew Boulton[2], Prof Rayaz Malik[2], Prof John Prins[3], Dr Anthony Russell[3], Nicola Pritchard[1] , Katie Edwards[1] , AProf Andrew Cotterill[4]

1 Queensland University of Technology, 2 University of Manchester, 3 Princess Alexandra Hospital, 4 Mater Children's Hospital

1. Introduction

You (or your child or the person you are responsible for) are invited to take part in this research project. This is because you (or your child or the person you are responsible for) are in the age range of 14-75 years and either have a history of diabetes, or have no history of disease that might affect the nerves of the eye or the body. People who have had eye injury or surgery, other eye diseases (e.g. glaucoma), other general health diseases which may affect the front 'clear window' of the eye, known as the cornea (e.g. keratoconus) or body (e.g. carcinoma, leukemia), large fibre neuropathy (damage to the large nerve fibres), congestive heart failure (weakening of the hearts pumping ability), major mental health problems, HIV-AIDS or diabetic foot ulcer or infection, or those participating in any other research trial will not be eligible.

The research project is aiming to investigate relationship between the nerves of the eye and a condition which involves the peripheral nerves of the body in people with and without diabetes. We hope to determine if some of the measures of the nerves in the eye and the sensitivity of the eye are reduced in people with peripheral nerve damage due to diabetes.

This Participant Information and Consent Form tells you (and your child or the person you are responsible for) about the research project. It explains the procedures involved. Knowing what is involved will help you (or your child or the person you are responsible for) decide if you (or they) want to take part in the research.

Please read this information carefully. Ask questions about anything that you (or your child or the person you are responsible for) don't understand or want to know more about. Before deciding whether or not to take part, you (or they) might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you (or your child or the person you are responsible for) don't wish to take part, you (or they) don't have to. You (or your child or the person you are responsible for) will receive the best possible care whether you (or they) take part or not.

If you (or your child or the person you are responsible for) decide you (or they) want to take part in the research project, you (or they) will be asked to sign the consent section. By signing it you (or they) are telling us that you (or they):

- understand what you (or they) have read;
- consent to take part in the research project;
- consent to participate in the research processes that are described;
- consent to the use of your (or their) personal and health information as described

You (or your child or the person you are responsible for) will be given a copy of this Participant Information and Consent Form to keep.

If you are the parent or guardian of a child or young person, as the 'person responsible' for the patient, you are invited to consider the patient's participation in this research project. Both the child/young person and the 'person responsible' must consent to participation in the study. If you (or they) decide to take part and later change your mind, you (or they) are free to withdraw from the project at any stage for any reason (stated or unstated) without comment or penalty.

2. What is the purpose of this research project?

This research project focuses on patients with different types of diabetes. As you (or your child or the person you are responsible for) may know, diabetes is associated with high sugar levels in the blood due to the body not producing enough insulin to convert this sugar into energy. We think there might be some differences in the nerves of the eyes of people who have different types of diabetes and we can measure this by using new, simple methods that measure the actual nerves and nerve function. These are the eye tests: corneal confocal microscopy (CCM; high magnification microscope) can be used to look at the nerves in the front of the eye; and corneal non-contact aesthesiometry (NCCA) is used to measure the sensitivity of the front of the eye; ocular coherence tomography (OCT) is used to assess the nerves and tissues at the back of the eye and flicker perimetry (FP) measures how well you can see dim lights (both these techniques are described in Section 3). The measures of nerves and nerve function made by these techniques are thought to be related to diabetic neuropathy, the damage of nerves in the peripheral limbs associated in some patients with diabetes. In the research project we aim to investigate the following:

- Changes in corneal (front of eye) nerve counts and corneal sensitivity over time.
- Changes in retinal (back of eye) nerve layer thickness and sensitivity to light over time.
- The relationship between the progression of nerve damage with the results of other traditional nerve tests such as electrophysiology, measuring electrical signals from the body), measuring how easily you can detect vibration and temperature sensitivity and assessment of level of pain and discomfort in people with different types of diabetes.
- The ability of these eye tests to detect nerve damage earlier than traditional means.
- Identify risk factors associated with changes in nerves and nerve function in people with different types of diabetes; these may include age, height, weight, duration of diabetes, blood pressure, smoking, and poor blood-sugar control.

Understanding these aspects of the nerves may provide healthcare professionals with a quick, simple, cost-effective and repeatable means to identify patients at risk, anticipate and monitor deterioration, and assess new treatments.

Diabetic nerve damage is a significant clinical problem that currently has no effective treatment, and in advanced cases, it is a major cause of ill-health and death worldwide. If left unmanaged, diabetic nerve damage can lead to foot ulceration and ultimately, in some cases, foot amputation. It is therefore important to have the capacity to detect this condition early, monitor its progression and assess the benefits of any treatments.

The results of this study will develop a better understanding of small fibre peripheral nerves in the arms and legs in patients suffering from diabetic nerve damage, and will determine the extent to which these changes are associated with the clinical signs and symptoms of the condition. The significance of this study is that it will reveal the potential for these eye tests to serve as sensitive, rapid, repeatable, 'patient-friendly' eye tests for the detection, diagnosis and monitoring of the progression of diabetic nerve damage. This information will provide a sound basis for the design of trials of treatments for diabetic nerve damage. Data will also be generated which will reveal the importance (or otherwise) of blood sugar control and other metabolic abnormalities and lifestyle factors which may impact on the progression of nerve damage in diabetic patients.

A total of 298 participants will take part in this study at the Institute of Health and Biomedical Innovation (IHBI) at QUT in Brisbane and a further 202 at the University of Manchester in the United Kingdom.

Five groups of people will be recruited in Brisbane:

Group 1: Patients with Type 1 diabetes and without nerve damage

Group 2: Patients with Type 1 diabetes with nerve damage

Group 3: Patients with latent autoimmune diabetes in adults (LADA; similar to Type 1 diabetes but occurring later in life) with nerve damage

Group 4: Patients with Type 2 diabetes with and without nerve damage

Group 5: Non-diabetic participants without nerve damage.

Some of the results of this research will be used by the researchers Ayda Moavenshahididi and Nicola Pritchard to obtain Doctor or Philosophy degrees.

This research is a collaborative project between researchers at QUT, Princess Alexandra Hospital (PAH) and University of Manchester (UM). It has been initiated by the investigators Professors Nathan Efron (QUT), Rayaz Malik, Andrew Boulton (UM), and John Prins (PAH); Dr Anthony Russell (PAH) and optometrists Nicola Pritchard and Dr Katie Edwards (QUT).

This research has been funded in part by the Juvenile Diabetes Research Foundation International and Australia's National Health & Medical Research Council and the George Weaber Foundation (to support Ms Moavenshahidi).

3. What does participation in this research project involve?

Your participation (or that of your child or the person you are responsible for) will involve asking you (or they) to reveal eye and past medical problems, and undergo an examination of the front part of the eye using a high powered microscope, read letters on an eye chart, and have the pressure of the eyes measured. We will ask you (or your child or the person you are responsible for) to complete a questionnaire about pain in your (or their) lower limbs, and undergo simple tests of your (or their) sensations of pain/touch, vibration and temperature. The tests are quick and involve use of a pointed tip, a tuning fork and warm and cool metal rods to test these three sensations. The presence of absence of the reflexes in your knees and ankles using a small hammer will be tested. Your (or their) height, weight and blood pressure will also be measured and a picture will be taken of the back of the eye.

Another high powered microscope, known as a corneal confocal microscope (CCM) will be used to examine the number of nerves at the front part of the eye, the cornea. A drop of anaesthetic is applied to numb the front of the eye and you (or they) will be asked to sit at an instrument and look a target while several images are captured. Initially the drop may sting for 1 or 2 seconds. Because the drop numbs the eye it is possible to scratch the eye without noticing it. Therefore please do not rub the eyes for at least 45 minutes after the drop has been placed in the eye.

Another test of your (or their) ability to feel different sensations will be done using an instrument that can measure when you (or they) just notice sensations of cool, warm and vibration on the foot. For example, for the coolness test you (or they) may feel like "a pulse of cooling" has touched the foot. It is important that before these tests no sedatives, tranquillisers, opiates, or stimulants have been taken in the preceding 12 hours, and not more than one hot drink has been consumed prior to the test.

Another test that can reveal alterations to the nerves is a test of heart rate variability. A measure of heart rate variability will also be conducted to show how the heart responds to deep breathing and to changes in blood pressure and posture.

Corneal non-contact aesthesiometry (NCCA) will be conducted to measure the sensitivity of the cornea. The smallest noticeable air pressure is determined by directing gentle, almost imperceptible puffs of air to the eye, and you (or they) indicate whether the air on the eye can be felt or not. We will also take a small sample of tears (50µl) to examine the proteins; this involves holding a tiny glass tube near the eye for a few seconds.

The speed the nerves conduct messages will also be tested as a measure of nerve damage. Nerve conduction velocity will be measured by putting sensors on the ankle, wrist and elbow. The limb will be kept warm with a heat lamp if necessary. A small electrical current will be applied to the sensor which may feel like a tingling sensation and it may be uncomfortable for you (or them). You (or they) should feel no discomfort once the test is finished. This test will be performed at PAH.

Ocular coherence tomography (OCT) involves having a drop inserted into one eye to dilate the pupil. Then you (or they) will be asked to fixate a target while seated at the instrument, and at least two OCT images are captured. A photograph of the back of the eye will also be taken using a specialised digital camera. Due to the increased size of the pupil, your (or their) sensitivity to glare may be increased for 4 to 6 hours, so you (or they) may wish to wear dark glasses when outside and/or have someone drive or escort you (or them) home.

Flicker perimetry (FP) involves viewing a light stimulus of varying intensity, and sometimes flickering, which appears in different parts of the visual field. You (or your child or the person you are responsible for) will be required to click a button if you (or they) see the light while looking at a central spot.

At the end of the study procedures the eye will be examined again; follow-up appointments will be made if the investigator believes it is in your (or their) best interests. This study will be carried out at IHBI at QUT and PAH, Woolloongabba.

We expect the visit will be approximately 2 to 3 hours at IBHI at QUT, Kelvin Grove and another 1 hour at PAH at a time suitable to you. You (or they) will not be paid for participation in this research, but will be provided transport to and from QUT/PAH (e.g. parking / vouchers for petrol or cab vouchers will be provided up to approximately $40) and will receive light refreshments during the visit (approximate value $10).

4. What will happen to my test samples?

You (or your child or the person you are responsible for) will be asked to provide consent for the collection of your (or their) blood (approximately 20-25ml, or 2-3 tubes) and urine

(approximately 10ml) during the research project. From these samples the levels of protein, glucose, lipid and a test for antibodies for glutamic acid decardoxylase (GADAb) and antibodies to islet cells (ICAb) will be determined and recorded. This will help investigators decide which group to assign you (or them) to. All samples will be individually identifiable at the time of collection, analysis and report. These results will only be used for research purposes, and will be stored separately from the main body of study data to protect your (or their) privacy/confidentiality and anonymity, and a re-identifiable code will be assigned your (or their) blood results. All blood and urine samples will be assessed through a contracted pathology service and samples are usually destroyed 7 days after collection. Separate consent will be obtained regarding storage of blood samples. Unused tear samples will be destroyed typically within 7 days of collection.

5. What are the possible benefits?

There will be no direct benefit to you (or your child or the person you are responsible for) from your (or their) participation in this research. However, it may benefit the many people who have problems with diabetic neuropathy, because with these instruments and techniques we are able to look at the tissues of the eye under very high magnification. Also these new technologies may reveal features that have not, to date, been discovered but which might serve as sensitive, rapid and useful techniques for the detection, quantification and monitoring of the progression of nerve disease in patients with diabetes as well as other diseases where the nerves of the body are affected. Some people find the opportunity to learn and be a part of something new an interesting experience.

We can provide you (or your child or the person you are responsible for) with state-of-the-art images of your (or their) eye if you (or they) would like them.

6. What are the possible risks?

The risks associated with participation in this study are minimal, and similar to routine diabetic and primary eye care. Minimal scratching the front surface of the eye can occur with corneal confocal microscopy, similar to that which might occur if you (or they) rub the eyes too hard; however, in our experience it is like that noted with normal daily wear of contact wearers. This type of abrasion heals quickly, without intervention, typically within 12 hours.

Having a blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which tissue is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

Nerve conduction tests involve applying a small electrical current to the limb which may feel like a tingling sensation; this may be uncomfortable for you (or them). You (or they) should feel no discomfort once the test is finished.

If you (or your child or the person you are responsible for) become upset or distressed as a result of your (or their) participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team. In addition, you (or they) may prefer to suspend or end participation in the research if distress occurs without comment or penalty.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you (or they) get.

7. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you (or your child or the person you are

responsible for) will be told about this new information and the researcher will discuss whether this new information affects you (or them).

8. Can I have other treatments during this research project?

It is important to tell your (or their) doctor and the research staff about any treatments or medications you (or they) may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your (or their) doctor and the researchers about any changes to these during participation in the research.

9. Are there alternatives to participation?

Since this study does not involve any treatments, you (or your child or the person you are responsible for) will receive the best possible care whether you (or they) take part or not. Participation in the study does not replace full eye or medical care. You (or they) may also request that your (or their) general practitioner be informed of participation in the study.

10. Do I have to take part in this research project?

Participation in any research project is voluntary. If you (or they) do not wish to take part you (or they) don't have to. If you (or they) decide to take part and later change your mind, you (or they) are free to withdraw from the project at any stage for any reason (stated or unstated) without comment or penalty.

The decision whether to take part or not to take part, or to take part and then withdraw, will not affect your (or their) routine treatment, your relationship with those treating you (or them), nor your (or their) relationship with Princess Alexandra Hospital or Queensland University of Technology.

11. What do I need to do if I decide to withdraw from this research project?

If you (or your child or the person you are responsible for) decide to withdraw, please notify a member of the research team before you (or they) withdraw.

If you (or they) decide to leave the project, the researchers would like to keep the personal and health information about you (or them) and your (or their) blood results that have been collected. This is to help them make sure that the results of the research can be measured properly. If you (or they) do not want them to do this, you (or they) must tell them before joining the research project.

12. Could this research project be stopped unexpectedly?

There are no foreseeable reasons why this research project would be terminated before completion. In the unlikely event this did occur, you (or they) will be informed in writing and asked to attend a final study visit.

13. How will I be informed of the results of this research project?

The research team will provide regular newsletters on the progress of the study. You (or your child or the person you are responsible for) will also receive a copy of any publications that are generated as a result of this study. We expect this research project to be completed in approximately 5 years and a full summary of the results will be provided to you (or them) then. Results from the tests we perform will be sent, with your (or their) permission, directly to your (or their) medical practitioners.

14. What else do I need to know?

Any information obtained in connection with this research project that can identify you (or your child or the person you are responsible for) will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your (or their) permission, except as required by law. Information about you (or them) may be obtained from your (or their) health records held at PAH (where applicable) for the purposes of this research e.g. additional blood results related to your (or their) PAH clinic visit. If you attend another clinic we will seek your (or the person you're responsible for) permission to obtain your (or their) blood results from your (their) doctor.

Data is stored on paper records in locked filing cabinets at PAH and QUT, and the data in electronic form (i.e. entered into a computer) is only available to the research team members and is kept secure by using password-protected limited-access environment. Data is stored during the project in a re-identifiable format i.e. coded. Your (or their) name and contact details will be held separately to the study data to protect your (or their) privacy and anonymity. In any publication and/or presentation, information will be provided in such a way that you (or they) cannot be identified, except with your (and/or their) permission. This will be done by only using the code number assigned to you (or them) for the purpose of this study.

At completion of the project your (or their) data will be decoded, such that it will not be possible to determine which data belong to which participant. Data for this project will be kept for 15 years or 5 years after the last publication. Paper files will be shredded and electronic files will be carefully removed from their storage location (not just deleted).

Information about your (or their) participation in this research project may be recorded in your (or their) health records.

How can I access my information?

In accordance with relevant Australian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you (or your child or the person you are responsible for). You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you (or they) would like to access your (or their) information.

What happens if I am injured as a result of participating in this research project?

If you (or they) suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you (or them) if you (or they) elect to be treated as a public patient.

Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the Princess Alexandra Hospital and Queensland University of Technology.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

15. Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Queensland University of Technology concerning my health and treatment that is needed for this project. I understand that such information will remain confidential.

I consent to the use of blood samples taken from me for use in this specific research project only, as described in Section 4 of this document.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) _____

Signature_____ Date _____

Declaration by parent, guardian or person responsible (where appropriate): I agree for my child/young person or the person named above who I am responsible for to participate in this research and I believe that they have understood the explanation of the study, its procedures and risks.

Name of parent/guardian to participant's (printed) _____

Signature_____ Date _____

Name of witness to participant's signature (printed) _____

Signature_____ Date _____

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed) _____

Signature_____ Date _____

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the consent section must date their own signature.

16. Who can I contact?

Who you (or your child or the person you are responsible for) may need to contact will depend on the nature of your (or their) query; therefore, please note the following:

For further information or appointments:

Landmark Study Email: landmark@qut.edu.au or Katie Edwards, Ph: 07 3138 6154, Email: katie.edwards@qut.edu.au.

If you (or they) have any medical problems which may be related to your (or their) involvement in the project (for example, any side effects), you can contact Dr Anthony Russell Ph: 07 3240 5914 If you (or they) want any further information concerning this project you can contact the following people:

Katie Edwards	Nicola Pritchard	Prof.Nathan Efron
Ph: 07 3138 6154	Ph: 07 3138 6414	Ph: 07 3138 6401
Email: katie.edwards@qut.edu.au	E-mail: n.pritchard@qut.edu.au	E-mail: n.efron@qut.edu.au

If you (or they) feel emergency medical care is required, then go to the nearest hospital Emergency Department.

For complaints:

If you (or they) have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you (or they) may contact:

Ethics Manager	QUT Research Ethics Officer
Princess Alexandra Hospital Human Research Ethics Committee	Queensland University of Technology Human Research Ethics Committee
Ph: (07) 3240 5856	Ph: (07) 3138 2340
Email: PAH_Ethics_Research@health.qld.gov.au	E-mail: ethicscontact@qut.edu.au

Researcher Ethics Officers/Managers are not connected with the research project and can facilitate a resolution to your (or their) concern in an impartial manner.

LANDMark Biobank

c/o Anterior Eye Lab, Institute of Health & Biomedical Innovation, Queensland University of Technology, 60 Musk Ave, Kelvin Grove Q 4059; n.pritchard@qut.edu.au

Tissue Availability and Tissue Access Policy Statements

Tissue Availability

The aim of the LANDMark Biobank (LB) is to provide access to quality tissue samples for researchers throughout the world to support research investigating biomarkers of diabetes and its complications, improving or creating diagnostic tests and identifying potential new treatments for diabetes and diabetic neuropathy. Tissue collection for the Biobank began in late 2009 at Queensland University of Technology in Brisbane Australia and University of Manchester, UK.

Tissue/clinical data collection

Samples of blood products are banked at the Brisbane site and both blood products and skin tissue are banked at the Manchester site. Clinical and pathological data at baseline and follow-up visits over 5 years is collected at each site, and datasets will be available from the LANDMark study Biobank Manager.

Timing for release of tissues

Blood Products: Because of the importance to research of clinically annotated tissue samples, a limit has been placed on the quantity of fresh frozen tissues to be released to researchers while 5-year clinical follow data is being collected. A maximum of 50% of any single participant's tissue samples will be released in the first 5 years after accrual. This applies to Guthrie blots, frozen serum, plasma, and buffy coat cells and skin tissue.

Tissue Access Policy

The Biobank welcomes requests for blood product and skin tissue from researchers worldwide. Tissues will only be released, however, to researchers who provide a statement of ethics approval from the human research ethics committee of their host institution. This applies to researchers who request even a single sample for testing, in order to safeguard participant expectations. In order to conserve the limited tissue resources during the first 5 years (2009-2013), frozen blood products and skin tissue will only be released to highly rated projects, and there will be no access for commercial, pharmaceutical or biotechnology companies or international researchers without LANDMark or JDRF-approved collaborators. A level of priority access is available to individuals or groups providing services in kind to tissue sample collection and storage processes. Such individuals should contact the Biobank Manager before making an application.

All projects, whether previously reviewed or not by peer review committees, will undergo a peer review by the LANDMark Biobank Tissue Access Committee (TAC) in order to determine the standard of the proposed research project, the likelihood of successful outcomes and the quantity and types of tissue(s) requested. The committee retains the right to prioritise projects and will not necessarily support all funded or fundable projects to protect the longevity of this limited resource. This ruling applies irrespective of the types or numbers of specimens sought from the Biobank.

LANDMark Biobank

Guidelines for Applications for Tissue and Data Access

Timing: A Letter of Intent may be submitted at any time. Full applications must be submitted one month from request. Meetings of the access committee will be scheduled within 6 weeks of receipt of an application.

Procedure:

1. A letter of intent (LOI) must first be provided to the Biobank Manager, containing:

a) Your name, institution, mailing and email addresses, telephone / fax numbers
b) The types of cases required and approximate numbers for each type
c) Statistical justification for the number and types of cases required
d) A statement of the aims / hypotheses of the proposed research
e) A brief description of the technical approach.
f) Evidence that the proposed measurement technique(s) can be used on the specimens requested
g) Clinical and outcome data required
h) Funding available to project
i) Copy of ethics approval to conduct proposed research, or details of pending approval

This LOI will be reviewed on receipt, and if the Biobank Manager determines that the Biobank can meet your needs, and the TAC determines there are no apparent technical problems, you will be asked to submit a full application, subject to the above timing constraints. This application must be made within one year of submitting the LOI, otherwise a new LOI must be submitted prior to the full application.

2. *Pilot/Small Projects* are subject to the same guidelines as full applications, projects requiring only a small number of specimens and/or which would have low impact on the LB holdings may be assessed via an expedited application process. Full peer review may be waived, and the application will be dealt with by the Biobank Manager without TAC involvement based on scientific merit, impact on holdings and value of research to the LB and JDRF. In general, pilot projects will involve limited numbers of specimens or data, for example 1 to 4 participants blood product samples. These test specimens will be supplied *without* clinical annotation, and in the expectation that if the pilot is successful, a full application will be lodged later. Approval for pilot projects will be for one year only. A copy of approval of the proposed work by a human research ethics committee will need to be provided to the LB prior to release of material.

3. Full Applications - Procedure:

I. Before making an application, researchers may wish to confer with the Biobank Manager to discuss the appropriateness of LANDMark Biobank specimens for the proposed study.

II. Guidelines and application forms can be obtained from the Biobank Manager. At least 2 weeks before the application is submitted, applicants must send an LOI to the Biobank Manager. This LOI will be provided to the TAC for comment. In the case that DNA or RNA is to be produced from buffy coat cells by researchers, the amount produced is likely to far exceed the immediate requirements of the project for which tissues were provided. Consequently, excess materials may be requested to be returned to the Biobank by arrangement, on production. When resources permit, the Biobank will undertake production of DNA/RNA for release to researchers.

III. Applications must be made on and according to the application form, attaching relevant documents. Completed applications containing all documents and bearing the investigators' signatures **must be**

provided electronically (pdf file sent by e-mail) to the Biobank Manager according to the above timing schedule.

IV. Full applications that have not had prior peer review will be sent out by the TAC to appropriate referees. If a proposal is currently under peer review by a granting agency, the Biobank Manager can provide a letter stating that the samples requested are available, subject to approval by the TAC once funding is obtained. The TAC would appreciate receiving any available peer reviews for the project.

V. Applications will be reviewed by the TAC, which will assess whether the application comprises a scientifically justifiable, feasible, and high priority use of the biological material currently available. The applicant may be asked to respond to the reviewers' comments in writing. The TAC may suggest some changes to the proposed application and will try to facilitate communication and collaboration between groups working on similar topics. Any member of the TAC with a conflict of interest will be excluded from this review. Reasons will be given for refusal of all or part of the proposed use of material, and this may occur even if the overall grant proposal has approved funding. Conditions on, or restrictions of, use may be made.

VI. Simultaneously, the application will be reviewed by the Biobank Manager so that a mechanism and timescale for the delivery of the requested specimens and data can be determined.

VII. An acceptance letter will be provided to approved applicants, outlining the conditions on tissue provision as per this policy document. On receipt of a Material Transfer Agreement signed by the applicant(s), and evidence of ethical approval, the project can proceed according to the agreed protocol.

VIII. Any significant deviations from the agreed protocol must be sent by the applicant(s) in writing for approval before proceeding.

IX. Data and biological material will be supplied as soon as possible after a request is approved. The onus is on the investigator to re-submit the application at a later date if additional material is required for the same project.

X. The Biobank will levy cost recovery fees to the applicants for the preparation and shipping of biological materials (Manchester only, or in Brisbane by permit issued by the Chief Health Officer at Queensland Department of Health).

XI. The Biobank reserves the right to withhold the supply of further material if the rate of progress is unacceptable.

XII. Annual progress reports may be requested to be sent to the Biobank Manager for presentation the TAC. The Biobank Manager will notify investigators in this instance.

XIII. At the conclusion of the project, residual materials must be returned or destroyed by agreement of the Biobank, all requested research data will be transferred to the Biobank database, and a final report prepared by the applicants.

Responsibilities of Investigators who use Biobank material

The Chief Investigator(s) of the project must agree:

LANDMark Biobank

- To sign the LANDMark Biobank Material Transfer Agreement and not to distribute the material or data to investigators or institutions who are not named in the approved application.
- To include as an author on any resulting publications any Biobank members who fulfil authorship criteria for the study as it progresses. This is required as an outcome measure of Biobank productivity.
- To lodge copies of relevant manuscripts utilising the LANDMark collection with the Biobank Manager of the LANDMark Biobank, for examination, prior to journal review.
- To acknowledge the JDRF that supported the core activity of the LANDMark Biobank in any resulting publications.
- To submit an annual report on request.
- To propose a timeline for monitoring the project.
- To meet the costs involved in preparing and shipping biological specimens and in extracting data from the central database (see note above).
- To notify the Biobank of study completion. All studies will be deemed complete after three years unless re-application is lodged.
- To submit all requested research data back to the Biobank Manager for inclusion in the Biobank database, within 12 months following completion of the project. The research data requested will be decided between the Biobank Manager and the researcher. This will facilitate powerful collaborative meta-analyses by the Biobank. It will benefit the researcher providing the data, the Biobank, and LANDMark research.
- To return unused materials to maintain the longevity of the resource, or destroy the material by agreement of the Biobank.
- To obtain a signed MTA from any collaborator to whom they wish to pass on material for use in the approved project. This should be forwarded to the Biobank Manager with a request that the TAC consider the addition of the collaborator to the project.

Contact Information and Officers of the Biobank (Years 2009-2014)

First Point of Contact for the LANDMark Biobank:

Biobank Manager
Dr Nicola Pritchard
Institute of Health and Biomedical Innovation
Queensland University of Technology
60 Musk Ave, Kelvin Grove 4059 Australia
E: n.pritchard@qut.edu.au

Members of the Biobank Management Committee

LANDMark Biobank

- Dr Nicola Pritchard, Biobank Manager, Brisbane
- EProf Nathan Efron, CI, Brisbane
- Prof Rayaz Malik, CI, Manchester

Members of LANDMark Biobank Tissue Access Committee:

- Adjunct Prof Anthony Russell, endocrinology representative
- Dr Dimitrios Vagenas, biostatistics representative
- Professor Nigel Calcutt, molecular pathology representative
- JDRF representative - tba

Principal Investigators of the JDRF Grant underpinning the LANDMark Biobank:

- Professor Nathan Efron, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland
- Professor Rayaz Malik, Cardiovascular and Endocrine Sciences, University of Manchester
- Professor Andrew Boulton, Cardiovascular and Endocrine Sciences, Manchester Royal Infirmary
- Professor John Prins, Mater Medical Research Institute, Brisbane