Research Protocol
Biological studies of reproductive disorders using samples from the Newcastle Uteroplacental Tissue Bank
Version 7 April 2017

Dr Paul Ayuk, Consultant Obstetrician
Newcastle upon Tyne Hospitals NHS Foundation Trust
Paul.Ayuk@nuth.nhs.uk
0191 282 4132 (Jean Birtles, Newcastle Uteroplacental Tissue Bank secretary)

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Background

The group's research focus is to understand the molecular mechanisms that underlie cellular remodelling in the uterus and placenta in pregnancy and implantation. Failure or impairment of placentation, vascular adaptation or myometrial/cervical remodelling will manifest clinically as miscarriage, growth restriction, preeclampsia or preterm labour. These conditions are important and common causes of maternal and neonatal morbidity and mortality. By understanding the molecular processes underpinning gestational changes in structure and function, we can begin to consider how pathways might be manipulated to improve pregnancy outcomes.

Research Plan

The Reproductive and Vascular Biology Group has an international reputation for high quality science projects and collaborations investigating cellular signalling mechanisms in human reproductive tissue. The Group has expertise in a range of experimental techniques including

- Cell culture, whole cell imaging, analysis of cellular extracts (including measurement of protein, RNA and metabolite expression)
- In vitro functional molecular studies (protein:protein /protein:RNA interactions, nuclear splicing assays)
- High quality 'in-situ' cellular technologies (immunohistochemistry, TISH and laser capture microscopy/PCR) with large scale gene, RNA and protein expression profiling (subtraction hybridisation, SAGE [serial analysis of gene expression], RNA Sequencing, LCMSMS proteomics).
- Novel in vivo approaches to trophoblast / myometrium/ leukocyte interactions (incorporating trophoblast invasion assays and co-culture techniques)
- In vitro functional contractility studies and mathematical modelling techniques as part of a systems biology strategy to describe smooth muscle function.

Crucially, all experimental data can be interpreted within a clinical context as a result of the careful characterisation of tissue collected and the maintenance of an anonymised database with clinical information. Expansion of our database characterising the source of the tissues collected will be a powerful tool allowing important clinical questions to be investigated. Our database is well established and fully compliant with all HTA regulations. Efficiencies will be seen when individual samples could be used to contribute to more than one project e.g. a single myometrial biopsy might provide tissue for a contractility study, an immunohistochemistry study and cell culture. The database would include details of all instances where a given sample was used. Tissue will not be used for studies involving cellular cloning or used in animal models.

Samples obtained

1. Uterine myometrium (pregnant)
2. Uterine myometrium (nonpregnant)

3. Placental bed biopsies (pregnant)
4. Uterine cervix (nonpregnant)
5. Placenta
6. Uterine endometrium (nonpregnant)
7. Uterine cervix (pregnant)
8. Cord blood from the placenta

Tissues from pregnant patients (1,3,5,7,8) will be collected from women undergoing Caesarean section, after vaginal delivery (5,7,8), women undergoing termination of pregnancy (1,3,5,7) or women having surgical management of miscarriage (5).

In addition, all women having a cervical biopsy in pregnancy will have a cervical brush sample collected to evaluate the background microbiological and biochemical inflammatory status.

Tissues from non-pregnant patients (2,4, 6) will be collected from women undergoing hysterectomy for non--malignant gynaecological disease (2,4,6) or women attending general gynaecology or reproductive medicine clinics (6).

Consent procedures

Non pregnant

Hysterectomy samples: Women are identified from the gynaecological operating list by a research nurse, midwife or Clinical Trials Assistant (CTA) from the Reproductive Health and Childbirth Research Team (who holds an honorary Trust contract). They are initially approached by a member of the clinical care team to check that they are happy to talk to the research team about a study they are eligible for. Women will be given the study information sheet (PIS NP (hyst) V7 April 2017 by the research team. After a period of consideration (minimum 1 hour), written consent will be) obtained by a member of the research team.

Out-patient samples: Women attending general gynaecology or reproductive medicine clinics will be given information about the study by a clinical researcher or research nurse / midwife from the Reproductive Health and Childbirth Research Team (who holds an honorary Trust contract). Suitable patients will be identified from the hospital notes. Potential recruits will receive a copy of the relevant patient information (PIS NP (pip) V7 April 2017) and will be consented by a clinical researcher or research nurse / midwife.

Pregnant (early pregnancy)

Normal pregnancy samples: Healthy pregnant women admitted for termination of pregnancy (TOP) under general anaesthesia will be identified when they are admitted to the gynaecological ward at the Royal Victoria Infirmary. They will be given the study information sheet (PIS EP myo/placenta or EP cervix V7 April 2017) by the research nurse / midwife from the Reproductive

Health & Childbirth Research Team (who holds an honorary Trust contract). After a period of consideration (minimum 1 hour), written consent will be obtained by the research midwife / nurse.

Pregnant (except cervical biopsies) (elective LSCS)

All pregnant women receive information about current research studies with their pregnancy booking information (usually prior to 14 weeks of pregnancy). This includes brief details of the purpose of the research and highlights that they may be approached later in pregnancy about participation. Women undergoing elective Caesarean section (LSCS) are identified by the clinical care team and receive a copy of the relevant patient information (PIS ElCS V7 April 2017) at the time consent is taken for surgery (typically several weeks prior to delivery). Consent is taken by a nurse, midwife or Clinical Trials Assistant (CTA) from the Reproductive Health & Childbirth Team at the time of the preoperative appointment which is scheduled during the week before the date of surgery.

Pregnant (except cervical biopsies)(emergency LSCS)

Women will be identified as being eligible for recruitment by the research midwife / nurse from the labour ward board. Women in the induction suite or in the first stage of labour can be approached. Potential recruits will receive a copy of the relevant information (PIS EmLSCS V7, April 2017). Consent forms completed by women who do not subsequently deliver by LSCS will be destroyed following delivery.

Alternatively, women may be identified as being eligible by the clinical care team at the time the decision for surgery is made and given a copy of the relevant information (PIS EmCS V7, April 2017. Women who need an urgent procedure (Grade 1 or 2) would not be considered suitable for emergency consent because it is anticipated that the decision to delivery interval would be less than 40 minutes, thereby precluding the opportunity for the patient to give considered consent. Such patients are consented by a member of the clinical care team as it is not currently feasible to have a research midwife allocated to the delivery suite on a 24hr basis.

Pregnant vaginal delivery (except cervical biopsies)

Following vaginal delivery, women will be approached by research nurse/midwife from the Reproductive Health & Childbirth Team and asked if they would be prepared to donate the placenta and / or cord blood, which would otherwise be discarded, to the Tissue Bank. They are given a copy of the relevant information (PIS Placenta V7 April 2017). If clinically indicated placental investigations are required, placental samples will only be taken from residual tissue.

Cervical biopsies

In contrast to some of the other pregnancy tissues included in the Bank (e.g. myometrium, placenta), collection of cervical samples in pregnancy is not a routine obstetric procedure. Samples will only be taken by Professor Steve Robson (SCR) (or a named individual trained by him and specifically approved by the Tissue Bank Management Committee). The operator will therefore be

responsible for identifying suitable women from their case loads.

Early pregnancy

Women having surgical termination of pregnancy will be given information about the study by a research nurse / midwife from the Reproductive Health & Childbirth Research Team (who holds an honorary Trust contract) or clinical researcher not involved in the care of the patient. Suitable patients will be identified from the hospital notes. Women who are entered into the National Cervical Screening Programme must have a current, normal smear history. On the day of surgery consent will be confirmed by the operating surgeon.

Late pregnancy (non labouring)

Women having an elective (Grade 4) caesarean section (LSCS) will be recruited from the antenatal clinic or the ward at the time of booking surgery. After identification by the clinical researcher, eligible women will be approached and given a copy of PIS LSCS Cervix V7, April 2017 and consented by a research nurse / midwife from the Reproductive Health & Childbirth Research Team (who holds an honorary Trust contract) or a clinical researcher who is not involved in the clinical management of the patient.

Late pregnancy (labouring)

Women having an instrumental delivery under spinal or epidural anaesthesia due to delayed progress in second stage or a Grade 3 (non-urgent) Caesarean section will be identified by SCR (or a named, trained individual) who will approach the woman providing she has a normal smear history for the past five years. The procedure will be explained and written information given (PIS CS cervix or VD cervix, V7 April 2017). Women will be consented by a research nurse, midwife or a GCP trained clinician who is not part of the research team.

Participants can withdraw their consent at any time without having to justify their decision or influencing their clinical care. If consent is withdrawn after the samples have been stored, these biopsies will be identified from the linked anonymised system and destroyed. Data collected up to the point of removal will be retained.

Sample collection

Upper segment myometrial biopsy/placental bed biopsy

(a) Caesarean section (late pregnancy beyond 24 weeks): Up to 5 punch biopsies will be obtained after delivery of the baby and placenta. Biopsies will be taken under direct vision, after identification of the placental site, using Wolf biopsy forceps introduced through the existing uterine incision. Placental bed biopsies include myometrium from under the placental site whereas this site is avoided for upper segment myometrial biopsies (these are taken from the opposite side of the uterus).

(b) Termination of pregnancy (early pregnancy): Up to 3 punch biopsies will be obtained after completion of the surgical termination procedure. Biopsies will be taken under ultrasound guidance using Wolf biopsy forceps introduced through the cervix. As with (a), placental bed biopsies include myometrium from under the placental site (identified be prior ultrasound) whereas this site is avoided for myometrial biopsies (these are taken from the opposite side of the uterus). Myometrial biopsy using forceps could potentially be accompanied by uterine perforation and/or haemorrhage, requiring additional surgical intervention e.g. insertion of a haemostatic suture at Caesarean section, or laparoscopy and possible laparotomy following surgical termination of pregnancy. The risk of perforation is minimised by the operator palpating the outer surface of the uterus to guide the depth of the biopsy at Caesarean section and by careful ultrasound guidance of the forceps after termination. We have previously published on the safety of the procedure (Robson SC et al. Am J Obst Gynecol 2002; 187: 1349–55).

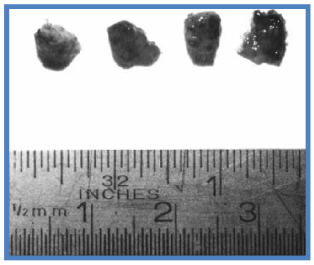


Figure 1: Placental bed biopsy specimens obtained transcervically under ultrasound guidance at 14 weeks gestation

Lower segment myometrial biopsy (pregnancy)

Biopsies of lower segment myometrium (~15mm x 10mm) will be obtained from the upper margin of the uterine incision using tissue scissors. Biopsies will be undertaken by trained obstetric consultants and specialist registrars working clinically in the Trust. The Principle Investigator will verify that the surgeons taking the biopsies are competent in the technique by observing their practice directly in the first instance. Extensive published and local experience indicates this procedure is without complication.

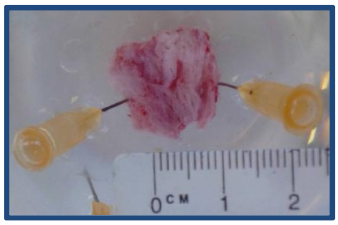


Figure 2: Lower segment myometrial biopsy specimen

Myometrial/endometrial biopsy and cervical biopsy (non-pregnant)

Following hysterectomy the specimen is collected from the operating theatre by a member of the research team and transported to the Cellular Pathology Department. After inspection by a clinical pathologist to exclude any suspicion of significant endometrial or cervical pathology a block of normal myometrium with overlying endometrium ~2x2cm is excised and transferred to the

laboratory. A member of the clinical care team reviews the recent smear history (from the pathology database) to exclude any significant cervical pathology. In the absence of significant cervical pathology three ~5mm x10mm punch biopsies will be taken from the cervix and transported to the laboratory.

Endometrial biopsy (non-pregnant)

Samples will be collected in the out-patient setting by a trained member of the research team. A speculum will be passed and the cervix visualised. The pipelle endometrial biopsy will be taken using a Wallach endocell sampling device which has been introduced through the cervix, and will be placed into transport medium. The sample will be transferred and processed in the research laboratory using established SOPs.

Placental tissue

Early pregnancy

Termination of (normal) pregnancy: The products of conception are collected in a sock within the suction apparatus and transferred to the laboratory where the placental and decidual tissue are isolated and removed. The remainder of the specimen is returned to the Pathology department and disposed of according to routine Trust protocols.

Late pregnancy (beyond 24 weeks)

The placenta is transported to the laboratory following vaginal or surgical delivery. Samples of membrane or placental tissue are excised before returning the remainder of the specimen into the routine clinical disposal system. An addition to previously approved procedures would be to obtain preterm samples in selected cases. Samples will only be taken from placentae less than 35 weeks gestation after examination by a clinical pathologist to ensure that no opportunity is lost to gain relevant information to inform ongoing care of the woman or the neonate.

Cord blood

Blood would be obtained from the umbilical vein by venipuncture using standard Trust procedures. Blood samples will only be obtained after clinical samples for cord blood gas analysis, Rhesus typing and any other clinically necessary investigations have been obtained.

Cervical biopsies and cervical brush samples

Early Pregnancy (surgical termination of pregnancy)

All samples are collected whilst the patient is under general anaesthetic. At the start of the procedure a cervical brush sample will be taken. Biopsy samples, taken after evacuation of the uterus, are obtained using a 5mm punch biopsy. Two samples are taken from each patient from the 11 o'clock and 5 o'clock positions. On the rare occasion when bleeding is not alleviated by simple pressure, a single, dissolvable haemostatic suture will be used. One biopsy is snap frozen at

-80 and the second placed in transport medium. The three samples (2 biopsies, 1 brush sample) are then transferred to and processed in the research laboratory using established standard operating procedures (SOPs).

Late Pregnancy (beyond 24 weeks; labouring /non-labouring LSCS)

All samples will be obtained under spinal or general anaesthetic. An assessment of the cervical Bishop Score and a cervical brush sample will be taken at the time of catheter insertion. After completion of surgery, at the time of cleaning out the vagina a speculum will be passed and the cervix visualised. Two biopsies will be taken, one each from the anterior and posterior lips of cervix using a 5mm punch biopsy. On the rare occasion when bleeding is not alleviated by a simple pressure, a single, dissolvable haemostatic suture will be used. One sample will be snap frozen and the second placed in transport medium. The three samples are then transferred to and processed in the research laboratory using established SOPs.

Late pregnancy labouring (beyond 24 weeks; instrumental delivery)

A vaginal swab will be taken prior to perineal cleaning (note: due to full dilatation a brush sample will not be possible and a Dacron swab will be used). Delivery will be conducted in the usual manner. Following delivery of the placenta, two cervical biopsies will be taken one each from the anterior and posterior lips of the cervix using a 5mm punch biopsy. On the rare occasion when bleeding is not alleviated by a simple pressure, a single, dissolvable haemostatic suture will be used. Women will not experience heavier vaginal loss than would usually be expected following vaginal delivery.

One sample will be snap frozen and the second placed in transport medium. The three samples are then transferred to and processed in the research laboratory. Samples will not be collected if vaginal delivery is not successful or if delivery is achieved without assistance.

Transfer of samples

(see Appendix 6 Transport of Specimens; Standard Operating Procedures Uteroplacental Tissue Bank)

Standard Operating Procedures (SOPs) are available that document the procedure for transport of samples collected into the Uteroplacental Tissue Bank (SOP UCS 07a Transport of specimens to the laboratory - Placental Group; SOP UCS 07b Transport of specimens to the laboratory - Myometrial Group). Tissues are collected from the Operating Theatre or Delivery Suite as soon as they are available. Tissues are collected in a fresh state for further handling in the laboratory.

Tissue samples are regarded as low hazard clinical and biological samples (Category B). A member of staff travels with the samples at all times. All staff are familiar with safe handling procedures, have read and understood the COSHH assessment and are familiar with the route to and from the operating theatres/wards. All staff are aware of the regulations regarding wearing of laboratory coats and protective gloves in the hospital corridors.

After receiving a telephone call regarding availability of specimens to collect, the equipment for collection is retrieved and staff proceed to the Operating Theatre/Delivery Suite. The sample is collected into a sealed plastic container which in turn is placed into a leak-proof bag which is clearly labelled with research group name, location and contact details. Placental and myometrial samples from pregnancy are taken directly to the laboratory. Hysterectomy specimens obtained for samples of non-pregnant myometrium or cervix are taken to the Department of Cellular Pathology for dissection of sample by a trained cellular pathologist

Processing of samples into paraffin wax takes place in the Department of Cellular Pathology, Royal Victoria Infirmary. After 24-48 hours fixation in formalin, specimens are transported to the Department of Cellular Pathology in a sealed plastic container contained within a leak-proof bag, which is clearly labelled with research group name, location and contact details. Samples are collected after processing and transported back to the Reproductive and Vascular Biology Group laboratories.

The main Tissue Bank storage site is on 3rd floor, William Leech Building, Newcastle University. A satellite freezer is located in the basement at the International Centre for Life. Anonymised clinical data will be stored on a secure computer database, linked via a study number to the original data collection sheet which will be kept in a separate location in a locked filing cabinet in a secure room. Copies of the signed patient consent form will be kept in the appropriate study site file within the NHS Trust Reproductive Health & Childbirth Research Team.

From April 2016 there will be members of the Reproductive and Vascular Biology Group based at the International Centre for Life (ICfL) Laboratories. These laboratories are registered under the Newcastle University HTA license (12534) and a dedicated storage facility will serve as a satellite site for the Newcastle Uteroplacental Tissue Bank. This has been agreed with the HTA Person Designate (Professor Susan Lindsay) and HTA co-ordinator (Ms Debbie Jones) for ICfL. All staff are familiar with safe handling procedures and have read and understood the COSHH assessment. All staff are familiar with the route to and from the operating theatres/wards and are aware of the regulations regarding wearing of laboratory coats and protective gloves in the hospital corridors.

Data collected

(see Appendix 3 Sample Information Sheet)

All information collected is linked anonymised. Patient notes will only be accessed for information after consent is taken. Patient age, parity, gravidity, BMI, smoking status and exposure to relevant drugs and hormones will be collected from all individuals. Details of gestational age and pregnancy complications will be collected from all pregnant women. Details of the mode and/or indication for delivery, cervical dilation and infant birth weight will be collected following delivery where appropriate.

Collection of such data is required to define the clinical characterisation of tissue samples and is crucial for investigations pertaining to parturition and pregnancy complications. Reproductive tissue derived from different hormonal, physiological and pharmacological environments cannot be

assumed to have comparable characteristics.

Anonymisation procedures

Samples will be 'linked anonymised' with the clinical data. At the point of tissue collection (following consent) a sample information sheet will be completed by a Trust employee, an individual who holds an honorary contract with The Newcastle Foundation Hospitals NHS Trust or an Approved Individual who has signed a confidentiality agreement.

Samples will be identified using the Trust MRN number only. Research staff do not have access to NHS computers.

Anonymised clinical data will be stored on a secure computer database, linked via a study number to the original data collection sheet which will be kept in a separate location in a locked filing cabinet in a secure room. This system allows the sample to be identified and destroyed should the patient withdraw her consent at a later date. The system in current use is fully compliant with HTA regulations. Copies of the signed patient consent form will be kept in the appropriate study site file (in a locked filing cabinet) within the NHS Trust Reproductive Health & Childbirth Research Team.

Transfer of residual samples to NUTB following completion of an NRES approved study in pregnancy

The Newcastle Uteroplacental Tissue Bank (NUTB) will accept applications from PIs for the storage of human blood, urine and amniotic liquor which have been collected as part of ethically approved research and are surplus to requirements for the original study.

Approval for the acceptance of the samples into the NUTB storage facility will be subject to the following conditions:

- Appropriate storage space is available within NUTB to accommodate the samples.
- Approval for storage will not extend beyond the period for which ethical permission has been given for the retention of associated clinical data.
- The PIS form from used at the point of sample collection must contain information about the intention to store surplus samples in a biobank facility.
- The Consent form used at the point of sample collection must indicate specific consent for transfer of surplus sample to a biobank facility.
- The depositing PI is responsible for delivering the samples in appropriate storage containers.
- Each sample must be uniquely labeled. No patient identifiable data should be included on the label.
- The PI must provide NUTB with a Sample Linkage Spreadsheet in the form of an Excel spreadsheet containing the sample type, sample number and hospital MRN. This information will be transferred to the NUTB database and used to trace the sample in the event of the patient withdrawing consent for storage at a future date.
- The PI must provide NUTB with a paper copy of the Sample Linkage Spreadsheet which includes an ink signature of the PI against each patient to confirm that the patient has given specific consent for the sample to be transferred to a biobank facility. This document will be securely stored with the Patient Information Sheets completed for samples collected by the Biobank.
- The PI will retain responsibility for any clinical data that has been collected associated with the samples. The PI should keep copies of the original consent forms.
- PIs should be aware that applications may be received by the Tissue Bank Committee

from researchers for access to any samples deposited in NUTB. It is unlikely that stored samples would be scientifically useful without the associated clinical data and therefore it is not envisaged that samples would be released to researchers other than the depositing PI in the absence of a collaborative relationship with the depositing PI.

- Applications to withdraw stored samples from the Biobank should be made using the application forms available from the NUTB Manager.

- At the end of the agreed storage period NUTB will arrange for the appropriate disposal of any remaining samples. A new NUTB storage request form should be submitted to the NUTB Committee if an extension to the agreed storage period is sought.

- The PI must agree to cooperate fully with all NUTB requests for information for audit and inspection purposes.

Details of all samples held within the NUTB will be submitted to the Research Ethics Committee and NUTH R&D as part of an annual report

Governance arrangements

Applications for access to samples deposited in the bank will be made to the biobank manager (Dr Paul Ayuk). After determining whether suitable samples are held, the application will be sent to an independent assessment group. These initial assessors will consider the scientific merit of the application as well as the suitability of the applicants to conduct the research. The committee members are;

- The committee will be chaired by Emeritus Professor John Davison (Consultant Obstetrician, Royal Victoria Infirmary). He has over 30 years experience of undertaking obstetric research and delivering clinical obstetric care in Newcastle. He has no conflict of interest being independent of any groups who would be contributing or accessing the Tissue bank.

- A non-clinical research-active scientist within the Faculty of Medical Sciences will oversee the scientific rigor of applications.

- A senior research midwife.

- The Lead Obstetric Consultant on the Delivery Suite at the Royal Victoria Infirmary.

- A Principle Investigator from the Reproductive and Vascular Biology Group (RVBG). The RVBG representative will vary to ensure that no applicant of any proposal under discussion is present. They will be present in a non-voting capacity and will advise as to the technical feasibility of the proposed studies.

Applications to access tissue from the Bank will be submitted on a standard request form (Appendix 4) to the Biobank Manager. It will be this individual's responsibility to initially screen requests to

ensure that the Bank holds suitable tissue samples. In advance of each Governance Committee meeting the co-ordinator will forward applications to committee members along with a report of currently held tissue stocks to the chairman. Once removed from the bank a sample will not be returned to the storage facility with the exception of frozen and paraffin sections (in keeping with routine pathology practice).

The Biobank Manager will submit an annual report to the Ethics Committee and Newcastle Hospitals NHS Foundation Trust R&D including:

- Numbers of each sample type collected
- Summary information of all applications made to the Bank along with the protocols of successful applications.
- Reports from completed studies.
- Numbers of tissue samples released
- Summary of currently held samples

Responsibilities of successful applicants

Approved projects will not require separate R&D Trust Approval or Caldicott Approval providing the project does not require collection of any additional samples or data. The PI of the approved project must submit a brief report to the Governance Committee on completion of the study and is encouraged to acknowledge the Newcastle Uteroplacental Tissue Bank in any associated publications. The PI must cooperate with audit requests made by the Tissue Bank Governance Committee (e.g. sample tracking).

Appendices

Appendix 1: HTA license

Appendix 2: Sample information sheet

Appendix 3: Request to perform research using samples collected as part of the Newcastle Uteroplacental Tissue Bank

Appendix 4: Request to transfer samples for storage into the Newcastle Uteroplacental Tissue Bank

Appendix 5: Newcastle Uteroplacental Tissue Bank SOP UCS07a and UCS07b: Transport of specimens to the laboratory

Appendix 6: Newcastle University Human Tissue Act - Research Sector HTA-SOP-07: The Transfer of Human Material into and out of Newcastle University under the Newcastle University HTA research licence (Ref. 12534)

Reproductive and Vascular Biology Group Tissue Collection

Date of sample collection…… Hospital Number……..

Gestation (wk + day)…….. Age…….

Gravidity ……. Parity…….. Height …….Weight ……BMI …….

Ethnicity …… Term BMI……..

Birthweight ……M / F Smoker: True ☐ False ☐

Birth Centile ……

Samples collected:

- Placenta ☐
- Amnion/chorion ☐
- Placental bed ☐
- Myometrium Upper ☐ Lower ☐
- Cervix ☐

Delivery:

Vaginal delivery ☐ Elective CS ☐ Indication……

Emergency CS ☐ Dilatation…….cm) Indication……..……

Hysterectomy ☐ LMP …… Indication……

TOP ☐

Drugs:

Prostaglandin	True	☐	False	☐
Oxytocin	True	☐	False	☐
Steroids (within 48h)	True	☐	False	☐
Tocolytic (within 48h)	True	☐	False	☐
Progesterone	True	☐	False	☐
GnRH analogue	True	☐	False	☐

Other medical conditions: Preclampsia ☐ Diabetes ☐

Prolonged ROM Infecti ☐

Consent:

I confirm that this patient has given informed written consent for this sample

True ☐ False ☐

Signed……Print name……

Thank you for filling in this form

Please ring RVI Ext 28956 or RVI Ext 24132 for sample collection

Human Tissue Authority

Licensing Number **12534**

Licensed Premises

Newcastle University
The Medical School
Framlington Place
Newcastle Upon Tyne
NE2 4HH

Licence Holder **Newcastle University**

Designated Individual **Andrew G Hall**

This licence is granted under Section 16 (2) (e) (ii) of the Human Tissue Act 2004.

This licence authorises the storage of relevant material which has come from a human body for use for the following scheduled purposes:

- Determining the cause of death
- Establishing after a person's death the efficacy of any drug or other treatment administered to him
- Obtaining scientific or medical information about a living or deceased person which may be relevant to any other person (including a future person)
- Puolic display
- Research in connection with disorders, or the functioning, of the human body
- Clinical audit
- Education or training relating to human health
- Performance assessment
- Public health monitoring
- Quality assurance

The licensed activity should be carried on only at the licensed premises specified above, and under the supervision of the Designated Individual.

This licence is subject to the conditions set out in the Annexes accompanying this licence as may be subsequently varied pursuant to an application under paragraph 8 of Schedule 3 to the Human Tissue Act 2004.

This licence is valid from the date specified below and will remain in force until revoked.

Shirley Harrison
Chair

Dr. Sandy Mather
Director of Regulation

Dated **22 September 2009**

Request to perform research using samples collected as part of the Newcastle Uteroplacental Tissue Bank

Background

Approval has been obtained from Newcastle and North Tyneside Research Ethics Committee 1 (Ref:16/NE/0167~~10/H0906/71~~) to perform research on samples collected as part of the Newcastle Uteroplacental Tissue Bank without the need to obtain specific consent for individual projects. However, it is a condition of this approval that details of the projects included are submitted to the Research Ethics Committee as part of an annual report when they will be reviewed to ensure that they fall within the remit described in the accompanying protocol (Biological studies of reproductive disorders using samples from the Newcastle Uteroplacental Tissue Bank Version ~~3.1~~7). In order to do this please complete the sections below and send this form by e-mail to Dr Paul Ayuk (paul.ayuk@nuth.nhs.uk). Applications will be considered by a committee convened to judge the merits of the proposed research. Every effort will made to decide on the suitability of projects within 4-6 weeks. If access to samples is denied the reasons for this will be explained in writing.

Studies which are eligible will be expected to apply for CLRN portfolio status.

Please note that results of laboratory investigations covered by this protocol specifically exclude any which would be used to influence the treatment of individual patients. Experiments involving the use of animals are also specifically excluded.

Contact details

Name of Principal Investigator	
e-~~-~~mail	
Telephone	
Address	

Project details

Title of project	
Source and amount of funding	
Details of peer review (eg research committee, funding body).	
Eligible for CLRN portfolio adoption?	

Abstract (no more than 500 words). Please attach your research protocol.

Sample details

Number and specimen type required	
Please justify, including details of power calculations where performed.	

Request to transfer samples into the Newcastle Uteroplacental Tissue Bank

Background

Approval has been obtained from Newcastle and North Tyneside Research Ethics Committee 1 (Ref:~~10/H0906/71~~ 16/NE/0167) to store samples of urine, blood, amniotic liquor and cervical fluid collected as part of an ethically approved study, but surplus to requirements of the original study, in the Newcastle Uteroplacental Tissue Bank. However, it is a condition of this approval that details of the transferred samples are submitted to the Research Ethics Committee as part of an annual report when they will be reviewed to ensure that they fall within the remit described in the accompanying protocol (Biological studies of reproductive disorders using samples from the Newcastle Uteroplacental Tissue Bank Version 74). In order to do this please complete the sections below and send this form by e-~~-~~mail to Dr Paul Ayuk (paul.ayuk@nuth.nhs.uk). Applications will be considered by the Newcastle Uteroplacental Tissue Bank convened to judge the feasibility of sample storage. Every effort will made to decide on the storage availability within 4-6 weeks. If storage is denied the reasons for this will be explained in writing. Successful applicants must comply with the conditions specified in the NUTB protocol and a charge may be levied to cover administration and laboratory costs.

Contact details

Name of Principal Investigator	
e-~~-~~mail	
Telephone	
Address	

Original study details

Title	
Approving REC and project reference	
CLRN portfolio study?	Y / N
Study finish date	
Duration of ethical approval for retention of clinical data beyond study end point.	

Abstract (no more than 500 words). Please attach your research protocol including details of sample preparation and a copy of the PIS and consent form (specific consent must have been given for transfer of samples to a tissue bank storage facility)

Sample details

Number and specimen type	
Storage conditions required	
Samples to be deposited in single episode (preferred) or as collected (please state estimated frequency and volume of each deposition)	

Transport of specimens to the laboratory – Myometrial Group

1.0 Purpose and scope

Tissue samples may be collected from patients for research purposes. Tissues should be collected from the Operating Theatre/Delivery Suite as soon as they are available after notification from the Operating Theatre/Delivery Suite staff. Tissues will usually be collected in a fresh state for further handling within the laboratory.

Fresh tissues may be rapidly frozen directly into liquid nitrogen (with cryoprotection) in liquid nitrogen cooled isopentane. Fresh tissues may be subjected to enzyme digestion for cell purification, dissected for storage for protein and RNA extraction or dissected for functional studies.

2.0 COSHH / Health & Safety

Tissue samples should be regarded as low hazard clinical and biological samples (Category B).

This SOP refers only to collection of samples from the RVI operating theatres or delivery suite to be transported to the ICfL. A member of staff will travel with the samples at all times.

Appropriate BIOCOSHH assessment should be completed because of the risk of exposure to unfixed tissues.

Ensure that all staff are familiar with safe handling procedures and have read and understood the COSHH assessment.

Ensure that all staff are familiar with the route to and from the Operating Theatres/Delivery Suite.

Ensure that all staff are aware of the regulations regarding wearing of laboratory coats and protective gloves in the hospital corridors.

3.0 Equipment / reagents

- Primary container: watertight sealed opaque plastic container.
- Secondary container: Clean, sealed polythene bag
- Outer container: sealed leak-proof bag which is clearly labelled with research group name, location and contact details.

4.0 References

4.1 HTA
4.2 University/Faculty Policy
4.3 Delivery Suite, Obstetrics, Royal Victoria Infirmary
4.4 Royal Victoria Infirmary Guidelines for Transport of Specimens

5.0 Procedure

Collection of Specimens from Operating Theatre in Delivery Suite and Transport to Reproductive and Vascular Biology Group laboratories ICfL

1. Receive telephone call regarding availability of specimens to collect from Operating Theatre/Delivery Suite.
2. Retrieve equipment for collection and proceed to Operating Theatre/Delivery Suite.
3. Collect sample with the sample information sheet
    a. **The sample information sheet must be collected with the sample**
    b. **Do not accept a sample unless there is a sample information sheet**
    c. **Check that the consent is documented on the front of the sample information sheet**
    d. **For Termination of Pregnancy (TOP) samples check that the back of the form has been signed by the surgeon**
4. Place the sample into a sealed plastic container. Place the sealed plastic container into a polythene bag and seal. Place polythene bag containing the specimen into leak- proof bag which is clearly labelled with research group name, location and contact details.
5. Take the specimen to RVBG laboratory 3rd Floor Leech Building to be assigned a Biobank number.
6. Phone colleague at ICfL to inform them of your intention to return with the specimen.
7. Return directly to ICfL Laboratory.

6.0 Site Specific Details

Personnel:	Staff and students within Reproductive and Vascular Biology Group, Institute of Cellular Medicine
Location:	Operating Theatres and Delivery Suite, Royal Victoria Infirmary
Transport to:	Reproductive and Vascular Biology Group Laboratories 3rd Floor Leech Building
Induction:	All are provided with a written protocol with safety details. Demonstration is given with continuing supervision as necessary.

Transport of specimens to the laboratory – Placental Group

1.0 Purpose and scope.

Tissue samples may be collected from patients for research purposes. Tissues should be collected from the Operating Theatre as soon as they are available after notification from the Operating Theatre staff. Tissues will usually be collected in a fresh state for further handling within the laboratory.

Tissues may be fixed in formalin for 24-48 hours and subsequently processed into paraffin wax blocks.

Fresh tissues may be rapidly frozen directly into liquid nitrogen or (with cryoprotection) in liquid nitrogen cooled isopentane. Fresh tissues may be subjected to enzyme digestion for cell purification and subsequent storage for protein and RNA extraction.

Tissues may be transported to the Department of Cellular Pathology for processing into paraffin wax.

After use tissues may be transported to the Department of Cellular Pathology for disposal.

2.0 COSHH / Health & Safety

Tissue samples should be regarded as low hazard clinical and biological samples (Category B).

This SOP refers only to collection of samples from the RVI operating theatres or delivery suite to be transported to the Leech Building. A member of staff will travel with the samples at all times. This SOP is not appropriate for transport of samples between local sites that involves transport outside of the building eg Centre for Life/Freeman Hospital to the Medical School.

Appropriate BIOCOSHH assessment should be completed because of the risk of exposure to unfixed tissues.

Ensure that all staff are familiar with safe handling procedures and have read and understood the COSHH assessment.

Ensure that all staff are familiar with the route to and from the operating theatres/wards.

Ensure that all staff are aware of the regulations regarding wearing of laboratory coats and protective gloves in the hospital corridors.

3.0 Equipment / reagents

- Primary container: watertight sealed opaque plastic container.
- Outer container: sealed leak-proof bag which is clearly labelled with research group name, location and contact details.
- Clean polythene bags.

4.0 References

4.1 HTA
4.2 University/Faculty Safety Policy
  4.2.1 Internal transport of biological/clinical samples to university laboratories
  4.2.2 Biological transport of category B biological agents
4.3 Royal Victoria Infirmary Guidelines for Transport of Specimens
4.4 Department of Cellular Pathology, Royal Victoria Infirmary

5.0 Procedure

Collection of Specimens from Operating Theatre

1. Receive telephone call regarding availability of specimens to collect from Operating Theatre/Delivery Suite.
2. Retrieve equipment for collection and proceed to Operating Theatre/Delivery Suite.
3. Collect sample with the sample information sheet
   - **The sample information sheet must be collected with the sample**
   - **Do not accept a sample unless there is a sample information sheet**
   - **Check that the consent is documented on the front of the sample information sheet**
   - **For Termination of Pregnancy (TOP) samples check that the back of the form has been signed by the surgeon**
4. Place the sample into a sealed plastic container.
5. Place sealed plastic container into leak-proof bag which is clearly labelled with research group name, location and contact details.

For placental samples

6. Return directly to Laboratory.

For samples of non-pregnant myometrium or cervix

6. Take sample to Department of Cellular Pathology for dissection of sample by trained cellular pathologist

Transport of Specimens to Department of Cellular Pathology for processing

1. For processing into paraffin, after 24-48 hours fixation in formalin, transport specimens in a sealed plastic container contained within a leak-proof bag, which is clearly labelled with research group name, location and contact details, to the Department of Cellular Pathology.
2. Specimens will be processed in this accredited pathology laboratory.
3. Collect specimens as arranged after processing.

6.0 Site Specific Details

Personnel: Staff and students within Reproductive and Vascular Biology Group, Institute of Cellular Medicine

Location: Reproductive and Vascular Biology Group Laboratories 3rd Floor Leech Building

Induction: All are provided with a written protocol with safety details. Demonstration is given with continuing supervision as necessary.

STANDARD OPERATING PROCEDURE NUMBER:		HTA-SOP-07 v.1	
HUMAN TISSUE ACT – RESEARCH SECTOR			
TITLE	The Transfer of Human Material into and out of Newcastle University under the Newcastle University HTA research licence (Ref. 12534)		
AUTHOR	**Name and role**	Mhairi Anderson Quality Assurance and Development Manager	
	Signature & Date	19 Mar 2015	
APPROVER	**Name and role**	Professor Andy Hall Designated Individual, Newcastle University Research HTA licence (Ref: 12534)	
	Signature & Date	18/3/15	
EFFECTIVE DATE:	1st April 2015	**REVIEW DATE:**	1st April 2017

Distribution

This document will be retained in the following locations:

- Human Tissue Act VRE (https://researchtools.ncl.ac.uk/portal).
- Newcastle Joint Research Office Website (www.newcastlejro.org.uk)

Change control

To request any changes to this document please submit a change request using the following form, in accordance with HTA-SOP-8 "Change Control". http://forms.ncl.ac.uk/view.php?id=6528

Revision Category

Category 1	This is a new/revised document. All personnel required to follow content must read this version and complete training	
Category 2	This is a revised document in which only the area of applicability has changed. All newly impacted personnel required to follow content must read this version and complete training	
Category 3	This is a new/revised document. All personnel required to follow content must read this version	✓
Category 4	No significant change to document content – no requirement to read or train	

Note: As applicable, documentation of reading and/or training must be completed prior to performing the procedure.

1. BACKGROUND

The Human Tissue Act (HTA) is a legal framework which regulates the "removal, storage, use and disposal of human bodies, organs and tissues". The Act came into effect on the 1st September 2006 and applies to England Wales and Northern Ireland.

To ensure compliance with the terms of the Act it is a HTA requirement to have documented policies and procedures in place for the distribution of bodies, body parts, tissues or cells. These procedures must protect the quality and integrity of human material during transport and delivery to a destination and protect the safety of all personnel coming into contact with the material. This includes:

- Risk assessment for transportation, including a system to ensure that traceability of relevant material is maintained during transportation
- Environmental controls must be in place to avoid potential contamination and ensure safety. Staff must be provided with appropriate protective equipment/facilities and procedures that minimise risk.
- The maintenance of an audit trail which details when and where the bodies/body parts were put, when the bodies/body parts were transferred and to whom.
- Records of transportation and delivery including transfer agreements with recipients of relevant material. In accordance with the Act, and Code of Practice 9 for Research (section 112):

> *"If human tissue is transferred between establishments consideration must be given to minimising the likelihood of theft, damage or loss during transport. Some form of formal arrangement, for example, as part of a Material Transfer Agreement (MTA) should define how the human tissue is preserved, any potential contamination risks associated with it and who is responsible for disposal if applicable"*

This SOP sets out the procedures that must be conducted under the Newcastle University research HTA licence (ref. 12534) when transferring/distributing material.

2. SCOPE

This SOP applies to all personnel involved in research activities under the Newcastle University Research Human Tissue Act licence (Ref. 12534) responsible for the transfer of "relevant material" as defined by the HTA, independent of whether the material has research ethical approval for use, or not.

This SOP does not apply to material out-with the scope of the Human Tissue Act (i.e. non-relevant material); however it is good practice to manage all human material according to the same procedure.

3. DEFINITIONS

DI	Designated Individual
HTA	Human Tissue Act
PD	Person Designate
QADM	Quality Assurance and Development Manager
SOP	Standard Operating Procedure
MTA	Material Transfer Agreement
Non-relevant material	Material out-with the scope of the Human Tissue Act
Relevant Material	Material within the scope of the Human Tissue Act, and defined as "Material other than gametes, which consists of or includes human cells"
REC	Research Ethics Committee
RTB	Research Tissue Bank
VRE	Virtual Research Environment
NJRO	Newcastle Joint Research Office
G&C	Grants and Contracts
SLA	Service Level Agreement
R&D	Research and Development
IP & Legal	Intellectual Property and Legal Services Department

4. PROCEDURE

The procedure for managing transfer agreements is set out in section 4.1. Once a transfer agreement has been finalised, the material can be transferred into our out of Newcastle University. The arrangements for sample transportation and safety are described in section 4.2.

Sample tracking during the transfer process, and receipt are described in section 4.3 and 4.4 respectively.

4.1. TRANSFER AGREEMENTS

If a member of staff at Newcastle University wishes to transfer human material in to, or out of the University from another establishment (i.e. external transfers), some form of formal transfer agreement is required to maintain traceability of the samples during transfer, document the terms and conditions of the transfer and any key responsibilities.

For internal transfers (i.e. within Newcastle University) transfer agreements are not required. However, materials should be transferred in accordance with local Health and Safety procedures and packaged accordingly. For further information please refer to the Safety Office website: http://safety.ncl.ac.uk/transportofbiologicalhazards.aspx

At Newcastle University, the main type of transfer agreement which is used to establish arrangements for transfers to other establishments is called a "Material Transfer Agreement", or MTA.

Material Transfer Agreements are described in section 4.1.1. Alternatives transfer agreements, or

cases where MTAs may not be required, are described in section 4.1.2.

4.1.1 Material Transfer Agreements (MTAs)

A Material Transfer Agreement (MTA) is a legal contract that governs the transfer/exchange of tangible research material between two organisations, where the researcher wishes to use the material for their own research purposes.

This legal document is important as it clearly defines the rights of the parties in respect to scope of use of material, confidentiality, publication, and ownership of Intellectual Property. In addition, in compliance with the Human Tissue Act and associated Codes of Practice, this aims to protect the material from theft, damage or loss, and clearly establish the terms of the transfer.

There are two types of MTA

1. **Incoming MTA -** For material coming INTO Newcastle University from another establishment/organisation
2. **Outgoing MTA -** For material going OUT of Newcastle University to another establishment/organisation

The process required to organise both an incoming, or outgoing MTA is provided below in sections 4.1.1.1 and 4.1.1.2 respectively, and Figure 1.

In addition, a summary of the information required when setting up a MTA, is provided in section 4.1.1.3. Instances where an MTA may not be required are set out in section 4.1.1.4.

4.1.1.1. Incoming MTA

If a researcher wishes to receive tissue into Newcastle University from an external organisation, they must submit the "Incoming MTA" questionnaire on the Newcastle Joint Research Office website. http://forms.ncl.ac.uk/view.php?id=1682

This form asks the Principle Investigator to detail the proposed transfer, including:

When setting up a MTA the following information is usually required to arrange the transfer:

1. Contact details: for the sending establishment and intended recipients at Newcastle University.
2. Details of the Material: what it is; how much is required, and safety information (e.g. contamination issues).
3. Details of what the Material is going to be used for - A brief outline of research plan, including confirmation of ethical approval to use the tissue, where appropriate).

4. Details of the research funder for the use of the Material including associated reference numbers?
5. Details of whether the research using the Material is likely to lead to a patent application/commercial exploitation
6. Details of where the material is going to be stored e.g. copy of HTA licence for the premises, where appropriate.
7. Details of what is to happen when the study is completed e.g. on completion of research using tissue from a REC approved research tissue bank, the individual researcher must either:
    a. transfer the tissue back into the bank, or to an alternative HTA-licensed establishment
    b. apply for their own HTA licence
    c. apply for specific project approval by a Research Ethics Committee (REC)
    d. dispose of the human tissue.
8. Copy of any MTA provided by the sending organisation - Typically, the sending organisation provides an MTA template to be completed. If this has been provided, this may also be attached to the form.

4.1.1.2. Outgoing MTA

If a researcher wishes to transfer material out of Newcastle University to an external organisation, they must submit the "Outgoing MTA" questionnaire on the Newcastle Joint Research Office website. http://forms.ncl.ac.uk/view.php?id=1698

This form asks the Principle Investigator to detail the proposed transfer, including:

- Details of the organisation the material is to be transferred to
- Material type/details
- Collaborator details and research outcomes

4.1.1.3. Submitting a MTA request

Once a researcher has completed all required forms on either the incoming or outgoing MTA form, they should submit the form for review.

Completed forms are received to the Grants and Contracts (G&C) team in the Newcastle Joint Research Office, who manage contracts on researcher's behalves.

For any support or advice with your MTA, please contact the G&C team using the details on the NJRO website (www.newcastlejro.org.uk).

4.1.1.4. Completing an MTA

When setting up a new MTA, a number of different formats may be used. These may be project or research tissue bank specific, or a generic template.

The Grants and Contracts team will negotiate with the sending/receiving organisation to establish an appropriate MTA to be used.

Regardless of the template used, it is important that:

- The terms of the MTA are agreed, and the MTA is signed by both parties before the transfer can take place.
- Signatories should be authorised legal signatory of the party i.e. for Newcastle University this must be an individual authorised/from the Research and Enterprise Services.
- MTAs should not include payment for the material, other than the reimbursement of transport costs or any other reasonable costs associated with the collection of the tissue. Essentially, tissues should not be sold for profit.
- Before any material is transferred between institutions a risk assessment should be conducted for transportation by the person responsible for arranging the transfer, including consideration of maintaining the integrity and traceability of the material during transportation, and safety.

It should be noted that although the exchange of research material between academic institutions is generally relatively straightforward, issues relating to confidentiality, publications and intellectual property may need to be negotiated, in particular if a commercial organisation is involved in the research. Any negotiations should therefore be managed by the University's legal team, or the Newcastle Joint Research Office.

A signed copy of the MTA should be retained by each party and may be requested during regulatory audits (e.g. Human Tissue Act) as evidence that the terms of the transfer have been formally agreed.

The process for establishing an incoming or outgoing MTA is summarised in Figure 1.

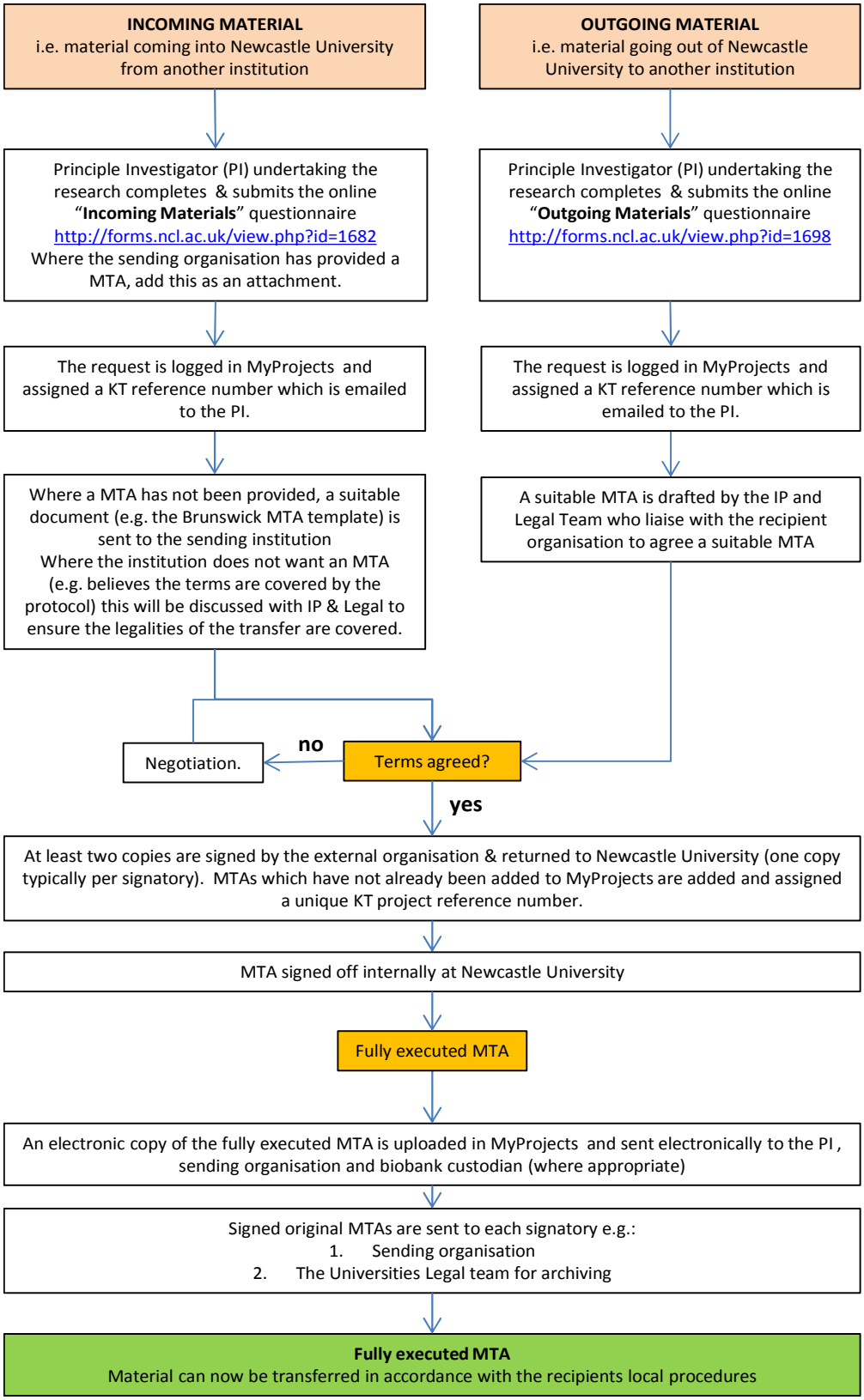


Figure 1: Transfer of materials under a Material Transfer Agreement (MTA)

4.1.2. Alternative arrangements for sample transfer

In some instances, it may be believed by the sending or receiving institution that the terms of the transfer of a material may be covered by another formal agreement e.g. a collaboration agreement, tri-partite agreement or protocol.

In these instances researchers must be confident that the arrangement considers the minimisation of the likelihood of theft, damage or loss during transport, and should define how the human tissue is preserved, and any potential contamination risks associated with it and who is responsible for disposal if applicable.

Please contact the Grants and Contracts team for advice. For contact details, please see: www.newcastlejro.org.uk

In the past at Newcastle University, documents called Service Level Agreements (SLAs) were used. Although new versions of these documents are not typically used now (MTAs used in preference), the procedure for pre-existing SLAs is summarised below.

4.1.2.1. Service Level Agreements (SLAs)

Service Level Agreements (SLAs) which have been established in the past, are now managed via the Intellectual Property (IP) & Legal services team. Signed copies of these SLAs are retained by the legal team, in MyProjects, and by the 3rd party institution.

Should any changes wish to be made to these documents; the researcher will be referred to the IP & Legal services team for advice.
http://www.ncl.ac.uk/res/about/office/intellectual/

To track the movement of any material under these broad SLAs, the Research & Development (R&D) team in the Newcastle Joint Research Office ask researchers to complete a "Service Level Agreement Monitoring Form" to track the movement of tissue (see Appendix 1). These completed forms are added to study files, and retained to monitor sample movement. A copy can also be found on the HTA VRE.

4.2. SAMPLE TRANSPORTATION AND SAFETY

Once a transfer agreement has been formally agreed, the material can be transported into our out of Newcastle University.

Material which poses a biological hazard, such as human tissue, is required by law to be transported in a safe and contained manner to prevent contamination or exposure to infectious substances.

Researchers interested in transporting biological materials should contact their Schools Biological Safety Supervisor or School Safety Officer in the first instance and refer to the Newcastle University Safety Office Website:
http://safety.ncl.ac.uk/transportofbiologicalhazards.aspx.

A summary of the safety requirements is provided below however all staff should refer to the Safety Office website for full information.

There are 2 categories of infectious biological agents:

Category A	An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life threatening or fatal disease to humans or animals.
	Classified as code: **UN 2814**
	For example: Poliovirus or rabies virus (cultures only) or Ebola virus. A full list of UN2814 materials can be found on the USO website under Biotransport tab
	Only personnel who have attended approved IATA/ICAO course and passed examinations can handle and package these substances. Staff who do not hold or do not wish to obtain accreditation are advised to use an approved Category A courier that will package samples on your behalf
Category B	Any infectious substance that does not meet the criteria for inclusion in Category A.
	Classified as code: **UN 3373**
	Only personnel who are aware of the regulations and correct packaging requirements and have completed relevant forms for transportation can handle and package these substances.

As nearly all the relevant material sent out of, or brought into the University falls in to "Category B" the transport requirements for Category B material is provided below in section 4.2.1.

Exemptions to these rules may apply are summarised in section 4.2.2.

4.2.1. Transport of Category B Material

For category B (UN 3373) material only approved/tested packaging must be used in accordance with International Air Transport Association (IATA) packaging instruction 650, which can be found on the following website:

http://www.iata.org/whatwedo/cargo/dgr/Pages/infectious_substances.aspx

A copy of this packing instruction is also attached in Appendix 2.

The Royal Mail/Parcel Force may be used for Category B Biological Substances only, and NOT for category A materials. A guidance document for the transport of infection substances can be found at the following link:

http://www.royalmail.com/sites/default/files/Guidance-Document-Infectious-Substances-171012.pdf

A figure taken from this guidance document demonstrating how Category B material should be packaged is found in Appendix 2 of this document.

4.2.2. Biological transport exemptions

An element of professional clinical judgment is required to determine if a substance is exempt from the transport arrangements set out in 4.2.1, for example, in cases where there is minimal likelihood of pathogens.

Examples of biological materials which are exempt from these transport arrangements include:

- Non-pathogenic micro-organisms or neutralized / inactivated pathogens
- Environmental samples, including "harmless" food and water samples
- Dried blood spots, collected by applying a drop of blood onto absorbent material, or faecal occult blood screening tests
- Blood or blood components collected for the purposes of transfusion
- Patient specimens for which there is minimal likelihood that pathogens are present

In these instances materials should be transported in packaging which will prevent any leakage and which is marked with the words "Exempt human specimen".

A figure taken from the IATA infections substances guidance document demonstrating the packaging and marking of exempt material is found in Appendix 3 of this document.

4.3. SAMPLE TRACKING

To ensure an audit trail is maintained for any material being transferred between two institutions, local sample tracking records (e.g. Access or Excel Database, or bespoke software) should be updated with the details of when and where the bodies/body parts were put, when the bodies/body parts were transferred and to whom

Records of transportation and delivery should also be retained as evidence (e.g. waybill numbers, emails confirming satisfactory receipt by the other institution). In addition, for imported/exported tissue, documentation of the consignment should be retained for at least 5 years after disposal of the last part included in the consignment.

When a transfer agreement expires any remaining material should be managed in accordance with the terms agreed in the original transfer agreement.

4.4. SAMPLE RECEIPT

Samples should only be accepted into a laboratory if they have been packaged and labelled appropriately. Therefore all collaborators should be informed that they must send packages in accordance with UN3373 regulations.

All personnel should be provided with suitable personal protective equipment (e.g. gloves, lab coats, safety cabinets) and be suitably trained to handle the material. Where appropriate, risk assessments should be in place for transportation, including a system to ensure that traceability of relevant material is maintained during transportation, and suitable safety measures are in place when receiving samples.

In instances where a package is not clearly labelled or the risks are unknown, the packages should not be opened and should be placed in a quarantine area and more information sought. If in doubt, researchers should contact the University's safety team for advice.

Materials should only be used in accordance with the terms and conditions set out in the transfer agreement (where appropriate) and stored appropriately.

5. DOCUMENT REVISION HISTORY

Section affected	Description of changes	Reason for change
All	New SOP code – HTA replacing NBB This SOP replaces NBB-SOP-07.v1	Due to the rebranding of the Newcastle Biomedicine Biobank, any reference to NBB is being removed. Reference will now be made to the Newcastle University HTA licence, with HTA as the new SOP code. All NBB quality documents will now be reissued under the new code "HTA" and issued as version 1. Version history can be tracked on the SOP document log.
Cover	Change of website link to Newcastle Joint Research Office website, to take you to the home page, rather than human tissue page	Due to a redesign of the NJRO website, and future proofing should things be moved around
Background	Formatting. To include box around the quote from the HTA regulations. Removal of second half of last sentence	To make this stand out for the reader and remove duplication.
Definitions	Addition of DI, HTA, QADM, VRE, NJRO and G&C. Removal of SLA	Due to new procedure which now involves new terminology and removal of use of SLAs
4.1. and 4.1.2	Removal of all references to Service Level Agreements throughout	SLAs are no longer in use and MTAs are the standard transfer agreement used.
4.1.1.	Rewording and separation in to different sections 4.1.1.1 Incoming MTAs 4.1.1.2. Outgoing MTAs 4.1.1.3. Submitting MTAs	Clarification of the MTA process following feedback from PIs.

Section affected	Description of changes	Reason for change
	4.1.1.4. Completing MTAs	
4.1.2	Removed from previous version "SLAs"	SLAs are no longer in use and MTAs are the standard transfer agreement used
4.1.3.	Information required when establishing a transfer agreement removed from here and added to section 4.1.1. "Incoming MTAs"	This information did not flow in the previous version. Moved to a more logical order.
4.2.	Addition of introductory sentence introducing topic and linking back to previous section	To indicate where the sequential steps required.
4.3	Reworded	Minor rewording to make the information flow
Appendices	Addition of Service Level Agreement Monitoring Form as appendix 1	Missing in last version

6. REFERENCES

Human Tissue Act
http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1

HTA Relevant Materials
http://www.hta.gov.uk/_db/_documents/Supplementary_list_of_materials_200811252407.pdf

HTA – Code of Practice 9 Research
http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code9research.cfm
Newcastle Joint Research Office website: http://www.newcastlejro.org.uk/research-governance/research-involving-human-tissue-3/newcastle-biomedicine-biobank/

The Human Tissue Authority www.hta.gov.uk

Questionnaire for incoming material to Newcastle University:
http://forms.ncl.ac.uk/view.php?id=1682

Questionnaire for outgoing material from Newcastle University:
http://forms.ncl.ac.uk/view.php?id=1698

7. APPENDICES

7.1. Appendix 1 - Service Level Agreement Monitoring Form

The Newcastle upon Tyne Hospitals NHS Foundation Trust and the University of Newcastle

SERVICE LEVEL AGREEMENT (SLA) - MONITORING FORM

This form tracks the movement of human tissue classed as "relevant material" under the Human Tissue Act (2004) under the Service Level Agreement in place between The Newcastle Upon Tyne Hospitals NHS Foundation Trust and Newcastle University.

REC number:	
R&D Ref. No:	**[Ref No.]** [Project Title]
Recipient details at Newcastle University:	Name: Address: Email: Telephone:
Provider: *Trust group that are providing the samples to the University*	Name: Address: Email: Telephone:
Relevant Material*: *Please provide details of the material being transferred*	
Physical storage location of tissue in University: *Please indicate where the material is to be stored at the University. Where multiple locations are to be used, please indicate this on the form* *PD = Person Designate named on the on the Human Tissue Act licence*	**TISSUE BANK?**

Central Biobank, Medical School PD: Dr Amy Peasland	☐	**Institute of Genetic Medicine, Centre for Life** PD: Prof. Susan Lindsay	☐
Paul O'Gorman Building, NICR PD: Dr Zoe Davison	☐	**Human Nutrition Research Centre** School of Agriculture, Food and Rural Development PD: Wendy Bal	☐
Musculoskeletal Medical School, ICM PD: Tim Williamson	☐	**Uteroplacental** Medical School, ICM PD: Barbara Innes	☐
Centre for Ageing and Vitality (CAV) PD: Dr Chris Morris	☐	**Respiratory, Freeman Hospital** Dr Chris Ward	☐
Mitochondrial Research Group Medical School, ICM PD: Debra Jones	☐	**Dental School** PD: Prof. Philip Preshaw	☐
Dermatology Medical School, ICM PD: Carole Todd	☐	**Haematology** Medical School, ICM PD: Prof. Anne Dickinson	☐

Form 004 – Service Level Agreement (SLA) Monitoring Form - Version 4 Page 1 of 2

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

	REC APPROVED RESEARCH TISSUE BANK? **Title of research tissue bank:** | **REC number:** | **Location of storage:** | **Curator:** | For a full list of research tissue banks at Newcastle University, please refer to http://www.newcastlejro.org.uk/research-governance/research-involving-human-tissue-3/newcastle-biomedicine-biobank/ **OTHER:** Where the material is not to be transferred to a biobank or research tissue bank, please provide information on the location: **TO BE ARRANGED?** ☐
Date of transfer: *If multiple dates, this should be recorded in study files*	

NOTE TO RESEARCHERS

When the REC approval for this study expires, it is the responsibility of the researcher to either:

- Apply for an extension of the REC approval to continue to store the material
- Transfer the material to a biobank for storage under the Human Tissue Act (2004)
- Dispose of the material

This must be conducted in full consideration of donor wishes and the terms set out in the original REC approval.

ONCE COMPLETED PLEASE SUBMIT A COPY OF THIS FORM TO:

- Trust R&D, Joint Research Office, Level 6 Leazes Wing, Royal Victoria Infirmary or electronically: (Trust.R&D@nuth.nhs.uk), and
- The recipient identified on page 1, and
- The Person Designate and curator or biobank manager

NEED HELP?

*For a definition of a relevant material under the Human Tissue Act (2004) please refer to: http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/definitionofrelevantmaterial.cfm

If you have any questions regarding this form, the Human Tissue Act, or the process of tracking samples under the Service Level Agreement please contact either the:

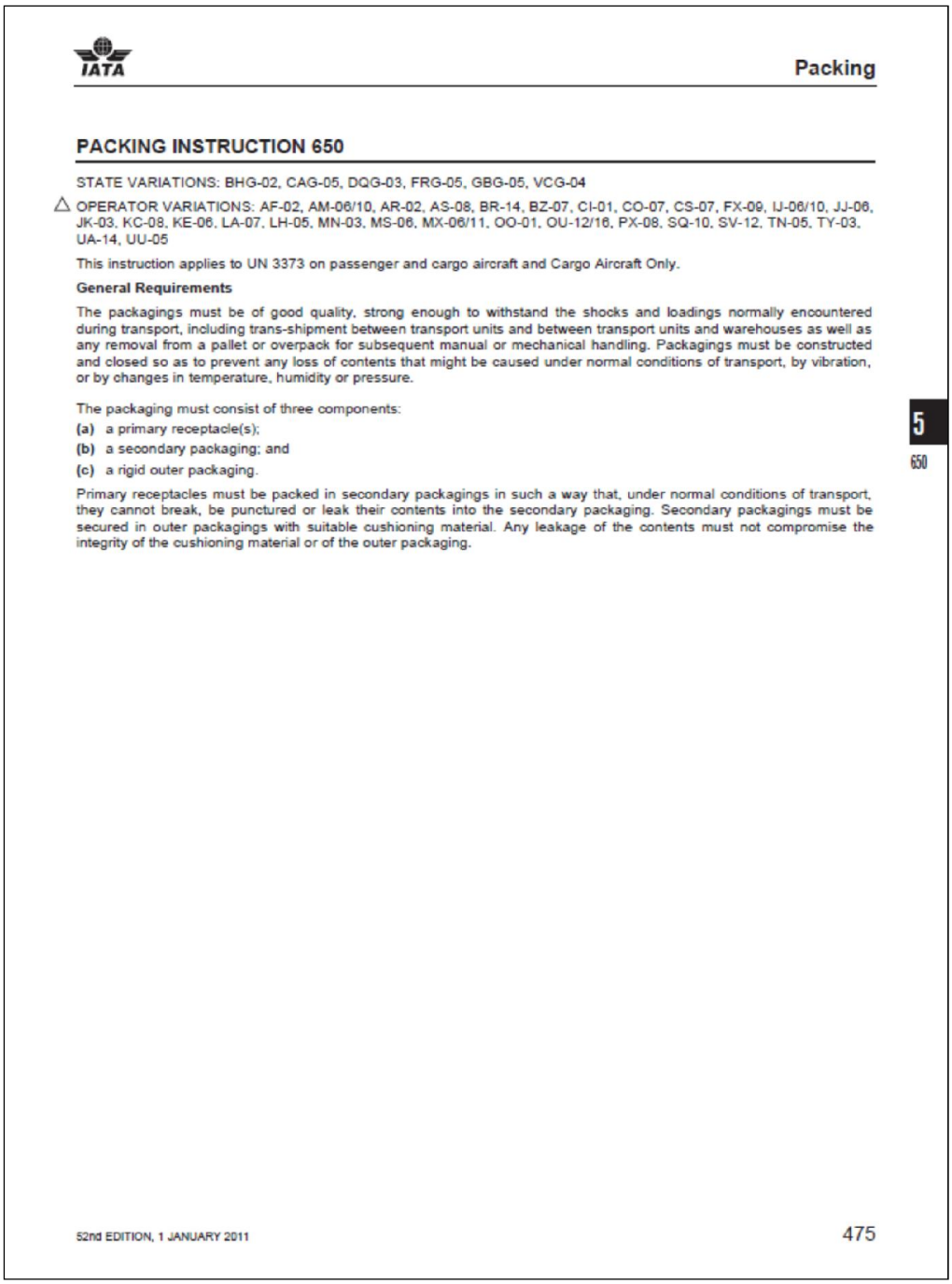
Newcastle Joint Research Office
http://www.newcastlejro.org.uk/contact/
Telephone: 0191 282 5959

Quality Assurance Manager for the Newcastle Biomedicine Biobanks at Newcastle University
http://www.ncl.ac.uk/nbb/staff/
Telephone: 0191 282 5501

Form 004 – Service Level Agreement (SLA) Monitoring Form - Version 4 Page 2 of 2

7.2. APPENDIX 2 - International Air Transport Association (IATA) Packing Instruction 650

For the most up-to-date version of this instruction please refer to
http://www.iata.org/whatwedo/cargo/dgr/Pages/infectious_substances.aspx



IATA Packing

PACKING INSTRUCTION 650

STATE VARIATIONS: BHG-02, CAG-05, DQG-03, FRG-05, GBG-05, VCG-04

△ OPERATOR VARIATIONS: AF-02, AM-06/10, AR-02, AS-08, BR-14, BZ-07, CI-01, CO-07, CS-07, FX-09, IJ-06/10, JJ-06, JK-03, KC-08, KE-06, LA-07, LH-05, MN-03, MS-06, MX-06/11, OO-01, OU-12/16, PX-08, SQ-10, SV-12, TN-05, TY-03, UA-14, UU-05

This instruction applies to UN 3373 on passenger and cargo aircraft and Cargo Aircraft Only.

General Requirements

The packagings must be of good quality, strong enough to withstand the shocks and loadings normally encountered during transport, including trans-shipment between transport units and between transport units and warehouses as well as any removal from a pallet or overpack for subsequent manual or mechanical handling. Packagings must be constructed and closed so as to prevent any loss of contents that might be caused under normal conditions of transport, by vibration, or by changes in temperature, humidity or pressure.

The packaging must consist of three components:

(a) a primary receptacle(s);

(b) a secondary packaging; and

(c) a rigid outer packaging.

Primary receptacles must be packed in secondary packagings in such a way that, under normal conditions of transport, they cannot break, be punctured or leak their contents into the secondary packaging. Secondary packagings must be secured in outer packagings with suitable cushioning material. Any leakage of the contents must not compromise the integrity of the cushioning material or of the outer packaging.

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IATA Dangerous Goods Regulations

PACKING INSTRUCTION 650 *(continued)*

Packages must be prepared as follows:

(a) For liquid substances:

- The primary receptacle(s) must be leakproof and must not contain more than 1 L;
- The secondary packaging must be leakproof;
- If multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated to prevent contact between them;
- Absorbent material must be placed between the primary receptacle and the secondary packaging. The absorbent material, such as cotton wool, must be in sufficient quantity to absorb the entire contents of the primary receptacle(s) so that any release of the liquid substance will not compromise the integrity of the cushioning material or of the outer packaging;
- The primary receptacle or the secondary packaging must be capable of withstanding, without leakage, an internal pressure of 95 kPa in the range of -40°C to 55°C (-40°F to 130°F).

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Note:
The capability of a packaging to withstand an internal pressure without leakage that produces the specified pressure differential should be determined by testing samples of primary receptacles or secondary packagings. Pressure differential is the difference between the pressure exerted on the inside of the receptacle or packaging and the pressure on the outside. The appropriate test method should be selected based on receptacle or packaging type. Acceptable test methods include any method that produces the required pressure differential between the inside and outside of a primary receptacle or a secondary packaging. The test may be conducted using internal hydraulic or pneumatic pressure (gauge) or external vacuum test methods. Internal hydraulic or pneumatic pressure can be applied in most cases as the required pressure differential can be achieved under most circumstances. An external vacuum test is not acceptable if the specified pressure differential is not achieved and maintained. The external vacuum test is a generally acceptable method for rigid receptacles and packagings but is not normally acceptable for:

- flexible receptacles and flexible packagings;
- receptacles and packagings filled and closed under a absolute atmospheric pressure lower than 95 kPa.
- The outer packaging must not contain more than 4 L. This quantity excludes ice, dry ice or liquid nitrogen when used to keep specimens cold.

(b) For solid substances:

- The primary receptacle(s) must be siftproof and must not exceed the outer packaging weight limit;
- The secondary packaging must be siftproof;
- If multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated to prevent contact between them;
- Except for packages containing body parts, organs or whole bodies, the outer packaging must not contain more than 4 kg. This quantity excludes ice, dry ice or liquid nitrogen when used to keep specimens cold;
- If there is any doubt as to whether or not residual liquid may be present in the primary receptacle during transport then a packaging suitable for liquids, including absorbent materials, must be used.

An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.

At least one surface of the outer packaging must have a minimum dimension of 100 mm × 100 mm (4 in × 4 in).

The completed package must be capable of successfully passing the drop test described in 6.5.1.1 except that the height of the drop must not be less than 1.2 m. Following the appropriate drop sequence, there must be no leakage from the primary receptacle(s) which must remain protected by absorbent material, when required, in the secondary packaging.

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PACKING INSTRUCTION 650 *(continued)*

For transport, the mark illustrated below must be displayed on the external surface of the outer packaging on a background of a contrasting colour and must be clearly visible and legible. The mark must be in the form of a square set at an angle of 45° (diamond-shaped) with each side having a length of at least 50 mm (2 in), the width of the line must be at least 2 mm and the letters and numbers must be at least 6 mm high. The proper shipping name "Biological Substance, Category B" in letters at least 6 mm high must be marked on the outer packaging adjacent to the diamond-shaped mark.

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☞ Unless all package markings are clearly visible, the following conditions apply when packages are placed in an overpack:

- the overpack must be marked with the word "Overpack"; and
- the package markings must be reproduced on the outside of the overpack.

A Shipper's Declaration for Dangerous Goods is not required.

Alternative packagings for the transport of animal material may be authorized by the competent authority in accordance with the provisions in 5.0.6.7.

Specific Requirements

Refrigerated or frozen specimens: Ice, dry ice and liquid nitrogen:

- When dry ice or liquid nitrogen is used to keep specimens cold, all applicable requirements of these Regulations must be met. When used, ice or dry ice must be placed outside the secondary packagings or in the outer packaging or an overpack. Interior supports must be provided to secure the secondary packagings in the original position after the ice or dry ice has dissipated. If ice is used, the outside packaging or overpack must be leakproof. If dry ice is used, the packaging must be designed and constructed to permit the release of carbon dioxide gas to prevent a build-up of pressure that could rupture the packagings.
- The primary receptacle and the secondary packaging must maintain their integrity at the temperature of the refrigerant used as well as the temperatures and the pressures, which could result if refrigeration were to be lost.

Infectious substances assigned to UN 3373 which are packed and marked in accordance with this packing instruction are not subject to any other requirement of these Regulations except for the following:

(a) the name and address of the shipper and of the consignee must be provided on each package;

(b) the name and telephone number of a person responsible must be provided on the air waybill or on the package;

(c) the classification must be in accordance to 3.6.2;

(d) the incident reporting requirements in 9.6.1 must be met; and

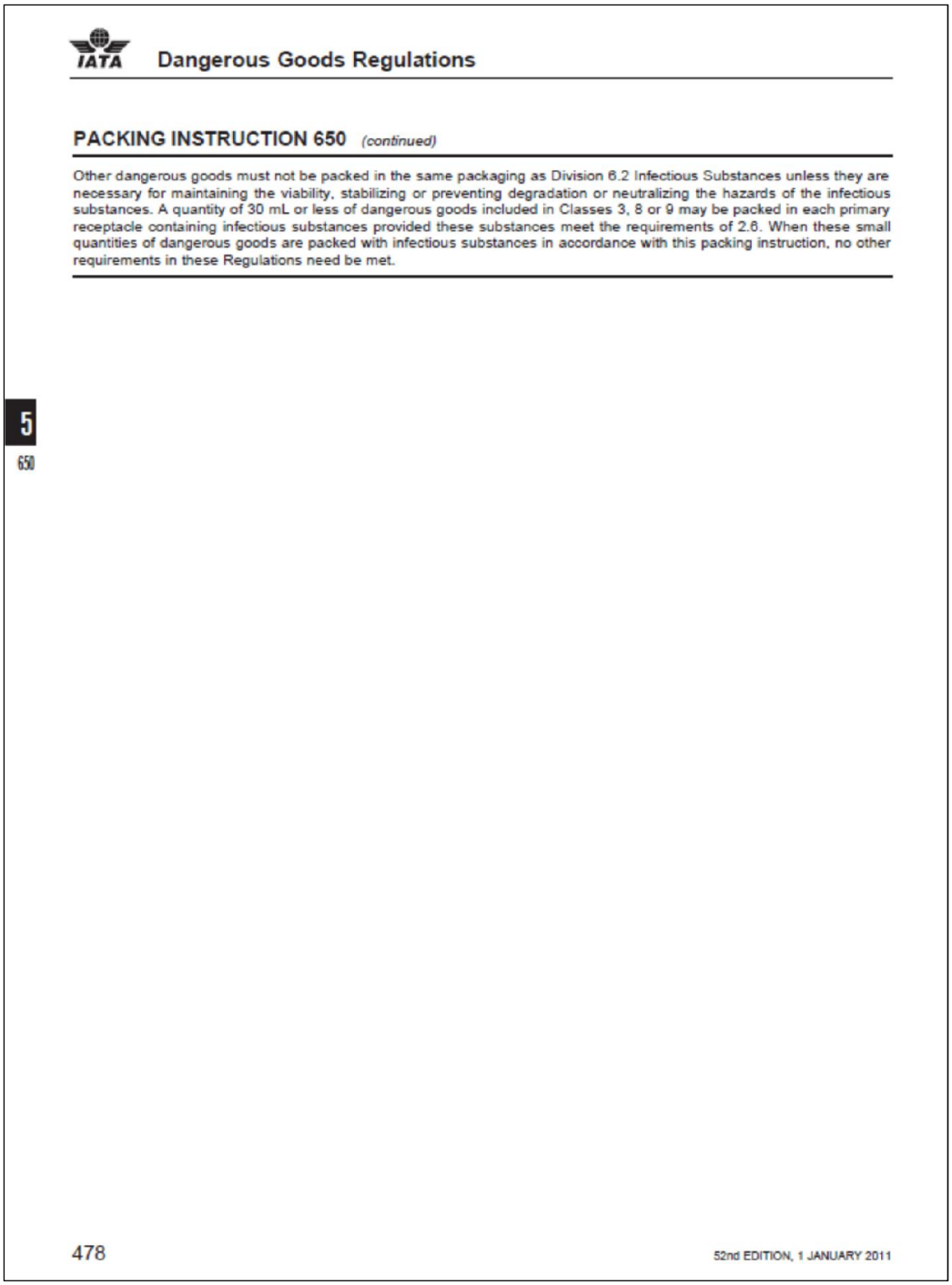
(e) the inspection for damage or leakage requirements in 9.4.1 and 9.4.2.

Note:
When the shipper or consignee is also the 'person responsible' as referred to in b) above, the name and address need be marked only once in order to satisfy the name and address marking provisions in both a) and b), above.

Passengers and crew members are prohibited from transporting infectious substances as or in carry-on baggage, checked baggage or on their person.

☞ If an Air Waybill is used, the "Nature and Quantity of Goods" box must show "UN 3373", the text "BIOLOGICAL SUBSTANCE, CATEGORY B" and the number of packages.

Clear instructions on filling and closing such packages must be provided by packaging manufacturers and subsequent distributors to the shipper or to the person who prepares the package (e.g. patient) to enable the package to be correctly prepared for transport.



IATA Dangerous Goods Regulations

PACKING INSTRUCTION 650 *(continued)*

Other dangerous goods must not be packed in the same packaging as Division 6.2 Infectious Substances unless they are necessary for maintaining the viability, stabilizing or preventing degradation or neutralizing the hazards of the infectious substances. A quantity of 30 mL or less of dangerous goods included in Classes 3, 8 or 9 may be packed in each primary receptacle containing infectious substances provided these substances meet the requirements of 2.6. When these small quantities of dangerous goods are packed with infectious substances in accordance with this packing instruction, no other requirements in these Regulations need be met.

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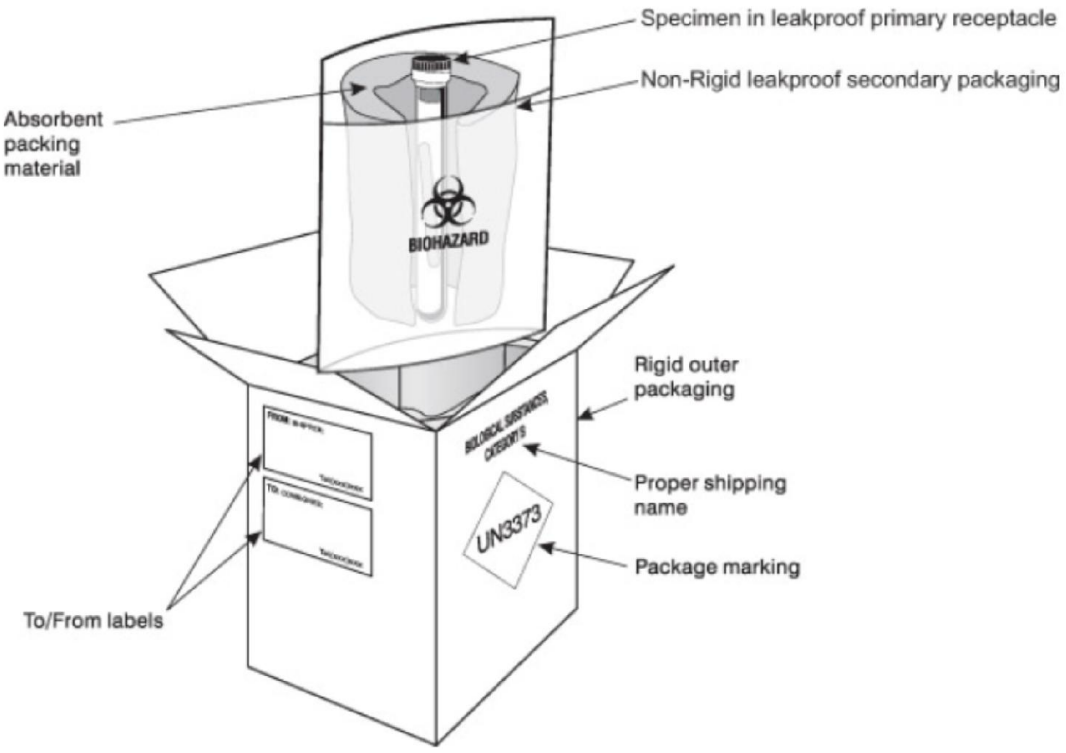
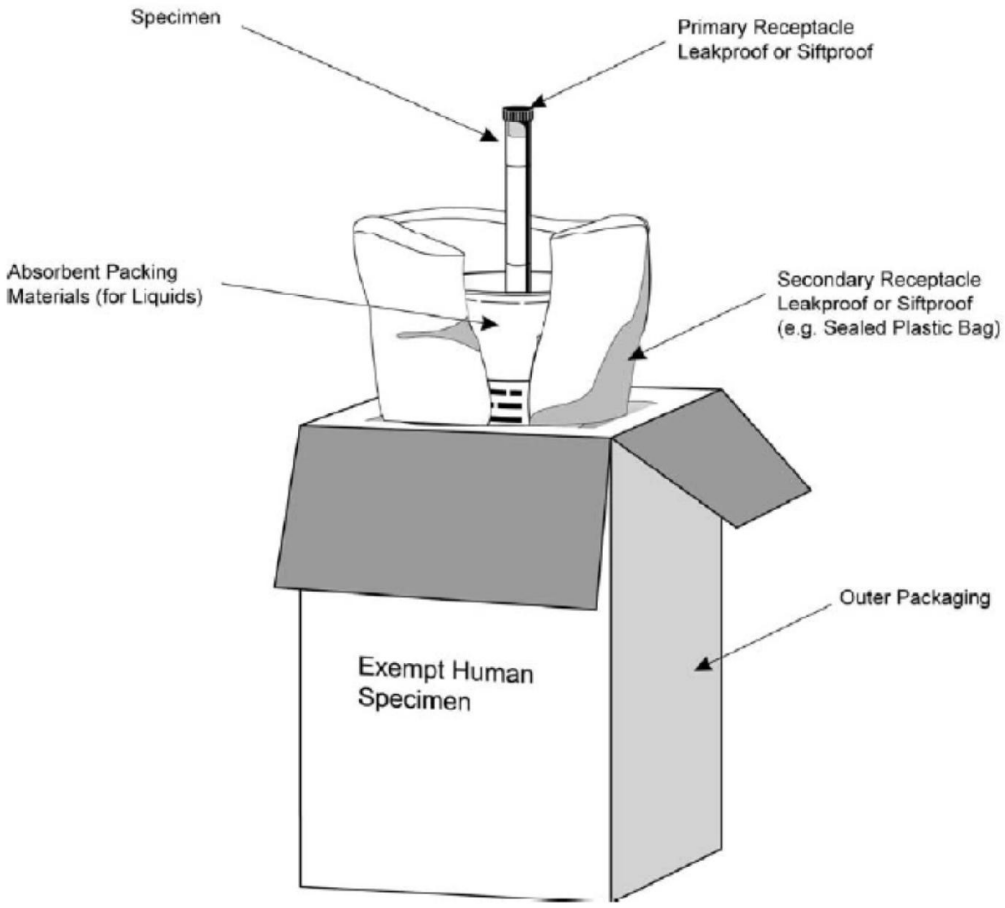
7.3. APPENDIX 3 - Example of Packing and Marking for Category B Infectious Substances



Taken from IATA infectious substances guidance document
http://www.royalmail.com/sites/default/files/Guidance-Document-Infectious-Substances-171012.pdf

7.3. APPENDIX 3 - Example of Packing and Marking for Exempt Specimens



Taken from IATA infectious substances guidance document
http://www.royalmail.com/sites/default/files/Guidance-Document-Infectious-Substances-171012.pdf