RESEARCH ETHICS AND CONSENT ON THE COLLECTION AND USE OF HUMAN BIOLOGICAL MATERIALS: A SINGAPORE PERSPECTIVE

Chan Tuck Wai

B.Sc. (Pharmacy), NUS

MBA, GGU

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

NUS CENTRE FOR BIOMEDICAL ETHICS

YONG YOO LIN SCHOOL OF MEDICINE

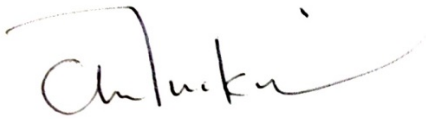
NATIONAL UNIVERSITY OF SINGAPORE

2015

DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety, with inputs and advices from my supervisors. I have duly acknowledged all the sources of information that have been used in this thesis.

This thesis has also not been submitted for any degree in any university previously.



_____

Chan Tuck Wai

3 June 2015

ACKNOWLEDGEMENTS

To complete the PhD programme by the age of 50 has always been part of my dream. However, with a full-time job, suffering from several medical conditions and a list of learning disabilities, it would have been impossible to achieve this dream. Despite genuine concerns from friends and colleagues, I went on to enrol into this program in 2009. I have thoroughly enjoyed my journey, even with a heart attack in the 2nd year of the program.

There are many people whom I like to thank for this miraculous learning journey. My gratitude goes to my supervisors, Prof Leonardo De Castro and Dr Calvin Ho, who provided inputs and comments to multiple draft versions of my thesis. Special acknowledgements to my Thesis Advisory Committee – AP Chong Siew Meng, AP Jacqueline Chin and PhD Examiners – AP Anita Ho, Prof Graeme Laurie, Prof Chia Kee Seng and Dr Tamra Lysaght; Prof Desley Hegney, Prof Vicky Drury, Dr Grace Zeng, Dr Azhar Bin Ali, Ms Chia Chiu Yuin, Ms Iris Wee An-Li for their kind assistances, supports and advices in this thesis. I would like to thank Prof Lee Hin Peng and colleagues in NUS Institutional Review Board for all their hard work to help my work duties during my course and study leave. I would like to express my appreciation to NUH Department of Pathology, NUH Tissues Repository, and NUS Centre for BioMedical Ethics for supporting this thesis and with great gratitude to all patients who had patiently and willingly participated in this study.

Thank you all and I am overwhelmed with gratitude.

Chan Tuck Wai

3 June 2015

TABLE OF CONTENTS

SUMMARY

Biobanking of residual human biological materials (HBMs), usually obtained from surgeries, is crucial for the advancement of science and public health and improves current treatment of various diseases. However, biobanking of residual HBMs comes with ethical, social and legal implications (ELSI) that require attention. This thesis will focus on residual HBMs tissue repository, which is considered as a biobank.

The current ethical paradigm and academic debates have focused on informed consent and ownership of residual HBMs, and subsequent discussion on the rights of patients through benefits sharing, returning of results from the research and profit sharing when the residual HBMs are commercialised. In this thesis, I will attempt to critique this paradigm and its' application in the Singapore context.

A key aim of this thesis is to contribute to the knowledge with regards to patients' knowledge, attitudes, preferences and expectations in donating residual HBMs for research. This study will also examine the current approach to consent in a major healthcare institution in Singapore compared with other consent regimes, in relation to preferences expressed by patients when contributing their tissues.

The outcome of a 3-part explanatory sequential research using mixed methods design is a main component of this thesis. It comprises of a systematic literature review, a quantitative research using consent forms for a period of ten years (from 2002 to 2011) in a major Singapore hospital and a qualitative interview of 100 patients who had contributed HBMs to the hospital's tissue repository. The empirical results have been analysed in comparison with previous reports in academic publications on ethical issues of tissue repositories and

biobanking, with primary focus on informed consent and the relationship between residual HBMs repositories and patients.

I defend in this thesis that specific informed consent is neither morally meaningful nor important to the donors of residual HBMs. A regime of general consent with mediated communication and respecting donor intent is proposed, together with the establishment of a moral institution with proper governance, safeguards and control for the collection, storage, distribution and use of HBMs in tissue repositories.

LIST OF PUBLICATIONS

This dissertation is based on the following original publications:

1. Chan TW, Mackey SJ, Hegney D. 2011. Patients' experiences towards the donation of their residual biological samples and the impact of these experiences on the type of consent given for secondary use: A systematic review. *JBI Library of Systematic Reviews. 08 Aug 2011; 9(42): 1714-1781.*

2. Chan TW, Mackey SJ, Hegney D. 2012. Patients' consent and donation of their residual biological samples: A systematic review. *International Journal of Evidence-Based Healthcare - International Journal of Evidence Based Healthcare* 2012; 10: 9-26.

3. Chan TW. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.* Vol 16, No 4, April 2012: 40-43

4. Chan TW, Mackey SJ, Hegney D. 2012. Donation of residual biological samples and consent given for secondary use. *The Joanna Briggs Institute*, Vol 15, No 9, Page 1-4, 09/12/2011

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Chapter 1. Introduction

Biobanking of residual human biological materials (HBMs), usually obtained from surgeries, is crucial in biomedical research for the advancement of science and public health. Research results obtained from studies involving HBMs invaluably improves drug discovery, clinical management and current treatment of various diseases. However, biobanking of residual HBMs comes with ethical, legal and social implications (ELSI) that require attention.

The current ethical paradigm and academic debates have focused on informed consent and ownership of residual HBMs and subsequent discussion on the rights of patients through benefits sharing, returning of results from research and profit=sharing when the residual HBMs are commercialised. In this thesis, I will critique this paradigm and its' application in the Singapore context.

In the discussion of informed consent, opinion leaders within biobanking disciplines have proposed various regimes, which include the mode of informed consent and type of information required to render it valid. Some experts have also suggested a highly explicit and structured approach to taking specific informed consent while others have suggested implicit, presumed or general consent. These options are described later in this Chapter.

The aim of this thesis is to contribute to Singapore and international knowledge with regards to patients' knowledge, attitudes, preferences and expectations in donating residual HBMs to tissue repositories for research. This study also examines the various models of consent currently used and compares them with a broad consent regime that is arguably more consistent with preferences expressed by patients when contributing their tissues.

This thesis also reviews the development of informed consent in tissue banking (as well as biobanking more generally), with comparisons to the notion of informed consent that is considered necessary in clinical trials and medical management. It will discuss current ethical requirements of informed consent in tissue banking in Singapore, together with other important ethical issues that have not been adequately discussed in this context.

Informed consent is meant to protect human subjects from harm. The prevailing paradigm of informed consent is characterized by providing specific and sufficient information about risks, all known uses of samples collected, benefits to participants, rights to ownership of HBMs, withdrawal of participation and its consequences. However, in the context of biobanking of HBMs, this paradigm does not work well since these biobanks that collected tissues are unlikely to be fully certain of the types of future research that will use these tissues. For example, biobanks that collected HBMs 20 years ago were not in a position to describe the type of genetic research that is now conducted using the collected HBMs. This limitation is further described in Chapter 2, together with the current tissue banking situation in Singapore, and the experiences and preferences of Singaporeans as observed in my empirical research.

This thesis will draw on and apply the findings from systematic literature reviews and two empirical research projects, which were conducted with the objective of understanding patients' perceptions, attitudes and experiences on tissue banking and their preferences on informed consent. The empirical results in Chapter 3 will be discussed in relation to academic publications on ethical issues of tissue banking, with focus on informed consent and the relationship between tissue repositories (and biobanks more generally) and tissue contributors (particularly contributors of residual HBMs).

My empirical findings indicate that specific informed consent is not morally meaningful or important to contributors of residual HBMs contributors. Rather, a broad consent regime with the right to withdraw from participation is proposed, and supported by a governance regime whereby tissue repositories serve as moral institutions with stewardship responsibilities over stored HBMs. These include proper control and safeguards for the collection, storage, distribution and use of residual HBMs in tissue repositories to promote accountability and gain public trust.

I defend the view that specific informed consent is neither morally meaningful nor important to the contributors of residual HBMs to tissue repositories. To reiterate, a regime of broad consent with emphasis on mediated communication, together with the establishment of a moral institution characterized by proper governance, safeguards and control for the collection, storage, distribution and use of the HBMs will better meet ethical goals and reasoned public expectations. The theoretical basis in support of these propositions will be presented and discussed in chapter 4.

1.1 The need for Human Biological Materials for research

In the year 2009, the Times magazine listed HBMs in tissue repositories and biobanks as one of "10 Ideas Changing the World Right Now."[1] The report concluded that HBMs were transforming the manner researchers and medical professionals gain a better understanding of diseases and discover strategies to treat these illnesses. HBMs have been identified as

[1] PARK, A. 2009. 10 Ideas Changing the World Right Now. *Time*. http://content.time.com/time/specials/packages/article/0,28804,1884779_1884782_1884766,00.html assessed on 0902013

crucial to the core research infrastructure of tissue repositories for advancing medicine and public health.[2] An example would be the identification of disease-specific information or biomarkers revealed by comparison of DNA sequences between tissue samples derived from patients and healthy donors which would assist researchers in improving treatment success through the identification and significance of genomic and proteomic difference between healthy and diseased individuals.[3] HBMs have since become an important source for academic medical research and the development of diagnostics and therapeutics.[4]

The practice of collecting and storing HBMs for research has been documented since the beginning of medical science.[5] There are however variations in the definition of HBMs which are sometimes collectively referred to as human 'tissues', human 'bio-specimens' or 'bio-samples'. The term 'human biological materials' includes any human materials removed or derived from the body, such as solid body tissues, organs, blood, cord blood, other bodily fluids and their derivatives, secretions, body parts, biopsy specimens obtained for diagnostic purposes, organs removed during surgery, foetuses, gametes and embryos, and DNA/RNA

---

[2] GOTTWEIS, H., GASKELL, G. & STARKBAUM, J. 2011c. Connecting the public with biobank research: reciprocity matters. *Nat Rev Genet,* 12**,** 738-9. ibid. ibid. ibid.

[3] BALKO, J. M., COOK, R. S., VAUGHT, D. B., KUBA, M. G., MILLER, T. W., BHOLA, N. E., SANDERS, M. E., GRANJA-INGRAM, N. M., SMITH, J. J., MESZOELY, I. M., SALTER, J., DOWSETT, M., STEMKE-HALE, K., GONZALEZ-ANGULO, A. M., MILLS, G. B., PINTO, J. A., GOMEZ, H. L. & ARTEAGA, C. L. 2012. Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance. *Nat Med,* 18**,** 1052-9.

[4] GODARD, B., SCHMIDTKE, J., CASSIMAN, J. J. & AYME, S. 2003. Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. *Eur J Hum Genet,* 11 Suppl 2**,** S88-122. ibid.

[5] ALLEN, M. J., POWERS, M. L. E., GRONOWSKI, K. S. & GRONOWSKI, A. M. 2010. Human Tissue Ownership and Use in Research: What Laboratorians and Researchers Should Know. *Clin Chem,* 56**,** 1675-1682.

and cells, from either living or dead persons.[6] These materials are commonly obtained either during routine surgical and medical diagnostic procedures or via direct contributions by individuals when they participate in clinical research. The term "Human Biological Materials" is also used by the Council of Europe in its recommendation on "Research on biological materials of human origin"[7], the National Bioethics Advisory Commission (USA) in its report on *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, and Canada's Tri-Council Policy Statement on *Ethical Conduct for Research Involving Humans*.[8] Singapore's Bioethics Advisory Committee (BAC), established to address the ethical, social and legal issues of bio-medical research in Singapore, chose to use a more commonly accepted term, "human tissues", in their reports on human tissues research. They defined human tissues as "all kinds of human biological materials derived from living or cadaveric donors including solid body tissues, organs, foetuses, blood and other bodily fluids and their derivatives, cord blood, embryos, gametes (sperm or eggs), or any part or derivative thereof." [9] Based on this definition, the BAC's made referenced to "human tissue" to encompass both human biological materials and human tissues, which include whole embryos, sperms and eggs, in a strict biological sense. In essence, the definition of "human tissues" by Singapore's BAC is similar to those in US and EU guidelines. This thesis will use

---

[6] MESLIN, E. M. & QUAID, K. A. 2004. Ethical issues in the collection, storage, and research use of human biological materials. *J Lab Clin Med,* 144**,** 229-34; discussion 226.

[7] The Council of Europe's Recommendation (2006)4 on research on biological materials of human origin. Accessed on 1 may 2014 http://www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/default_en.asp

[8] HELFT, P. R., CHAMPION, V. L., ECKLES, R., JOHNSON, C. S. & MESLIN, E. M. 2007. Cancer patients' attitudes toward future research uses of stored human biological materials. *J Empir Res Hum Res Ethics,* 2**,** 15-22.

[9] BAC, S. 2002. Human Tissue Research: A report by Bioethics Advisory Committee Singapore. November 2002. Section 2.1, Page 3

the term “human biological materials” (and abbreviated as HBMs), which includes human tissues and all biological materials of human origin.

In the context of this research, HBMs are usually collected using different strategies. Some HBMs are specifically collected from healthy volunteers for the sole purpose of research and others are collected from patients after diagnosis, surgery or therapy. In the second scenario, residual or excess residual HBMs obtained in the course of diagnosis, surgery or medical management of patients that were originally collected for non-research purposes, were sometimes stored and subsequently used for research.[10] Residual HBMs are the most frequent and convenient source of HBMs as large quantity of materials were collected as biological wastes after a surgery or procedure.[11] The discussion and research on residual HBMs in this thesis will exclude whole reproductive organs, embryos, eggs, sperms and other reproductive cells and tissues, which have different ethical impacts and issues. The use of patients’ residual HBMs stored in tissue repository is distinct from other biobanking projects in which the tissue is specifically collected from healthy volunteers.[12] In this part of thesis, we will focus on the ethical issues for the collection and use of residual HBMs for research by an institution or tissue repository. Some have argued that the use of residual HBMs poses no ethical issue, but from the scandal involving Alder Hey Hospital in the UK,[13]

---

[10] GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. *J Med Ethics,* 38**,** 351-5.

[11] GIESBERTZ, N. A., BREDENOORD, A. L. & VAN DELDEN, J. J. 2012. Inclusion of residual tissue in biobanks: opt-in or opt-out? *PLoS Biol,* 10**,** e1001373.

[12] RIEGMAN, P. H. & VAN VEEN, E. B. 2011. Biobanking residual tissues. *Hum Genet,* 130**,** 357-68.

[13] SQUE, M., LONG, T., PAYNE, S., ROCHE, W. R. & SPECK, P. 2008. The UK postmortem organ retention crisis: a qualitative study of its impact on parents. *J R Soc Med,* 101**,** 71-7.

unauthorized organs retention and other similar cases of non-consensual storage and use of residual HBMs proved otherwise.

Residual HBMs, such as cancer or diseased tissues removed by surgery, have emerged to be an important and rich resource for biomedical research and clinical studies. These specimens are typically utilized by biomedical researchers to gain a deeper understanding of mechanisms of cellular and molecular processes of diseases such as cancers that could ultimately be translated into improvements in diagnosis and treatment to prolong the survival of cancer patients.[14] Through genomics and proteomics research, scientists may uncover molecular clues to the cause of a particular cancer type, or target a specific protein found specifically in diseased but not in healthy individuals as a form of personalized treatment of an otherwise untreatable condition. New molecular techniques on residual HBMs, coupled with advances in information technology, are now transforming the research arena with high-throughput robotic systems that can utilize HBMs for tissues microarray (TMA) testing. TMA consists of multiple paraffin blocks in which up to one thousand unrelated tissue cores from different patients, are assembled in an array fashion to allow high-throughput histological analysis of disease biomarkers and protein expression. The residual HBMs used in TMA, are leftover formalin fixed paraffin-embedded (FFPE) tissues that are originally used for diagnosis and have been compulsorily stored in the hospital as part of archival pathological record.[15] The requirement of large quantities of HBMs for TMA

---

[14] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.

[15] WOLFF, C., SCHOTT, C., MALINOWSKY, K., BERG, D. & BECKER, K.-F. 2011. Producing Reverse Phase Protein Microarrays from Formalin-Fixed Tissues. *In:* KORF, U. (ed.) *Protein Microarrays.* Humana Press.

has since raised concerns over potential shortages of residual HBMs for cancer and other research.[16]

Clinical treatments and new drug developments have progressed and benefitted from the numerous research studies on residual HBMs obtained from patients after surgical procedures.[17] Residual HBMs are crucial in improving the efficacy of clinical studies as they present an alternative to *in vivo* animal models thus reducing the need for animal testing in clinical research.[18] Traditionally, drug development requires animal testing for toxico-efficacy research before clinical trials can be conducted on human subjects. With residual HBMs collected from patients, newly invented chemical compounds can be safely tested on established human cell lines, as *in vitro* models, generated from residual HBMs without exposing patients to physical harm or as an alternative to the sacrifice of laboratory animals.[19] The intrinsic benefit of using HBMs instead of laboratory animals for screening and testing of new drug compounds is that when utilizing HBMs models, it is likely to yield results that are more representative of the effects of the new compound on an actual human subject. This is something that cannot be achieved in laboratory animal testing. Several studies have shown that positive results on safety and efficacy of the new compound obtained from animal models (e.g. mice and monkeys) couldn't be replicated in human

---

[16] SCHMIDT, C. 2006. Tissue banks trigger worry about ownership issues. *Journal of the National Cancer Institute,* 98**,** 1174-1175.

[17] ASHBURN, T. T., WILSON, S. K. & EISENSTEIN, B. I. 2000. Human tissue research in the genomic era of medicine: balancing individual and societal interests. *Arch Intern Med,* 160**,** 3377-84. ibid.

[18] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.

[19] BERUBE, K. A. 2013. Medical waste tissues - breathing life back into respiratory research. *Altern Lab Anim,* 41**,** 429-34.

models.[20] These collections of residual HBMs also enable scientists to determine cellular toxicity by experimenting on the extracted tissues, before conducting Phase I clinical trials on actual human subjects. Residual HBMs can also be utilized to validate *in vitro* scientific findings,[21] to identify potential new biomarkers for diagnostic and/or prognostic values,[22] and to determine the suitable treatment regimen for patients in personalized medicine.[23]

There has been an increasing demand for HBMs, in recent years, due to scientific advancement of new research and increase in awareness of HBMs' value in research.[24] A survey of 700 cancer researchers showed that 47% of researchers had difficulty finding HBMs of sufficient quality and 81% of them reported that their scope of work was limited due to shortage of HBMs, whereas 60% said they questioned the statistical evidence in the findings of their studies, due to insufficient HBMs.[25] Thus, having access to a larger number of HBMs for research, will create better research opportunities with the ultimate goals of advancing medical science and public good.

---

[20] SHANKS, N., GREEK, R. & GREEK, J. 2009. Are animal models predictive for humans? *Philosophy, Ethics, and Humanities in Medicine,* 4**,** 2.

[21] ZATLOUKAL, K. & HAINAUT, P. 2010. Human tissue biobanks as instruments for drug discovery and development: impact on personalized medicine. *Biomark Med,* 4**,** 895-903.

[22] HEWITT, R. E. 2011. Biobanking: the foundation of personalized medicine. *Current Opinion in Oncology,* 23**,** 112-119 10.1097/CCO.0b013e32834161b8.

[23] PARKINSON, D., DRACOPOLI, N., PETTY, B., COMPTON, C., CRISTOFANILLI, M., DEISSEROTH, A., HAYES, D., KAPKE, G., KUMAR, P., LEE, J., LIU, M., MCCORMACK, R., MIKULSKI, S., NAGAHARA, L., PANTEL, K., PEARSON-WHITE, S., PUNNOOSE, E., ROADCAP, L., SCHADE, A., SCHER, H., SIGMAN, C. & KELLOFF, G. 2012. Considerations in the development of circulating tumor cell technology for clinical use. *Journal of Translational Medicine,* 10**,** 138.

[24] HAWKINS, A. K. 2010. Biobanks: importance, implications and opportunities for genetic counselors. *J Genet Couns,* 19**,** 423-9.

[25] ASHBURN, T. T., WILSON, S. K. & EISENSTEIN, B. I. 2000. Human tissue research in the genomic era of medicine: balancing individual and societal interests. *Arch Intern Med,* 160**,** 3377-84. ibid.

Large scale research biobanks are being prospectively established, with the purpose of storing residual HBMs collected for research purposes, together with information on donors' lifestyles and health status to aid studies on relationships between disease, genes and donors' environments.[26] Genetic research can help improve global health through greater understanding of the basic mechanism of the disease, susceptibility and resistance, thereby guiding the development of preventive intervention of such disease.[27] A greater understanding of the effects of genetic variation on response to drugs allows researchers to help develop cures for malaria, HIV, tuberculosis, cancers and other diseases.[28] From genomic analysis, prognosis and treatment response to certain chemotherapeutic drugs, personalized treatment can then be tailored once researchers have identified specific disease markers by comparing data from HBM contributors who respond to treatment with non-responders.[29]

This thesis will focus primarily on the collection and use of residual HBMs in research and define the term "residual HBMs" as materials taken from the patient in the course of a diagnostic or therapeutic procedure, which can be stored and subsequently used for research.[30]

---

[26] SHICKLE, D. 2006. The consent problem within DNA biobanks. *Stud Hist Philos Biol Biomed Sci,* 37**,** 503-19.

[27] RISCH, N. J. 2000. Searching for genetic determinants in the new millennium. *Nature,* 405**,** 847-56.

[28] WEATHERALL, D. J. 2003. Genomics and global health: time for a reappraisal. *Science,* 302**,** 597-9.

[29] ZATLOUKAL, K. & HAINAUT, P. 2010. Human tissue biobanks as instruments for drug discovery and development: impact on personalized medicine. *Biomark Med,* 4**,** 895-903.

[30] VAN VEEN, E. B., RIEGMAN, P. H., DINJENS, W. N., LAM, K. H., OOMEN, M. H., SPATZ, A., MAGER, R., RATCLIFFE, C., KNOX, K., KERR, D., VAN DAMME, B., VAN DE VIJVER, M., VAN BOVEN, H., MORENTE, M. M., ALONSO, S., KERJASCHKI, D., PAMMER, J., LOPEZ-GUERRERO, J. A., LLOMBART BOSCH, A., CARBONE, A., GLOGHINI, A., TEODOROVIC, I., ISABELLE, M.,

1.2 Description of residual HBMs in Research

Biobanks routinely collect and store different types of HBMs. HBMs can be obtained from different parts of the human body; from different types of subjects depending on whether the contributor is a healthy volunteer or patient; for different purposes of removal of materials depending on whether it is primarily intended only for research; or for different uses of HBMs collected. This thesis will focus on residual HBMs obtained from surgical activities or collected as pathological archived materials, and used for future research.

1.2.1 What are residual human biological materials?

As explained above, residual HBMs refer to materials taken from patients in the course of a diagnostic or therapeutic procedure, which can be stored and subsequently used for research.[31] Gefenas *et al*. further clarified that residual -HBMs are materials removed during surgical treatment or biological material leftover after diagnostic testing. [32] The leftover materials are originally supposed to be processed as medical wastes and disposed, if they are not used for research. In the published literature, residual or leftover HBMs may also be

---

PASSIOUKOV, A., LEJEUNE, S., THERASSE, P. & OOSTERHUIS, J. W. 2006. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer,* 42**,** 2914-23.

[31] VAN DIEST, P. J. 2002. No consent should be needed for using leftover body material for scientific purposes. For. *BMJ: British Medical Journal,* 325**,** 648-651.

[32] GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. *J Med Ethics,* 38**,** 351-5.

referred to as ‘residues from medical procedures’, ‘surplus materials’, ‘body waste’, ‘medical waste’, ‘excess clinical material’, ‘redundant tissue’, or ‘leftover tissues’, etc.[33]

In addition to the surgical leftover materials, Gefenas *et al*. also used the term ‘residual’ to refer to previously stored biological materials in pathological diagnostics archives. Such collections may be found in a variety of healthcare institutions including hospitals, pathology laboratories, tissue banks, blood banks and genetic laboratories. For example, residual archived HBMs include diagnostic collections of pathology slides, existing collections of biological materials taken for non-research purposes during different stages of diagnostic or therapeutic procedures, like formalin-fixed, paraffin embedded tissues, which have been used for primary diagnosis and subsequently archived and stored by hospitals or their research institutions.[34]

The use of such residual archived HBMs for research purposes is only allowed when extra histological sections are available or when the archived materials are no longer needed for diagnostics purposes. In most countries, such diagnostic materials are compulsorily and legally kept in archived storage for a stipulated period and it is a professional duty to keep the original diagnostic sample lesion intact for further verification. The College of American

---

[33] BROCHHAUSEN, C., ROSSRICKER, N. & KIRKPATRICK, C. J. 2007. Biological waste, ownership and personality - future perspectives for the secondary use of human tissue in the view of national and international regulations. *Pathology Research and Practice,* 203**,** 404-404. And RIEGMAN, P. H. & VAN VEEN, E. B. 2011. Biobanking residual tissues. *Hum Genet,* 130**,** 357-68.

[34] GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. *J Med Ethics,* 38**,** 351-5.

Pathologists recommends a minimum of 10 years for the retention requirement of paraffin tissue blocks.[35]

1.3 Sources of HBMs

HBMs are usually collected and stored using 2 different strategies: (1) as materials specifically collected for one specific research use, which can later be research leftover samples or research residual HBMs after the specific research has been completed; and (2) as surgical leftover or residual HBMs obtained in the course of medical management of patients, including clinical care, diagnostics (e.g. health screening), therapy and transplant.[36]

The most common purposes of harvesting or collecting HBMs are for clinical diagnosis, medical treatment and health screening. These HBMs are usually stored as pathological samples after diagnosis is made, as part of the clinical records. Surgical excess tissues or clinical residual HBMs, which are not required for diagnosis, have been an important source of materials for medical education and research. Residual HBMs samples from research are valuable, especially when they are accompanied with genomics and proteomics information that may save time and effort for other researchers who wish to use tissues for their own research. By systematically transferring residual HBMs from previous research projects to a repository, the value of such residual HBMs can then be maximized through systematic

---

[35] FITZGIBBONS, P. L. 2011. Are there barriers to the release of paraffin blocks for clinical research trials? A College of American Pathologists survey of 609 laboratories. *Arch Pathol Lab Med,* 135**,** 870-3.

[36] GIESBERTZ, N. A., BREDENOORD, A. L. & VAN DELDEN, J. J. 2012. Inclusion of residual tissue in biobanks: opt-in or opt-out? *PLoS Biol,* 10**,** e1001373.

distribution, allocation and governance.

During surgery, some biological samples are removed from the body to aid in diagnosis and/or treatment of the patient's medical condition. In majority of these cases, not all tissues removed are needed for the primary use of clinical diagnosis and selection of treatment for the diagnosed condition. Excess leftover or residual tissues are normally discarded if they are not kept for future research. After clinical diagnosis, the diagnostic samples are stored as part of the medical records, normally within the pathology department of the hospital. These residual materials are normally discarded or destroyed when no further analysis is required. Although the primary use of surgically removed HBMs is for medical diagnosis of living patients (in clinical/ diagnostic pathology) or deceased persons (in autopsy specimen collections), these specimens are also useful for secondary uses such as biomedical research, education and training.[37]

HBMs are commonly stored in various premises in research hospitals, academic institutions and commercial research corporations, either at site of collection as an individual surgeon's personal research collection or an organized storage commonly known as 'Tissue Bank', 'Tissue Repository', or 'Biobank'.[38] The Organisation for Economic Co-operation (OECD) defines biobanks as "structured resources that can be used for the purpose of genetic research, which include: (1) human biological materials and/or information

[37] VERMEULEN, E., SCHMIDT, M. K., AARONSON, N. K., KUENEN, M., VAN DER VALK, P., SIETSES, C., VAN DEN TOL, P. & VAN LEEUWEN, F. E. 2009. Opt-out plus, the patients' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. *J Clin Pathol,* 62**,** 275-8.

[38] CAMBON-THOMSEN, A., RIAL-SEBBAG, E. & KNOPPERS, B. M. 2007. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J,* 30**,** 373-82.

generated from the analysis of the materials; and (ii) extensive associated information."[39] The UK Biobank Ethics and Governance Council states that "the most robust contemporary definition of 'biobanks' is rich collections of data plus bio-specimens, specifically developed as resources for research".[40] A research biobank or tissue repository is set-up and governed by either an institution or corporation for non-specific future research conducted by qualified researchers within its organization. The objective of such biobanks is to focus on and accelerate research, providing infrastructure for researchers to build a valuable resource for future research use.

Some biobanks have a comprehensive standard operations procedure (including informed consent procedures) and standardized protocols, which allow ethical re-contact and collection of related medical information of the participants and patients who have donated their tissues for research.[41] Different institutions and biobanks, however, have differing protocols observed by institutions for the 'banking' of residual HBMs, especially in Singapore.[42]

Individual clinicians and researchers may set up their personal collection of tissues for research. This is normally on an *ad-hoc* basis or for one-time use, and tissues collected are used specifically for their own research, normally stored in their laboratory and not shared

---

[39] OECD 2009. The Organisation for Economic Co-operation and Development: Guidelines on Human Biobanks and Genetic Research Databases.

[40] UK Biobank Ethics and Governance Council. Report on Public meeting of the UK Biobank Ethics and Governance Council, 11th June 2007 (2007).

[41] MCGUIRE, A. L. & BESKOW, L. M. 2010. Informed consent in genomics and genetic research. *Annu Rev Genomics Hum Genet,* 11**,** 361-81.

[42] CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.

with other researchers who are not related or collaborating with the collectors. If these collections are not systematically collected, well stored and processed, they will lose their value for future research use due to doubts on sample and data integrity. When these 'private' collections become too large, some of these researchers may convert their collections to 'biobanks' and allow other researchers to use the collected HBMs, if permitted by their institutions and funding agencies. Alternatively, they may donate their collections to an established biobank when their funding for storage is exhausted. Before the establishment of institutional biobanks, most researchers with privately stored HBMs either discarded them after one use or kept them indefinitely, not knowing the function of these residual HBMs after their research is completed. Such HBMs from research are normally not shared or stored for future research, and thus results in much wastage if they are discarded after a single research use, as substantial funds have been spent to collect, store and process them.

Surgical leftover or residual HBMs are most valuable and an easily accessible source if they are stored in biobanks for the purpose of future biomedical research.[43] With the pooled storage of research and clinical residual HBMs stored in well-established biobanks, researchers are no longer required to directly approach patients or wait for new patients to be diagnosed each time they embark on a new study. Residual HBMs can be stored either as untreated fresh frozen tissues or as Formalin-Fixed Paraffin-Embedded (FFPE) tissues in the form of paraffin blocks, stained or unstained sections in pathology laboratories.

---

[43] VOIDONIKOLAS, G., GINGRAS, M. C., HODGES, S., MCGUIRE, A. L., CHEN, C., GIBBS, R. A., BRUNICARDI, F. C. & FISHER, W. E. 2009. Developing a tissue resource to characterize the genome of pancreatic cancer. *World J Surg,* 33**,** 723-31.

Since the late 1990s, biobanks have become an important resource for HBMs supporting a variety of contemporary research studies, which include genomics and personalized medicine.[44] Due to the increasing demand for larger quantity of residual HBMs from surgery and diagnosis, this mode of collection in biobanks has become an important source of research materials. The collection of residual or leftover HBMs, if performed ethically and professionally, will ease the current shortage of human biological samples for research. Research biobanking is an active initiative by a research institution or organization to prospectively collect HBMs from healthy volunteers and patients for current research. These HBMs can also be stored for future research if there are leftovers and patients have given permission for such research use at the time of collection. Biobanks may also be disease-specific, like the Cancer Tissue Bank, which stores leftover cancer tissues for research specialized in the identification or discovery of new biomarkers affiliated with such cancer.[45] Disease-specific biobanks are usually associated with either an affiliated hospital or a research institution, and they may collect samples representing a variety of diseases. Large-scale population-based biobanks are also established to store HBMs of healthy volunteers meant for studies that investigate the interaction between genes and environment /lifestyle in epidemiological and public health research.[46] This thesis will focus on residual HBMs tissue repository, which is a type of biobanks.

---

[44] HOEYER, K. 2008. The ethics of research biobanking: a critical review of the literature. *Biotechnol Genet Eng Rev,* 25**,** 429-52.

[45] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.

[46] HOEYER, K., OLOFSSON, B. O., MJORNDAL, T. & LYNOE, N. 2004. Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scand J Public Health,* 32**,** 224-9.

1.4 Informed consent for Biobanking of residual HBMs for research

Research results obtained from studies utilizing residual HBMs from biobanks can greatly improve current treatment of various diseases. However, biobanking of residual HBMs is accompanied with many ethical, legal and social issues.[47] Budimir *et al*. conducted a systematic review of all publications on ethical aspects of human biobanks. The ethical issues identified from 154 articles included informed consent, privacy and confidentiality of the subjects, returning of results to the donors, ensuring and sustaining public trust, use of children and incompetent adults as study participants, commercialization of HBMs, roles of ethics review boards, data exchange, benefits sharing, ownership of the biological samples and data, legislative framework for biobanks and other emerging social issues.[48] One of the main issues discussed in this thesis was the need to define the type of consent deemed applicable for residual HBMs for biobanking. Informed consent in particular has been noted as being a highly discussed ethical topic in journal publications.[49] Opinion leaders have proposed various regimes of informed consent including the mode of consent-taking and type of information needed to render an informed consent valid. Some experts have suggested a highly structured and specific informed consent process, while others considered that implicit, presumed or general consent would suffice. Zubin Master *et al*. systematically reviewed 470 publications and found no evidence of consensus on any consent regime for biobanking,[50] although all authors agreed that contributors should not be

---

[47] BUDIMIR, D., POLASEK, O., MARUSIC, A., KOLCIC, I., ZEMUNIK, T., BORASKA, V., JERONCIC, A., BOBAN, M., CAMPBELL, H. & RUDAN, I. 2011a. Ethical aspects of human biobanks: a systematic review. *Croat Med J,* 52**,** 262-79.

[48] *Ibid.*

[49] *Ibid.*

[50] MASTER, Z., NELSON, E., MURDOCH, B. & CAULFIELD, T. 2012. Biobanks, consent and claims of consensus. *Nat Methods,* 9**,** 885-8. ibid.

exposed to additional privacy and other risks without their consent. We will review the various consent regimes for biobanking in the following chapter.

1.4.1 Types of Consent

Current established informed consent regimens in tissue banking of residual HBMs include explicit types like specific consent, tiered consent, general or broad consent, and implicit or presumed consent. Each of these regimes is considered below.

Specific consent

Specific consent is also known as project-based consent, where tissues requested for are only used in a specific project. Participants actively participate in the consent-taking process and explicitly consent to the contribution of HBMs by filling out a form. Specific written consent is regarded as offering the highest guarantees to the participant, in terms of specific assurances on the terms of participation. It is most appropriate in studies that contain some level of risk, such as when participants disclose personal or sensitive information. For this reason, experiments and in-depth interviews in particular commonly rely on written consent. However, specific consent is also appropriate for studies with no risk above those of daily life, when the participants are exposed to deception, or any experimental treatment, if researchers consider the need to provide participants with as much information as possible at the point of consent to be important. Information provided will often include specific uses of the HBMs, specific period of storage and whether the donors will be re-contacted for consent to the use of their specimens for purposes that fall outside of the scope of the original (and documented) consent.

Tiered consent

Tiered consent is considered as broader consent (when compared to specific consent); where patients agree to a menu of options, which may include broad or specific consent for future use such as whether it is for a related or unrelated disease, time period, commercial uses, genetic conditions and so on. Participants can choose from a list of different choices and level of participation. In addition, they can specifically decline certain future research applications. For example, participants can choose not to allow their HBMs to be used for cosmetic products or cloning.

Broad consent (or open consent)

Broad consent is also known as one-time open consent or generic consent for all future uses of tissues. Here, participants consent to a less limited range of options such as future types of research and time periods. Participants are given the explicit choice to opt-out during the initial consent process or to withdraw at any time after they have consented. Broad consent is different from blanket consent in that the latter allows donated HBMs to be used for all purposes without any control or restriction.[51] Broad consent permits some specific requirements (such as right to withdraw) and limitations on the future use of samples, whereas blanket consents does not allow any restrictions on future research studies. For example, if specific types of research are known to be in

[51] HANSSON, M. G., DILLNER, J., BARTRAM, C. R., CARLSON, J. A. & HELGESSON, G. 2006. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol,* 7**,** 266-9.

conflict with the fundamental values of contributors, such as studies on human cloning, these can be precluded in the initial broad consent.[52]

Presumed consent or implicit consent

Presumed consent is also known as opt-out or implied consent. Patients are informed that their specimens will be used for future research unless they deny permission by opting-out. Patients must actively opt-out if they do not wish to donate their tissues.[53] Participants are informed of the research or the collection of the HBMs for future research, and are considered to agree to participate unless they specifically decline or explicitly refuse to be included. In other words, when the patients allow their specimens to be collected for diagnostic purposes, they are presumed to have consented to research participation

Precautionary consent

The term 'precautionary consent' was used by the Council of Europe and the German Ethics Committee,[54] and explained as seeking broad consent for research use of bodily substances collected for diagnostic or therapeutic purposes. In the event of any concrete future research plans which requires the use of the retained samples, this

---

[52] WENDLER, D. 2013. Broad versus Blanket Consent for Research with Human Biological Samples. *Hastings Center Report,* 43**,** 3-4.

[53] VERHEIJDE, J. L., RADY, M. Y. & MCGREGOR, J. 2009. Presumed consent for organ preservation in uncontrolled donation after cardiac death in the United States: a public policy with serious consequences. *Philos Ethics Humanit Med,* 4**,** 15.

[54] Council of Europe and the German Ethics Committee Rec(2006)4,9

precautionary consent will suffice, in order to avoid the need and the trouble to seek re-consent or the waiver of consent by an ethics committee.[55] Similarly, the Irish Council for Bioethics also found it acceptable to routinely ask the patients for consent for possible future research use of "tissue or organs removed during surgical treatment or surplus biological material left over after diagnostic testing".[56]

Consent norms and policies in research ethics require that participants in research must be fully informed.[57] However, in a tissue banking context, due to the long-term nature of storage of HBMs in biobanks, it is impossible to predict the nature and risk of all future research at the time of collection. Furthermore, the large number of participants makes it impossible to obtain detailed specific consent or re-consent for every future research, thus making specific consent impracticable in many instances.[58] The regime of tiered consent, where participants can choose from a checklist of preferences like types of research or institutions allowed to use their stored HBMs, requires significant amount of administrative resources and also limits the usefulness of stored HBMs.[59] It is also difficult to rely on presumed or implied consent for prospective collection of residual HBMs, given that informed consent is the "norm" for use of HBMs in research.

---

[55] GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. *J Med Ethics,* 38**,** 351-5.

[56] Irish Council for Bioethics. Human Biological Material: Recommendations For Collection, Use and Storage in Research. 2005. http://www.bioethics.ie/uploads/docs/BiologicalMaterial.pdf

[57] BEAUCHAMP, T. L. 2011. Informed consent: its history, meaning, and present challenges. *Camb Q Healthc Ethics,* 20**,** 515-23.

[58] MASTER, Z., NELSON, E., MURDOCH, B. & CAULFIELD, T. 2012. Biobanks, consent and claims of consensus. *Nat Methods,* 9**,** 885-8.

[59] MASTER, Z. & RESNIK, D. B. 2013. Incorporating exclusion clauses into informed consent for biobanking. *Camb Q Healthc Ethics,* 22**,** 203-12.

1.5 Current Guidelines on Biobanks in Singapore

In the following chapters, I will present and discuss the status of biobanking in Singapore, and its ethical governance. I will primarily focus on Singapore's Bioethics Advisory Committee (BAC) report on Human Tissues Research, which was released in November 2002, and the current situation more than a decade after its first implementation. Biobanks and tissue repositories in Singapore must comply with BAC's recommendations, as they are adopted by the Ministry of Health, and enforceable by professional councils of healthcare professionals. In this thesis, the National University Hospital (NUH) Tissue Repository will be the key research focus, and is further illustrative of the current biobanking situation in Singapore. Various points discussed in this section will be emphasized and elaborated in the chapters that follow.

1.5.1 BAC Guidelines on Tissue Banking

As indicated above, Singapore's national guideline for human tissue banking and biomedical research was released in November 2002 by the Bioethics Advisory Committee (BAC). Currently, this is the first and only guideline on human tissues research published in Singapore. These Human Tissues Research guidelines have been revised in a draft report in 2012, however the final version has not been released when this chapter was written.

The BAC's report on Human Tissue Research focused mainly on two key issues: (1) respect for and welfare of the donor, and (2) confidentiality. As noted above, human tissue is

broadly defined in this report.[60] According to the guidelines, researchers and tissue banks are required to obtain "full, free and informed consent of the donor" before either taking or accepting any HBMs for research, and must ensure confidentiality of the contributor's personal information during collection, storage, and use of human biological materials for research. Contributors of HBMs should be adequately informed, and free from any coercion or undue influence. They should be able to understand and appreciate the risks, potential benefits, and alternatives of contributing their HBMs and have either 'competence' or have the 'mental capacity' to make a valid decision. This may include comprehension and retention of the information provided. HBMs may be collected for either clinical tests, diagnosis or treatment or specifically for one research and only residual materials from such collections can be transferred to a tissue repository for storage in anticipation of its future use in research. The BAC guidelines further stressed the importance of informed consent as autonomy-based governance, especially in cases where residual tissue is from either therapeutic or diagnostic purposes, which can be used for research.[61]

1.5.2 BAC - An outright gift model for tissue donation

The BAC has proposed that consent form should state the contribution of residual HBMs as either an "outright gift" or donation without any conditions,[62] and that all tissue samples contributed for research use must be given either without any personal or direct benefit from the contribution or claim to property and future rights on the HBMs. This unconditional

---

[60] BAC, S. 2002. Human Tissue Research: A report by Bioethics Advisory Committee Singapore. November 2002.

[61] *Ibid*, Section 8.9.

[62] *Ibid*, Recommendation 1.D and Section 8.5.

gift excludes future provision of information to contributors on either any medical condition or predisposition discovered in the course of research, unless it has been earlier agreed upon during the informed consent process. Contributors should be informed of the 'unconditional gifts' arrangement and if they disagree, their contribution of residual HBMs should not be accepted.

The outright gift model allows the accepting organisation or the 'donee' to have total control over the gifted HBMs. Accepting organisation of the donated HBMs would prefer the "outright gift" model as the mode of contribution because they can have complete control over the use and disposal of the HBMs any way they wanted without further consultation or consent from the contributors. The most obvious difficulty or disadvantage with outright gifts is the total loss of ownership and control of the gifted property by the contributors, as donors. The donors have no control or decisional rights over the HBMs once they are donated as outright gifts and they have to bear the risk of their donated materials being used for researches which they do not support (for example, cloning) or risk being identified through genetic research.

The 'gift' model of donation is also stated in the Medical Therapy, Education and Research Act (MTERA). The MTERA, however, make provision for the use of only the bodies of deceased persons or parts thereof for purposes of medical or dental education, research, advancement of medical or dental science, therapy and transplantation, and for other related purposes. Any person who is not mentally disordered and who is 18 years of age or above may give all or any part of his body for any of the purposes specified in section 7 of the Act, and the gift will only take effect upon death.

The BAC views that participation in research should be on an altruistic basis, and this includes contributing HBMs for research. Here, the benefit can be practical since research institutions need not be unduly concerned with the outcome of the research or with encouraging social participation and contribution to the common good. Some disadvantages include questions of fairness to the participants and extent of accountability on the part of the research institution. My empirical research findings in Chapter 3 will discuss this aspect further.

1.5.3 Recommendation on Governance and regulations

The BAC recommended that all research tissue banks ought to be statutorily approved and licensed, and advised the setting up of a statutory board to oversee and license institutions and companies carrying out human tissue research and banking thus making it necessary that all such research activities be approved and monitored.[63] Recommendation 2 of the BAC report stated that research tissue banking should only be allowed in institutions approved by appropriate authorities, and not by private individuals. They further recommended that a statutory authority must be set up to provide statutory regulation and supervision of research tissue banking, and that institutions must have transparent and appropriate systems, and standards for the ethical, legal and operational governance of research tissue banking.[64] The significance of this recommendation and its special relevance to this thesis will be discussed in Chapter 4.

---

[63] *Ibid*, Section 11.4 and 11.5.

[64] *Ibid*, Recommendation 3.

1.5.4 Where are we now in terms of Biobank governance?

Whilst this thesis supports autonomy-based governance and accepts the importance of informed consent, in terms of respect of autonomy and a contributor's right to choose,[65] I argue that informed consent alone does not carry much moral value and may not be effective in protecting participants from harm. Specific informed consent, in particular, provides participants with a choice on whether or not to donate their HBMs unconditionally and this consent type limits future use of HBMs that is undetermined at time of donation. It is argued that greater emphasis should be placed on effective governance of management of a biobank or tissue repository, transparency on the use of stored HBMs and frequency statutory monitoring of its operations. The subject of governance will be elaborated on in Chapter 4.

Current ethical governance on the use of stored residual HBMs in Singapore still lacks transparency, accountability and monitoring. The BAC's recommendations on statutory regulations, governance and supervision still have not been implemented. Contrary to BAC's recommendation, there is no statutory authority body to regulate and supervise all human tissue research in Singapore, and institutions and companies carrying out human tissue research and banking, are not transparent with their safeguards and there is no clear system of accountability over the collection, storage, distribution and use of residual HBMs. Further, there is a gap between the corresponding institutional duties and a contributor's rights in biobank research. This is evident especially in the absence of ethical governance of biobanks in terms of transparency and accountability, the inconsistencies in the issues of consent,

[65] CAMBON-THOMSEN, A., RIAL-SEBBAG, E. & KNOPPERS, B. M. 2007. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J,* 30**,** 373-82.

ethical governance and right of withdrawal. These issues have negative repercussions on public trust and long-term support, which are pivotal to the success of biobanking projects.[66] For example, the BAC guidelines stipulated that only institutions and companies approved by appropriate authorities and not by private individuals could set up tissue banks and be permitted access to residual tissues. A reason for the BAC's concern is that individual researchers may not have enough resources, expertise and motivation to properly maintain the tissue collection. The BAC is evidently interested to avoid an incident such as Alder Hey from occurring in Singapore. Unfortunately, without the presence of such an authority body, individual researchers in institutions and private companies can set up their own private collections of HBMs thus storing HBMs in their research laboratories for personal use, without supervision, governance or control. This shortfall in governance has been noted in the position paper on 'Human Tissue for Biomedical Research: Tumour Banks', written by the Chapter of Pathologist Committee (2001-2002), of the Academy of Medicine, Singapore for the BAC. Section 3.4 of the paper stated: "It has been common practice to store collection of tissues (including blood, blood products and body fluids) on completion of the project, with a view to use these for future yet to be specified projects. The principal investigators may also 'share' samples with other researchers." These investigators have their own storage for HBMs that they collected and not discarded after the completion of a research project. The main concern is that in the original protocol of the research and consent provided by the contributors did not clearly reflect that the HBMs would be stored in archive indefinitely, and shared with other researchers or used for future research. Ethically, an investigator must first obtain informed consent from the participants if he or she wants to store such materials and use them for future research either by themselves or

[66] TUTTON, R., KAYE, J. & HOEYER, K. 2004. Governing UK Biobank: the importance of ensuring public trust. *Trends Biotechnol,* 22**,** 284-5.

by others. All future researches must also be approved by an independent research ethics committee or IRB.

Until a statutory research tissue banking governance authority is established in Singapore to assure protection of donors in tissue research and guidelines or regulations for the management of biobanks in medical research are established and/or harmonized, the responsibility of ethical governance is shouldered by the IRB and biobank administrators, who may not be in the position to resolve deficiencies of the current regulatory or governance framework. Existing governance issues include lack of participant protection and uncontrolled use of biological samples, and potential security breaches that could compromise the privacy and confidentiality of data held by a biobank.[67]

1.5.5 Role of the Institutional Review Board (IRB) in tissue research

The IRB is empowered by its affiliated institution and the Ministry of Health to review all human subject research. IRBs have the mandate from respective institutions to approve, reject, propose modifications, or terminate any proposed or ongoing research involving human subjects conducted by researchers within the institution,[68] using considerations set forth according to BAC's third report entitled *Research Involving Human Subjects: Guidelines for IRBs* in Singapore. However, it is debatable whether IRBs are the most appropriate

[67] AURAY-BLAIS, C. & PATENAUDE, J. 2006. A biobank management model applicable to biomedical research. *BMC Med Ethics,* 7**,** E4.

[68] MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.

bodies to evaluate research projects involving biobanks.[69] Most IRB members fail to understand their roles as the safeguard and control of HBMs in biobanks,[70] and are not well versed in the ethical issues and operations of a biobank.[71] IRBs are not established solely to oversee biobank research but all research involving human subjects conducted within the institution. It may therefore be expected that IRBs are overwhelmed with different types of human subjects research and this situation can be aggravated by conditions such as manpower constraint.[72] Auray-Blais *et al*. presented a survey of 43 research ethics boards and IRBs in Canada, demonstrating difficulties for IRBs in reviewing and managing research projects with biobanks and a high percentage of rejection of protocols involving the use of HBMs stating that "the risks of discrimination and stigmatization being a recurrent issue."[73] Overly- cautious IRBs may however hinder research on HBMs. Further, the effectiveness of an IRB in the monitoring of biobank governance and control is also doubtful since it is only mandated to receive annual continuing review reports from approved projects.[74] Auray-Blais *et al*. also reported on the burden on IRBs attempting to evaluate research projects involving the use of storage samples in biobanks and demonstrated difficulties for IRBs to

---

[69] AURAY-BLAIS, C. & PATENAUDE, J. 2006. A biobank management model applicable to biomedical research. *BMC Med Ethics,* 7**,** E4.

[70] ROTHSTEIN, M. A. 2002. The role of IRBs in research involving commercial biobanks. *J Law Med Ethics,* 30**,** 105-8.

[71] MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.

[72] MOUTEL, G., DE MONTGOLFIER, S., DUCHANGE, N., SHARARA, L., BEAUMONT, C. & HERVE, C. 2004. Study of the involvement of research ethics committees in the constitution and use of biobanks in France. *Pharmacogenetics,* 14**,** 195-8.

[73] AURAY-BLAIS, C. & PATENAUDE, J. 2006. A biobank management model applicable to biomedical research. *BMC Med Ethics,* 7**,** E4.

[74] MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.

manage research projects with biobanks.[75] McHale *et al*. mentioned that despite good intentions, neither conventional research ethics committees nor IRBs can provide an effective solution to the legal and regulatory challenges arising from biobanks. They further proposed the setting up of either a specialist ethics or biobank ethics and governance committee to focus on ethics and governance and also provide oversight in relation to the operation of biobanks.[76] However, they cautioned that without a formal legal status for biobank ethics committees, these committees are 'toothless tigers' and thus unable to 'formally bite' and hold a biobank accountable. This discussion will be further elaborated on in Chapter 4.

In the next chapter, I will discuss the consent taking process of a major biobank in Singapore.

[75] AURAY-BLAIS, C. & PATENAUDE, J. 2006. A biobank management model applicable to biomedical research. *BMC Med Ethics,* 7**,** E4.

[76] MCHALE, J. 2011. Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger? *Health Care Analysis,* 19**,** 231-246.

Chapter 2. Human Biological Materials: Abandonment, Donation or Participation in Research?

The focus of this Chapter is on the consent regime of a major hospital and tissue repository in Singapore. It is in this context that the need of informed consent is traced to legal discourses on property and on fundamental rights, and their subsequent impact on the ethics of consent taking. Various consent regimes have since emerged, and the consent-taking process of the hospital being studied in my research could be regarded as a form of broad or even 'precautionary' consent. However, the hospital's tissue repository relies on the notion of donation. I argue that the 'general or broad consent' regime is a combination of legal theory on property and fundamental rights, which emphasizes respect for persons and individual choice. In important ways, the notion of donation goes beyond general consent. The differences between these two approaches are discussed in the context of Singapore, and current notions of informed consent in relation to biobanks are presented and critiqued.

Currently, there are two main research tissues repositories in Singapore, namely, SingHealth Tissue Repository (STR) and National University Hospital Tissue Repository (NUH TR). These tissues repositories collect HBMs from healthy volunteers, patients and post mortem cadaver for use in population based studies, clinical research or disease-specific diagnosis and treatment.

STR was established by SingHealth, the largest healthcare group in Singapore, and comprised a network of 2 hospitals, 5 National Specialty Centres and 9 Polyclinics. It is the largest

research tissue repository in Singapore.[77] STR operates under the guidance of the STR Committee, comprising clinicians practicing in local hospitals, research scientists, as well as lawyers and the Chairman of SingHealth Centralised IRB. The STR Committee oversees the development and implementation of institutional bio-specimen banking policies and guidelines, and reviews and approves requests to collect and access specimens.

The NUH TR was established by the National University Hospital (NUH), which comprised the National University Hospital (NUH), along with Yong Loo Lin School of Medicine, the Faculty of Dentistry and Saw Swee Hock School of Public Health of the National University of Singapore (NUS). The common governance structure was intended to create synergy to advance health by integrating clinical care, research and education in Singapore.[78] NUH TR was guided by the NUH TR Steering Committee, which oversees the development and implementation of institutional bio-specimen banking policies and guidelines whereas another committee, the NUH TR Scientific Review Working Committee, reviews and approves requests to collect and access specimens.[79]

Until 2011, the Singapore Biobank (SBB) was the third research tissue repository in Singapore. It was established in 2002 as a national tissue bank by Singapore's government-lead Agency for Science, Technology and Research (A*STAR) and Ministry of Health. The SBB was first known as the Singapore Tissue Network (STN) and changed its name to SBB on 1st

---

[77] SingHealth Tissue Repository website, accessed on 1 June 2014 http://research.singhealth.com.sg/Pages/SingHealthTissueRepository.aspx

[78] National University Health System website, accessed on 1 June 2014 http://www.nuhs.edu.sg/corporate/introduction.html

[79] National University Health System Tissue Repository website, accessed on 1 June 2014 http://medicine.nus.edu.sg/tissue/

April 2010. SBB collected bio-samples directly from researchers, NUH TR and STR. SBB was designed to be a core research infrastructure to support Singapore's Biomedical Sciences Initiative and facilitate bench-to-bedside translational research, as well as population based epidemiological research. In September 2011, the closure of SBB was announced to the surprise and dismay of biomedical researchers and research institutions in Singapore, for various reasons, which include funding shortage, low utilization rates, problems in collection of HBMs and lack of trust.[80]

In the following section, we discuss the consent regime of NUH TR and another consent regime of NUH with regards to residual HBMs from surgery. The latter regime relies on general consent and, very loosely, the notion of abandonment of residual HBMs from surgery. In contrast, NUH TR relies on 'donation' – an approach that is consistent with national ethics policy but with at least one important qualification. The notion of donation goes further in being broader than what general or broad consent permits. It relates to the giving of HBMs toward one or more purposes, and may even be conceived as having the character of a 'charitable' purpose. It is in this context that the various regimes of consent set out in Chapter 1 are discussed and critiqued. For reasons set out in Section 2.5 below, both approaches (i.e. general consent and donation) are better than a specific consent regime. As outlined in Chapter 3, empirical data is provided in support of this argument. However, I argue that the requirement of informed consent is insufficient to safeguard the welfare and interests of patients as research participant. The BAC's recommendations on human tissue research imply this point, and many systems-level issues have still remained

[80] CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.

unanswered. Some of these issues will be considered at the end of this Chapter, and further elaborated on in Chapter 4.

2.1 Consent Regimes in NUH for Biobanking

2.1.1 NUH – A Singapore example

NUH has been collecting and storing residual HBMs from patients over many decades. Two separate consent-taking processes are used: one in relation to the donation of residual HBMs from all surgical procedures - for medical research, education and study purposes, and another for the specific storage of both residual HBMs and associated medical information in NUH Tissue Repository (NUH TR), mainly for research purposes. In both consent-taking processes, patient is assured that (1) whether he/she decides to give consent or not, it will not affect the standard of medical care he/she will receive; (2) no additional HBMs will be removed beyond what is therapeutically necessary; and (3) the residual HBMs are stored only after information for diagnosis and treatment has been extracted. The consent in both processes may be characterised as broad consent, but with important differences as NUH TR is also concerned with donation of residual (and non-residual) HBMs. The contribution of residual HBMs from all surgical procedures seems to give effect to the concept of 'abandonment', whereas the language of 'donation' is relied on by NUH TR detailed informed consent, which allows donor the right to withdraw consent after agreeing initially. Both consent processes will be analysed further later in this chapter.

2.1.2 Consent-taking for storage and use of residual HBMs from surgeries

During pre-operative counselling, all patients admitted to NUH are provided with a copy of surgical consent form, which contains a simple paragraph to obtain broad consent for specified uses of their residual HBMs. The aim of this consent process is to provide general information to prospective donor about the choice of contributing surgically removed residual HBMs for research, education and study purposes, and only after they are no longer required for the medical care of donor.

Consent-taking for the use of residual HBMs not required for medical management, occurs simultaneously with consent taking for surgical intervention, as both are components of the same Surgical Consent Form (Figure 1. Consent for Operation/Procedure). Hence, a patient can decide how his/her residual HBMs should be disposed of at the point of consent taking for a recommended surgical intervention.

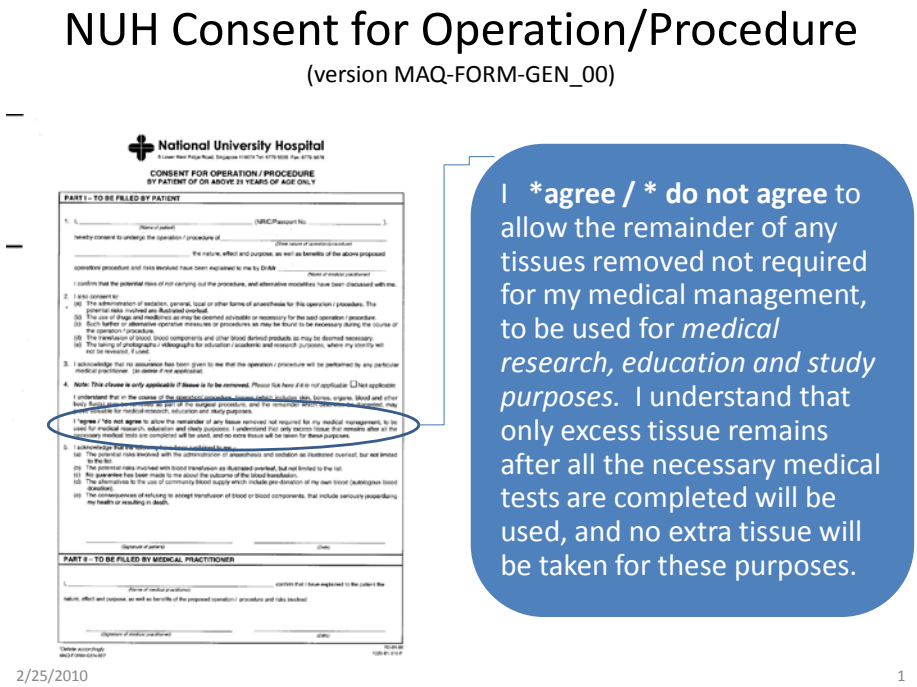


FIGURE 1: SAMPLE OF NUH CONSENT FORM

Patients can opt to either agree or disagree (by deleting the non-applicable option labelled with asterisks in the section) for their residual tissue to be used for research and education. If a patient refuses to provide consent, the surgical excess HBMs that are not required for diagnosis will then be destroyed as biological wastes. This refusal is recorded in the medical records, so that the same patient will not be asked to donate her HBMs to the NUH TR at a later stage.

There is no explicit statement on withdrawal of consent or for use of medical records in this consent form. Consequently, any residual HBMs donated through this process are anonymised tissue and can be used in research without any further restriction. In practice, a 'consent' nurse (if consulted) will assure patients that their medical care will not be affected if they declined.

2.1.3 Consent-taking for the banking of residual HBMs and medical information with NUH TR

Due to various factors including shortage of storage space, quality of HBMs, amount of residual HBMs after diagnostic tests and funding limitations, not all HBMs are 'banked' into NUH TR. Approximately 10% of all residual HBMs are usually found suitable for banking in the NUH TR. Hospital administration considers it too burdensome to obtain informed consent from every patient for the storage of residual HBMs, as most of them would not be banked. Furthermore, residual HBMs obtained from surgery (but not banked with NUH TR) do not contain personal identifiers or direct linkage to patients' medical records concerned.

The selection of suitable residual HBMs for 'banking' is primarily determined by a pathologist from the NUH TR, who reviews daily scheduled surgeries to identify potential residual HBMs suitable to be stored for future research. This selection is based on existing or anticipated research needs and that NUH TR is established as a cancer tissue repository primarily aim on the collection of residual cancer tissues for research purposes. After patients have consented to donate residual HBMs, these tissues are collected at the pathology department only after the completion of diagnostic tests. Collected tissues are then stored in pathology archives, either as paraffin-embedded tissue blocks for diagnostic purposes or frozen tissue materials obtained from leftover surgical diagnosis.

For HBMs found suitable for storage in NUH TR, a separate consent will then be requested from selected patients. This process involves a more detailed discussion with a trained 'informed consent' nurse from NUH TR. During discussion, the nurse will explain contents of the NUH TR 'Participant Information' pamphlet (set out in Appendix 2), which include description on the nature of donation, potential users of the donated HBMs, accessibility of HBMs to commercial companies, non-return of research results, potential risks and harm from donating, and no personal benefits for any research discovery. Patients are also informed that they can contact NUH TR if they change their minds and wish to withdraw from NUH TR after signing the consent form. NUH TR will then destroy any unused samples, as the collected biological sample(s) will not be returned to the patients for bio-safety reasons. Patients will again be provided with an assurance that no additional tissues will be removed and that only residual tissues from diagnosis and surgery will be collected after full diagnosis is established. They will also be informed that future research utilising their HBMs must first be approved by an IRB before NUH TR releases them. In addition to the IRB, a NUH TR Steering Committee, comprising senior clinicians and surgeons from the hospital, governs subsequent access, use and distribution of stored HBMs. Before any HBMs are

released from NUH TR, the Steering Committee must ensure that the proposed research has good scientific merits and has been given ethical approval. As noted earlier, consent will be sought for use of medical data, as well as additional HBMs such as blood, hairs, nails and urine (which are not strictly residual). At this stage, the patient may seek clarifications from the nurse and can still refuse to 'bank' his/her residual HBMs (and related medical information) in the NUH TR, despite having previously consented in the Surgical Consent Form.

For residual HBMs meant for banking with NUH TR, a computerized tracking system links the consent status of residual HBMs using individualised barcodes to avoid storage of residual HBMs without the requisite consent for use of medical data (i.e. leftover surgical tissue donated as anonymised HBMs). Once a patient consents to the banking of his/her residual HBMs with NUH TR, this system will link the individualised barcode to patient's hospital identification number on all of his/her medical investigations and diagnostic results. After the medical data corresponding to the residual HBMs are obtained, identifiers will then be coded via a coding system. All banked specimens are issued a NUH TR code number and identifiers are removed and stored in a separate database, to prevent disclosure of any personal identifiers to researchers when they request for HBMs (and accompanying information). The database with patient identifiers, that are linked to NUH TR code numbers, are kept by an institutionally designated information trustee, which is audited quarterly.

As both consent processes (in relation to residual surgical HBMs and NUH TR) do not impose serious limits on the range of research applications or duration of storage, they may be categorised as general or broad consent (following the categorization set out in Chapter 1). This is consistent with the recommendations of BAC, although we should note that the system of governance proposed by BAC, has not yet been fully implemented (to be discussed

in relation to governance in Chapter 4). The practicality of general consent is easy to understand, especially when informed consent has been regarded – at least in common law jurisdictions – as central to the lawful taking and use of HBMs. Given that it is impractical, and certainly impossible, to specify the range of research applications during consent-taking and avoid the need of having to seek re-consent later on, the BAC has gone further to encourage researchers to persuade research subjects to donate HBMs for research. In effect, general consent to collect and use a tissue, and a conditional donation of tissue, are broadly similar in outcome. Where informed consent has not been properly obtained, such taking or use is unlawful, unless the HBMs are regarded as 'abandoned' or otherwise approved by legislation. As we will discuss later, there is no serious difference in terms of the legal consequences between HBMs that have been donated for research and those that were regarded as 'abandoned'.

2.2 Abandonment in Property Law

When biological materials are removed during surgery, it is assumed that most patients no longer want such residual HBMs. It is uncommon that people ask about the status of their removed HBMs,[81] and this is also shown in my empirical research in the next chapter. The removed HBMs became either of secondary importance or of a lesser interest to the patients in comparison to the diagnosis and prognosis of their medical condition. When patients go into surgery, they do not undergo the procedure for the purpose of donating HBMs to research and do not think much of the "diseased" or excised HBMs with the

[81] CAENAZZO, L., TOZZO, P. & PEGORARO, R. 2013. Biobanking research on oncological residual material: a framework between the rights of the individual and the interest of society. *BMC Medical Ethics,* 14**,** 17.

exception of diagnosed results (such as if the excised tissues is either benign or malignant). Most patients undergoing medical or surgical procedures would have no further interest in their removed HBMs. To some individuals, it would be termed as 'abandonment' of these unwanted 'waste' materials. From a property law perspective, it has been argued that such residual HBMs have been 'abandoned' as unwanted materials.

Such an argument of 'abandonment' of surgically removed tissue was illustrated in the case of *John Moore v University of California*.[82] Mr. John Moore consented and underwent treatment and surgery for hairy cell leukaemia at UCLA Medical Center under the clinical care of Dr. David Golde. Tissues from his removed cancerous spleen were later developed into a cell line, which was then commercialised by Dr. Golde, without Moore's knowledge, information, permission or consent. Mr. Moore eventually sued the UCLA Medical Center, Dr. Golde and his team of researchers for breach of fiduciary duty and conversion for the use of his 'property' for commercial benefit without consent.[83] The court initially ruled in favour of Mr. Moore but the decision was subsequently reversed by the courts of appeal.

Additionally, there was no specific law that regulates the relationship between patients as source of HBMs and biobank when the *Moore case* was heard. The concept of property law was used together with other existing laws, such as the Uniform Anatomical Gift Act (UAGA), which regulates the use of body parts for research and donation of body parts of individuals after death. [84] The Supreme Court of California found that Mr. Moore had no property rights to his discarded organs and cells since they no longer belonged to him after they were

---

[82] Moore v. Regents of University of California (1990) 51 Cal.3d 120

[83] *Ibid*., Sect III A and IIIB

[84] *Ibid*., Section FN22

removed from his body. The court ruled that Mr. Moore did not have ownership rights in the newly generated cell line that was established from his removed organs, or in its patent rights. For this reason, a cause of action for conversion could not be sustained.[85] As Mr. Moore did not claim his excised spleen immediately after his surgery, he had actually abandoned his excised organ. Mr. Moore decided to sue to regain his rights of ownership only after he realised that there was a patent filed and the cell line was commercialised. Justice Broussard of the Supreme Court of California stated that "in common scenario, the patient has abandoned any interest in the removed organ and is not entitled to demand compensation if it should later be discovered that the organ or cells have some unanticipated value."[86] If individuals enjoyed property rights over their bodily tissues, individuals could then sell their tissues for biomedical research purposes, and a range of different transactions between donors and scientists would be possible.[87] However, existing regulations, such as Section 7054.4 of the Health and Safety Code, prohibit "commercial exploitation" and the buying or selling of human organs, and defined "scientific use" as "not-for-profit scientific use". These made it impossible for property rights to be granted to Moore in relation to his organ, as it would be illegal to profit from such rights.[88]

The court also mentioned that it would be a great burden for research physicians if they had to ensure that each tissue sample was obtained through extensive informed consent procedures. Further, the court stated that if the research physician needed to obtain specific information each time they collected a tissue sample, the progress of research

---

[85] *Ibid*., Pg. 487 Sect B

[86] *Ibid*., Pg. 500 Sect II

[87] Moore v. Regents of University of California (1990) 51 Cal.3d 120 Pg. 518 Sect 5

[88] *Ibid*., Pg. 492 FN 34

medicine would be significantly hampered.[89] The appeal case was subsequently terminated due to the demise of John Moore during the legal process and Mr Moore's claim for the lack of informed consent on the use of his tissues and breach of fiduciary duty of researchers were legally unanswered with the termination of this case.[90]

Another similar case that involved property rights and informed consent was the case of *Greenberg et al. v Miami Children's Hospital Research Institute et al.* The *Greenberg case* re-visited the *Moore's case,* when a group of individuals involved in a research on *Canavan* disease entered into collaborations with Dr Reuben Matalon and the Miami Children's Hospital Research Institute (MCH) to identify the gene responsible for the disease.[91] Dr Matalon successfully isolated the gene and secretly filed a patent application without Greenberg's consent, which led to Greenberg, suing Dr Matalon and MCH. Relying on the diverse nature of contributions to medical research, MCH argued that if every contributor had the right to decide on how and to whom the research results could be used or made available to, medical research would be impossible. Basing its rationale on the *Moore* decision, the defendants argued that short of an explicit agreement on property rights in the outcome of research, it should not be assumed that contributors of HBMs retained any property interests in these materials. In other words, it was argued that the plaintiffs did not have a right to exercise control over the commercialization of the patent, as they retained no recognized interests in the HBMs contributed to research. This case was ultimately settled through a confidential agreement. MCH was still able to license its patent and collect

---

[89] *Ibid*., Pg. 487 Sect B

[90] BIAGI, K. G. 1991. Moore v. Regents of the University of California: patients, property rights, and public policy. *St Louis Univ Law J,* 35**,** 433-62.

[91] 2003. Greenberg v. Miami Children's Hospital Research Institute. *Wests Fed Suppl,* 264**,** 1064-78.

royalties in relation to the use of clinical testing for *Canavan* disease, which it had developed. However, licence-free use of the *Canavan* patent in research directed at finding a cure for the disease was allowed as a compromise.[92]

In these two cases, the legal concept of abandonment was implicitly used to support a policy position. Abandonment is an act of either surrendering, deserting or relinquishing property or contract rights or giving up of something, which we are entitled. It is normally an act of intention and thus a permanent decision. In the *Moore* decision, majority of the judges agreed that a removed body part, by its nature, could never constitute 'property' for the purposes of a conversion action.[93] However, Justice Broussard in his dissent on the conversion cause of action in the *Moore* decision, stated that when a "patient consented to the use of his removed organ for general research purposes and the patient's doctor had no prior knowledge of the scientific or commercial value of the patient's organ or cells, I would agree that the patient could not maintain a conversion"[94] He further added he could not agree when "the unauthorized use of excised organ or cells, even against a party who knew of the value of the organ or cells before they were removed and breached a duty to disclose that value to the patient." In this case, when a patient does not know the value of his organ, and decided not to claim ownership and abandoned the organ to the disposal of the hospital, would this abandonment out of ignorance and lack of information still be valid? It can be argued that by withholding information from patients, especially when the researchers know that there is value in the materials and patients are intentionally misled (through non-

---

[92] ANDERLIK, M. R. & ROTHSTEIN, M. A. 2003. Canavan decision favors researchers over families. *J Law Med Ethics,* 31**,** 450-4.

[93] Moore v. Regents of University of California(1990) 51Cal.3d 120 Pg. 501 Sect II

[94] *Ibid*., Pg. 500 Sect II

disclosure) into abandoning them is unethical and maybe even illegal under the common law (for conversion).[95] I agree that although there can be no property rights to the removed organs, researchers must not be allowed to obtain the excised HBMs using deception, concealment and fraudulent practices. To ensure transparency in the collection of residual HBMs, researchers need to obtain informed consent and permission from patients when the medical procedures are being conducted. The court in the *Moore* decision also upheld Moore's claim for "cause of action for breach of fiduciary duty and lack of informed consent."[96]

In a third case, *Washington University v. Catalona*, research participants donated HBMs to Dr William Catalona, a clinician researcher at the Washington University (WU), by signing a WU Genetic Research informed consent form.[97] The HBMs would be stored in WU's biobank. Dr Catalona resigned from WU and wanted to transfer his collected samples to his new employer in Northwestern University. He wrote to his research participants requesting for their permission to release the WU retained sample to him. The court ruled that the research participants "parted with any semblance of ownership rights once their biological materials were excised for medical research".[98]

The 'abandonment' of the removed tissues was also discussed in studies focusing on expansion of biobanks' collection of research tissues and discourses of handling medical

---

[95] Moore v. Regents of University of California(1990) 51Cal.3d 120 Pg. 501 Sect II

[96] *Ibid*., Pg. 479

[97] Piccolo, Kaitlin M (2008) In the Wake of Catalona: An Alternative Model to Safeguard Research Participants' Interests in their Biological Materials. University of Pittsburgh Law Review, 69 (4). pp. 769-788. ISSN 0041-9915

[98] Wash. Univ. v. Catalona, 437 F. Supp. 2d 985, 988 (E.D. Mo. 2006), aff'd, 490 F.3d 667, 673 (8th Cir. 2007). at 997.

waste as a way of legitimizing biobanking activities.[99] Within biobanking discourses, the term 'medical waste' was often used when tissues samples that would otherwise be discarded after an operation or a procedure, were collected as waste and subsequently used for research.[100] The 'waste' discourse is closely related to the abandonment discourse in that both discourses imply that the contributor cannot lay claim of ownership once the waste material is no longer privately valued by its 'owner' (as defined by Porter).[101] The case of Mr. John Moore highlighted that removed tissues were viewed by the courts, in relation to the scientific production of knowledge and economic development, as abandoned 'waste'. In the *Catalona* decision, the court further ruled that the right to withdraw only meant that research participants had ceased providing HBMs pursuant to a research protocol and WU could either destroy the materials, or store indefinitely without further use or remove all identifiers and use the anonymized HBMs in 'exempted' research.[102]

Most patients do not know the value of their HBMs, and 'abandon' the HBMs for disposal by the hospital, due to ignorance and lack of information. It cannot be concluded that it is done intentionally since they do not have such knowledge before. Most of the time, there is no need for a thorough examination of the reasons behind an intention to abandon. In other words, a simple intent to 'abandon' will be enough, unless there is fraud, deceit or similar

---

[99] TUPASELA, A. 2011. From gift to waste: changing policies in biobanking practices. *Science and Public Policy,* 38**,** 510-520.

[100] BROCHHAUSEN, C., ROSSRICKER, N. & KIRKPATRICK, C. J. 2007. Biological waste, ownership and personality - future perspectives for the secondary use of human tissue in the view of national and international regulations. *Pathology Research and Practice,* 203**,** 404-404.

[101] PORTER, R. C. 2002. *The Economics of Waste*, Resources for the Future.

[102] PICCOLO, KAITLIN M (2008) In the Wake of Catalona: An Alternative Model to Safeguard Research Participants' Interests in their Biological Materials. University of Pittsburgh Law Review, 69 (4). pp. 769-788. ISSN 0041-9915

unlawful conduct on the part of the wrongdoer. Furthermore, a successful action in legal conversion does not imply that the patient will have a claim over a patent derived from his organ. In reality, it is difficult for the hospital or a researcher to clearly indicate whether a patient's residual HBMs will subsequently give rise to commercial profits, and the extent that is owed to the patient. Although Justice Broussard's dissent has ethical persuasion, the injustice that Mr. Moore suffered is also not difficult to appreciate. Jeffrey Potts wrote in support of Mr. Moore's cause of action for the physician's failure to gain the patient's informed consent and argued for the need of expanded disclosure to the patients in the spirit of promoting greater transparency.[103] Others have also argued for the action of battery to include instances where physical wrongdoing occurred without the person concerned having been sufficiently informed.[104] However, it is quite a different matter to say that an individual should suddenly acquire property interests in his or her HBMs for the reason of preventing unjust enrichment on the part of the wrongdoer. Clearly, no hospital or researcher should obtain HBMs through deception, concealment or fraudulent practices. In most of such jurisdictions, a range of legal recourses for such transgressions exists. For more ambiguous situations, a fair system of research governance should at least ensure clarity of expectations, responsibilities and entitlements on all parties involved. Arguably, property-based notion of HBMs is one of two most profound influences that the *Moore* and *Greenberg* decisions have had on research ethics and research governance of residual HBMs. Another critical element, which was mentioned earlier, is the legal emphasis on informed consent. As we shall consider in the next section, the underlying rationale for this

---

[103] POTTS, J. 1992. Moore v. Regents of the University of California: expanded disclosure, limited property rights. *Northwest Univ Law Rev,* 86**,** 453-96.

[104] BERGMAN, H. R. 1992. Case comment: Moore v. Regents of the University of California. *Am J Law Med,* 18**,** 127-45.

requirement rests on a property-based theory or property law, but more so on fundamental rights.

The *Moore* case has been influential in giving emphasis to certain values such as informed consent and the preclusion of property rights in the body. These legal values have been influential in shaping US bioethics, as a number of bioethicists have observed. Bioethics in Singapore has been heavily influenced by leading scientific jurisdictions, particularly the US and the UK, among others. Important lessons have been learnt on the need for informed consent, and some problems with overemphasis of informed consent. There is no established legal case on the use of HBMs in Singapore. Singapore legal system follows common law ruling and thus US and UK legal cases may have indirect implications in Singapore. Major areas of law – particularly administrative law, contract law, equity and trust law, property law and tort law – are largely judge-made, though certain aspects have now been modified to some extent by statutes. The Singapore court regularly draws on oversea common law cases, with considerations on the local contextual and sociocultural norms. The recent public consultation on the Human Biomedical Bill has brought the attention on the use and ownership of human tissues in research. According to one author, this issue is normally overlooked by Singapore and leftover tissues have been used for research without requiring specific consent from the patients.[105]

2.3 Legacy Tissue and the Rejection of Implied Consent

[105] ANDY HO 2014. Tissue samples: A need to protect owners' The Straits Times 05 Dec 2014

The centrality of informed consent is perhaps best illustrated in the BAC's rejection of implied consent as justification for the use of legacy HBMs. The BAC observed that, whether in Singapore or elsewhere, the "existence of large collections of tissue samples accumulated over the years for which no specific or adequate consent for research investigations has been obtained" posed a special difficulty.[106] An example of legacy tissue is the old collection of diagnostics sample tissues originally collected for diagnostic purposes in relation to conditions, such as cancer. Given the age of the collection, there is a strong likelihood that the patients might have died or can't be traced for consent. By virtue of their sheer size and range of coverage, the BAC recognised that legacy tissue collections are often very valuable to academic and commercial researchers.

As these patients do not have property rights in their residual HBMs retained as legacy tissues, it may be argued that implied consent has been provided as these materials are simply left at the disposal of the institutions concerned.[107] The implicit understanding was that the institution could collect and store all residual HBMs for its own purpose, unless a patient explicitly refused or expressed that he/she did not want the residual HBMs to be stored in the tissue repository or otherwise used in future research.[108] Specific refusal must be expressed each time a procedure is performed or a blanket refusal must have been articulated for all the medical procedures during the treatment period. In comparison with presumed consent in organs transplantation, Forsberg *et al*. stated that the use of presumed

---

[106] BAC, Human Tissue Research, Section 9, pages 28-29.

[107] PULLEY, J., CLAYTON, E., BERNARD, G. R., RODEN, D. M. & MASYS, D. R. 2010. Principles of human subjects protections applied in an opt-out, de-identified biobank. *Clin Transl Sci,* 3**,** 42-8.

[108] BROTHERS, K. B., MORRISON, D. R. & CLAYTON, E. W. 2011. Two large-scale surveys on community attitudes toward an opt-out biobank. *Am J Med Genet A,* 155A**,** 2982-90.

or implied consent would increase the amount of HBMs available for medical research, if the known purpose of the institution were to build a large collection of HBMs for research.[109] Informed consent need not be explicitly requested from each patient when biobank and institutional researchers presume that patients intend to contribute to medical advancement through biobanking for future research to improve future health and treatment of patients. Such an approach will save time, effort and expense in having to obtain informed consent from every patient.

Reliance on implied consent could also represent a positive endorsement of donation of residual HBMs as a good thing to do. It has been argued that formal acceptance of this approach could lead to donation becoming a norm, build trust in the system and thereby increasing donation rates.[110] However, the difficulty with implied consent is that some patients may either not be able to or not have the opportunity to refuse consent. Arguably, this problem may be mitigated, by allowing patients to withdraw their HBMs from the tissue bank at any time without having to provide any reason. Those in favour of implied consent further argue that the risk of harm from donation of residual HBMs is rather low (as privacy risks can be reduced by maintaining stricter confidentiality requirements) and there is no risk of physical harm, as no additional procedure will be performed on the patients. Overall, the benefits of implying consent for the donation of HBMs outweigh the risk to these individuals, especially when safeguards and controls are in place for the collection and subsequent use of the HBMs. More generally, adoption of a presumed or implied consent regime could be supported by applying an essentially utilitarian approach.

---

[109] FORSBERG, J. S., ERIKSSON, S. & HANSSON, M. G. 2010. Changing defaults in biobank research could save lives too. *Eur J Epidemiol,* 25**,** 65-8.

[110] *Ibid.*

Although the BAC did consider that a reasonable and consistent good stewardship to allow reasonable and respectful research use of legacy tissues collected in good faith, its rationale was not based on implied consent. While it did recognise that greater public good could be achieved in allowing a responsible research use of legacy tissue, it would be illusory to imply consent when research use might not have even been considered at the time which HBM was obtained. Rather, the principle of reciprocity was relied upon as justification. As the BAC noted elsewhere, the current proven medical treatments are a result of medical research on someone else's previously donated tissues.[111] To promote and support social good through medical research to discover new treatments for future patients, current patients should be expected to demonstrate solidarity in being willing to contribute their residual HBMs for research, as they have benefitted from the contributions of past patients.[112] On the issue of consent, the BAC noted that legislative intervention might be necessary to "cure the defect stemming from the problems with the lack of consent."[113] In the UK, the Human Tissue Act served as such a legislative intervention, although a similar legislation has yet to be enacted in Singapore.

2.4 Rights-based Jurisprudence

Based on both *Greenberg* and *Moore cases*, the courts were reluctant to grant property rights over tissues, primarily on public policy reason that parts of the human body should not

[111] GOTTWEIS, H., CHEN, H. & STARKBAUM, J. 2011b. Biobanks and the phantom public. *Human Genetics,* 130**,** 433-440.

[112] HENS, K., NYS, H., CASSIMAN, J. J. & DIERICKX, K. 2011. Risks, benefits, solidarity: a framework for the participation of children in genetic biobank research. *J Pediatr,* 158**,** 842-8.

[113] BAC, Human Tissue Report, Section 9.6, at page 28.

be commercialised.[114] In the case of residual HBMs, if a patient does not ask for his/her removed tissue after the surgery, to be retained or returned after the surgery, it will then be effectively considered as abandoned. The patient can have no claim of ownership over it, and the hospital is free to dispose or use it for research or any other purpose. Some experts have argued that, if no property rights are assigned to the excised tissues, informed consent or permission to use the residual HBMs would be legally redundant and unnecessary, and these residual materials should be used in medical research for the advancement of science.[115] However, this could encourage an ethically problematic practice of not informing patients about how their residual HBMs will be used or disposed of. A good case on point is the Alder Hey scandal.[116]

In 1999, Alder Hey Children's Hospital in Liverpool UK, was discovered to have retained unauthorized organs from post-mortem of deceased patients. These unauthorized retention of organs triggered public anger and distress, when Alder Hey and other hospitals within the National Health Service UK were found out to have retained deceased patients' organs without detailed family consent and approval. A public inquiry was conducted to uncover the retained organ scandal, which involved unauthorised removal, retention, and disposal of human tissue, including children's organs, during the period 1988 to 1995.[117] The scandal

---

[114] BAC, Human Tissue Report, Section 9.6, at page 28.

[115] FORSBERG, J. S., ERIKSSON, S. & HANSSON, M. G. 2010. Changing defaults in biobank research could save lives too. *Eur J Epidemiol,* 25**,** 65-8.

[116] BARNES, L., MATTHEWS, F. E., BARBER, B., DAVIES, L., LLOYD, D., BRAYNE, C. & PARRY, B. 2005. Brain donation for research: consent and re-consent post Alder Hey. *Bull Med Ethics***,** 17-21.; ENGLISH, V. & SOMMERVILLE, A. 2003. Presumed consent for transplantation: a dead issue after Alder Hey? *J Med Ethics,* 29**,** 147-52.

[117] BARNES, L., MATTHEWS, F. E., BARBER, B., DAVIES, L., LLOYD, D., BRAYNE, C. & PARRY, B. 2005. Brain donation for research: consent and re-consent post Alder Hey. *Bull Med Ethics***,** 17-21.

subsequently led to the set-up of the Retained Organs Commission, an independent commission that catalogued and returned 105,000 organs retained by hospitals in England. The Human Tissue Act 1960 was subsequently revised in 2004 to overhaul all existing legislations regarding the handling of human tissues and created the Human Tissue Authority in the UK.[118] This scandal also heightened the need for informed consent for collection and use of HBMs, and it was during the same period that Singapore hospitals saw the need to implement informed consent for the collection of leftover tissues, starting from NUH in 1 April 2002.

While it is evident that a person has no legal claim over his/her body or body parts as property, in a sense that they can be disposed for commercial gain, he/she is recognised to have some control over them. Broadly drawn from human rights theory, the requirement of informed consent is now accepted as the basic requirement for protecting patients and research subjects.[119] For informed consent to be valid the person concerned must have a good understanding of what is being asked of him/ her, has decision-making capacity and any decision made must be voluntary.[120] Past research abuses where human subjects were intentionally or unintentionally harmed in human experimentation or simply kept ignorant of risks that would have concerned them, served to reinforce the need of informed consent. Famously, informed consent is enshrined as a fundamental requirement in the Nuremburg

---

[118] MAVROFOROU, A., GIANNOUKAS, A. & MICHALODIMITRAKIS, E. 2006. Consent for organ and tissue retention in British law in the light of the Human Tissue Act 2004. *Med Law,* 25**,** 427-34.

[119] HOFMANN, B. 2009. Broadening consent--and diluting ethics? *J Med Ethics,* 35**,** 125-9.

[120] FADEN, R. R. & BEAUCHAMP, T. L. 1980. Decision-making and informed consent: a study of the impact of disclosed information. *Soc Indic Res,* 7**,** 313-36. ibid.

Code created in response to the Nazi experimentations.[121] This was also adopted by the World Medical Association in the Declaration of Helsinki. More recently, research scandals such as the Tuskegee syphilis study[122] and other events like the retention of organs from demised children in Alder Hey (as discussed above) emphasise its continuing relevance, particularly where biobanking is concerned.[123] It should therefore not be surprising that the requirement of informed consent was emphasised in both the *Moore, Greenberg* and *Catalona* decisions.

More recently, lawsuits relating to the retention and use of residual blood samples from new-born screening in the US continue to illustrate the central importance of informed consent. Many state governments in the US (through their department of health) collect blood samples from most infants born in the country each year, with the goal of detecting and treating a variety of potentially serious conditions. All 50 states, including the District of Columbia, operate new-born screening programmes. New-born screening is mandatory in 49 states, and most of the 4 million infants born each year in the United States undergo new-born screening.[124] The Texas Department of State Health Services (DSHS) has been collecting new-born blood samples from babies born within the state since the 1960s. Texas

---

[121] POST, S. G. 1991. The echo of Nuremberg: Nazi data and ethics. *J Med Ethics,* 17**,** 42-4.; COHEN, B. 1990. The ethics of using medical data from Nazi experiments. *J Halacha Contemporary Society,* No. 19**,** 103-26.

[122] ROY, B. 1995. The Tuskegee syphilis experiment: medical ethics, constitutionalism, and property in the body. *Harv J Minor Public Health,* 1**,** 11-5.

[123] STJERNSCHANTZ FORSBERG, J., HANSSON, M. G. & ERIKSSON, S. 2011. Biobank research: who benefits from individual consent? *BMJ,* 343**,** d5647.; WAUGH, P. J. 2004. Getting ethics into practice: comparing Alder Hey with Tuskegee is not helpful. Ibid.329**,** 513; author reply 513.; CURTIS, H. Ibid.Getting ethics into practice: Tuskegee was bad enough.;

[124] LEWIS, M. H., GOLDENBERG, A., ANDERSON, R., ROTHWELL, E. & BOTKIN, J. 2011. State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics,* 127**,** 703-12.

currently tests for 28 disorders including cystic fibrosis, endocrine disorders, fatty acid disorders, and genetic testing for hemoglobinopathy, phenylketonuria, and galactosemia. Leftover HBMs, in this case – new-born blood samples – were stored for future research.

In March 2009, a group of parents formed the Texas Civil Rights Project and filed a lawsuit in US District Court, claiming that the state's collection and storage of the leftover new-born blood samples without the consent of the parents amounted to "an unlawful search and seizure" and violated the privacy rights of the parents and their children. In their lawsuit, the parents argued that there was no legal authority for the hospitals to keep the blood indefinitely without consent. Under the settlement, the state agreed to destroy 5.3 million samples it has collected from 2002 when the Department of State Health Services began storing the blood. Similar actions were filed in other US states. In Minnesota, another lawsuit was spearheaded by the Citizens' Council for Health Freedom in St Paul demanded that the state obtained written informed consent to collect, store or use new-born infants' leftover blood samples.[125] The court ruled that Minnesota's Department of Health must destroy 1 million new-born blood samples in November 2011 and to pay nearly $1 million in legal costs.[126] Based on these events and developments, there is a great challenge to collect and store leftover diagnostic HBMs for future research without informed consent. While consent and permission for storage and use are needed, I argue that this is not a suitable regime of consent for biobanking in the next section.

---

[125] Bearder v. State of Minnesota 788 N.W.2d 144 (Minn. Ct. App. 2010).

[126] STEIN, R. 2009. Newborns' Blood Samples Are Used for Research Without Parents' Consent. *Washington Post*

2.5 'Donation': Beyond Abandonment and Fundamental Rights

In the *Moore* decision, the court considered a further approach. Since Mr. Moore did not ask for the return of his organ or demand compensation prior to the removal of his excised HBMs, he could be regarded as having made a gift of it to his physician. During the hearings, however, there was no evidence that Mr. Moore specifically intended to donate his excised residual HBMs and it could not conclude that Mr. Moore voluntarily gave his residual HBMs away.[127] Although the Supreme Court ruled that Mr. Moore had no ownership interest and property rights in his excised residual HBMs, he did have some other rights over it. As a 'bundle of rights', some types of personal property: "(1) may be sold but not given away, (2) while others may be given away but not sold, and (3) still others may neither be given away nor sold."[128] In the case of HBMs, the court ruled that while the sale of organs and tissues was prohibited by law, they could be transferred as a gift.[129] This transfer of HBMs does not amount to a sale of commodity when no 'valuable considerations' were given in exchange for them.

When a person donates something, whether it is money or tissue, he/she willingly transfers the possession of the item, for a purpose other than his/her own profit or benefit. Such a purpose may be an altruistic intention to donate to a specific cause or for a specific condition. This cause is what makes donation a morally significant action, and it includes giving to charity or medical research. In the case of patients who choose to donate their

[127] Moore v. Regents of University of California (1990) 51 Cal.3d 120 Pg. 507

[128] *Ibid*, at 509

[129] *Ibid*, at 510

residual HBMs to a biobank, it is a gift towards the generation of knowledge for medical purposes.

By treating tissue donation as a gift, most patients voluntarily transfer control over the excised HBMs to the tissue banks to benefit a cause or purpose. This action need not be purely motivated by true altruism, in a sense that most patients will decide that they have no use of the excised HBMs and will expect it to be thrown away. They may thus be willing to give the residual HBMs away for a worthy cause, rather than to have them discarded as medical waste.[130] This is unlike a truly altruistic cause of unconditional giving even when the gift is valuable to the donor. A patient may explicitly make a donation or gift to the biobank if he/she wishes to contribute to future research. This explicit wish to donate residual HBMs to the biobank may be expressed as part of consent taking for a medical intervention or as a separate process. Where the former is concerned, this can be achieved by adding a checkbox to the pre-existing consent form authorizing residual HBMs to be transferred to a biobank for future research use. As we have considered, the consent-taking process and consent form in relation to NUH TR present an invitation for patients to donate their residual HBMs and medical information for collection and future research use. Where appropriate, the donation could extend to additional HBMs. The nature of the giving is presented as a purposive one, and is therefore different from general or broad consent. But can it be construed as a conditional gift? After all, patients retain a right to withdraw, if they wish to in the future.

---

[130] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

As with any other donation, the patient may decide to make an unconditional or conditional gift with the residual HBMs.[131] An unconditional gift of residual HBMs would allow any researcher to use the specimens for any research, whereas a conditional gift would specify a patient's preference, for example, that the donated residual HBMs could only be used in future breast cancer research and nothing else. This condition may be acceptable for a tissue bank for breast cancer research, but a general biobank may not be able to comply with such a specific condition. Thus, a biobank must be certain that it has the capability to commit to, and comply with, the conditions that govern the use of residual HBMs, should it decide to accept donation on a restricted or conditional basis. Where NUH TR is concerned, no such limitation of purpose is provided for. There is also no explicit restriction on the duration for retention of HBMs and associated information. It may also be relevant to note that, up to the completion of my empirical research, no patient has withdrawn consent. Thus, the status of residual HBMs collected by NUH TR is best understood as materials donated for the purposes of research. The right of withdrawal, while not entirely consistent with the nature of the gift, is arguably an undertaking provided by NUH TR as institutional goodwill to honour any such request, if they should arise. In other words, the right to withdrawal is an expression of freedom of choice and transparency rather than a characteristic associated with the HBMs. This aspect of NUH TR's policy will be further discussed in Chapter 4.

2.6 The Illusion of 'Fully' Informed Consent

[131] GLANTZ, L. H., ROCHE, P. & ANNAS, G. J. 2010. Gift giving to biobanks. *Am J Bioeth,* 10**,** 33-4.

Based on these events and developments, it is legally challenging to just rely on abandonment or implied consent for prospective collection of residual HBMs, given that informed consent is the 'gold standard' for use of HBMs in research. Informed consent is required by key international guidelines on research ethics (like WHO, CIOMS, HUGO and UNESCO guidelines on tissue banking) before any tissues are removed and stored.[132] The difficulties rest on how much patients and potential research subjects should be 'informed'. Where biobanks are concerned,[133] the issue has been framed as whether fully informed consent is possible and practicable at the point of collection where the nature of future studies is unforeseeable when consent is first obtained.[134] The main challenge in this part of consent-taking process is that, the eventual purposes for the utilisation of the stored HBMs are not always foreseeable at the time of collection.

In the case of *Havasupai Tribe of Havasupai Reservation v Arizona Board of Regents*, secondary use of DNA samples first collected for diabetes studies, was subsequently used for migration patterns and mental illness. The original 'Diabetes Project' was consented to by the Havasupai participants and intended to include health education, collecting and testing of blood samples, and genetic association testing to search for links between genes and diabetic risk.[135] After several years, the Arizona State University (ASU) researchers then used the blood samples containing DNA, for other unrelated studies such as studies on

---

[132] FORSBERG, J. S., ERIKSSON, S. & HANSSON, M. G. 2010. Changing defaults in biobank research could save lives too. *Eur J Epidemiol,* 25**,** 65-8.

[133] HOEYER, K., OLOFSSON, B. O., MJORNDAL, T. & LYNOE, N. 2005. The ethics of research using biobanks: reason to question the importance attributed to informed consent. *Arch Intern Med,* 165**,** 97-100.

[134] O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7.

[135] GARRISON, N. A. & CHO, M. K. 2013. Awareness and Acceptable Practices: IRB and Researcher Reflections on the Havasupai Lawsuit. *AJOB Prim Res,* 4**,** 55-63.

schizophrenia, migration, and inbreeding, all of which are taboo topics for the Havasupai. These subsequent research projects were conducted without individual identifiers and without re-consent, but with IRB approval from ASU.[136] The Havasupai tribe claimed that they consented only to the use of the HBMs for diabetic research, and not to other research uses, even though they signed a consent form to "study the causes of behavioural/medical disorders".[137] They claimed that the dignity of its tribe members and community reputation were compromised by these secondary research applications. The case was eventually settled out of court with the Arizona University's Board of Regent agreeing to pay $700,000 to 41 of the tribe's members, returning the blood samples and providing other forms of assistance to the impoverished Havasupai.[138] The *Havasupai* case illustrates the restrictive nature of informed consent that is specific to one type of research application and failed to respect the sensitivities of the tribes and their members.

According to Onora O'Neill, informed consent relies on two ethical tests: legitimate uses of human tissue must not inflict gratuitous injury, and must not override the consent of those whose tissues are used. Any use of human tissue that either injures gratuitously or removes tissue without consent is an abuse.[139] But the requirements for a detailed and full-informed consent have been criticized by Onora O'Neill.[140] She argued that the ethical justifications

---

[136] Havasupai Tribe of Havasupai Reservation v. Arizona Bd. of Regents, 204 P.3d 1063 (Ariz. App. Div. 1 2008)

[137] 2010. After Havasupai litigation, Native Americans wary of genetic research. *Am J Med Genet A,* 152A**,** fmix.

[138] MELLO, M. M. & WOLF, L. E. 2010. The Havasupai Indian tribe case--lessons for research involving stored biologic samples. *N Engl J Med,* 363**,** 204-7.

[139] O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7..

[140] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.

for informed consent in medical treatment, human research and use of human tissues, have been supported by poor arguments and exaggerated claims.[141] Four major limitations of full informed consent have been set out as: (1) Some patients may lack competency to understand the information provided, e.g. the very young or old, very ill, demented or mentally impaired, unconscious or confused, bodily discomfort or merely frail, or in medical emergency; (2) informed consent is useless in selecting public health policies, which are uniform throughout the population; (3) medical treatment of one individual may use personal information of his family and relatives without their informed consent; and (4) people who are under duress or constraints, like prisoners and soldiers, the vulnerable and dependent that normally have the mental capacity to consent are still unable to refuse at the point of consent.

Onora O'Neill further cautioned that: "It is important not to lay exaggerated weight on some mythical notion of 'fully' informed consent, and to take account of the particular difficulties that arise in the case of those - children and others - who are not legally competent to consent."[142] O'Neill supports the need for consent and does not support the waiver of consent or the use of implied or presumed consent, where patients are not asked for consent but presumed that they have agreed if they have not opted-out or objected. In her opinion: "Inaction may be evidence of failure to notice or understand what is going on; acquiescence may reflect mere idleness or adaptive preferences, mere cynicism or

[141] O'NEILL, O. 2003. Some limits of informed consent. *J Med Ethics,* 29**,** 4-7.

[142] O'NEILL, O. 2001. Informed Consent and Genetic Information. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences,* 32**,** 689-704. Page 693 Para 1.

frightened awareness that dissent has costs."[143] She further stated that "consent that is uninformed (for example, based on ignorance or deception) does not legitimate; consent that is not free (for example, based on duress or manipulation) does not legitimate."[144] "Misinformed" consent with the purpose to deceive or coerce patients into donating their tissues or forcing the patients to donate their tissues under duress should be illegal.

With the advent of personalized medicine and genomics research, medical and scientific research and practice are making ever more varied use of human tissue. The cases of unscrupulous or unacceptable use of human tissue reported, even by a small handful of researchers or doctors, may bring important medical and scientific activities into disrepute, and lead to public demand for restrictions on the uses of human tissue calling for a betrayal of trust.[145] Thus, informed consent may not offer adequate protection for the patients and does not necessarily promote trust. O'Neill added that informed consent, while essential, is not enough to show that use of human tissue is acceptable. As we shall see, the empirical findings of this thesis (reported in the next Chapter) support her position.

For different reasons, it would often not be possible or practicable to re-contact the patients or research participants who have contributed residual HBMs for consent. For example, samples of HBMs collected in the 1980s could now be used for genetic research (including whole genome sequencing), which was an unknown type of research at the time of collection. Where research using retained and banked HBMs is expected to be socially beneficial and where no risk of harm to the individuals, some have argued that the concept

---

[143] *Ibid.,* Page 692 Para 1.

[144] *Ibid.*

[145] O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7.

of abandonment could still be relied upon, provided that they have also expressed agreement for their tissue to be stored and used in research. One such approach is recommended by the Nuffield Council on Bioethics.

The Nuffield Council explored the relationship between the HBMs contributors and the removed excised tissue, and especially the issue of whether the person retained any right of control over it, or if the consent to surgical removal was regarded as implying abandonment of the tissue.[146] In the case of removal of tissue from patients in the course of their medical treatment,[147] the Nuffield Council held that "consent to treatment should constitute abandonment of tissue, and that the possibility that tissue might then be archived or stored and subsequently used in the treatment of the patient or others, or in medical research and education, should be indicated in general terms in standard consent procedures." [148] This concurs with the *Moore* decision and related cases, and may explain NUH's consent taking for the storage and use of surgical residual HBMs for research (as discussed in the beginning of this chapter). Similar to NUH, many biobanks or tissue repositories now specify, in consent-taking, that agreement to contribute and store tissue is also an agreement to the use of such tissue in research as the biobank or repository consider appropriate (and typically subject to ethics review and approval).

Another approach has been to use general or broad consent in a way described by some as 'precautionary'. As discussed in chapter 1.4.1, 'precautionary consent' was used to seek

---

[146] 1995. Nuffield Council on Bioethics. Human tissue: ethical and legal issues. London: Nuffield Council on Bioethics.

[147] GRUBB, A. 1995. The Nuffield Council report on human tissue. *Med Law Rev,* 3**,** 235-6.

[148] O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7.

broad consent for research use of residual HBMs. The broad consent was requested as a form of precaution and in the event of any future research plans on retained samples, this precautionary consent would suffice, in order to avoid the need and trouble to seek re-consent or the waiver of consent by an ethics committee.[149] This was accepted by the Council of Europe and the German Ethics Committee. The Irish Council took into consideration that "such consent by its nature would have to be a broad consent, as the type of the research was completely unknown at the time [when it was taken from the subject]".[150] I am of the view that precautionary broad consent should accordingly be sought, in case a need arises in the future for the research use of stored HBMs. This option is an extension of the strategy of broad consent, and is administered to all patients and research participants, for the ease of consent-taking and is less burdensome in terms of detailed or 'full' information that these individuals will otherwise have to deal with. The latter is especially problematic with patients, who are often under physical discomfort and emotional stress, as their main concern would be the therapeutic outcome, rather than with research participation or the fate of the excised residual HBMs. Many patients also lack technical and scientific competency to understand biobanking and the nature and types of research that could be conducted. They are also unlikely to fully appreciate and understand the benefits and risks entailed, which is demonstrated in my research (discussed in Chapter 3). Some patients may feel stressed when asked for additional informed consent (in addition to consent for their medical procedure) before their surgery. Studies have shown that there is no perfect time for taking consent on the collection and use of residual HBMs from

---

[149] GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. Ibid.38**,** 351-5.

[150] *Ibid.*

patients, since they are likely to be in emotional distress and anxious before the surgery. After surgery, patients are invariably physically strained due to surgical pain and need to rest.[151] In the Chapter that follows, empirical evidence from Singapore derived for this thesis presents a finding that is consistent with these observations. As we shall see, patients (no less in Singapore) often decide on the fate of their residual HBMs without much consideration but would instead base their decision on mere trust to the establishment, professionals and that research would generate knowledge for public good and advancement of medical treatment. Thus obtaining "fully" informed consent for research use of residual tissues may not be practicable and ethical, if the vulnerable state of these patients is to be taken seriously.

Consent for future research use, even if by broad consent, should be more appropriately understood as a means of promoting transparency and respecting a person's autonomous decision on their choice to donate of the residual HBMs after surgery. Such permission or consent should explain the usefulness of these otherwise discarded HBMs. Individuals who have any objections (for whatever reasons) to having their residual HBMs stored and used for research would be given the opportunity to refuse consent. Although being 'informed' is crucial, in that permission for storage and use of residual HBMs should be given or refused based on the information provided, such information should be understandable and comprehended by the patients at that moment they were asked. It is almost always not helpful to provide patients with a long list of unverifiable and overly detailed information. Rather, reliance on basic general information that is comprehensible and pertinent is more

---

[151] HEWITT, R., WATSON, P. H., DHIR, R., AAMODT, R., THOMAS, G., MERCOLA, D., GRIZZLE, W. E. & MORENTE, M. M. 2009. Timing of consent for the research use of surgically removed tissue: is postoperative consenting acceptable? *Cancer,* 115**,** 4-9.

likely to empower patients to determine for themselves their willingness to be involved (through contribution of their HBMs) in research. A clear and simple general informed consent or permission is more likely to encourage trust, whereas a ten-page consent form with technical jargons, terms and conditions with exclusion clauses, will cause further confusion and mistrust.

2.7 Informed Consent is an Inadequate Safeguard – the importance of statutory governance in biobanking

As we have considered earlier in this chapter, most tissue repositories would have informed prospective donors that their HBMs will be banked for future and unspecified research in the form of a general consent.[152] The BAC goes further to emphasise donation towards a more generic purpose and by adopting this approach, the donation could be understood as being even more open-ended that that of general consent.

The recommendations of the BAC did not stop at outright donation of residual HBMs. It also recommended that all research tissue banks (including biobanks) ought to be statutorily approved and licensed, and advised the setting up of a statutory board to oversee and license institutions and companies that carry out human tissue research and banking, making it necessary that all such research activities be approved and monitored.[153] In addition, the BAC proposed that research tissue banking should only be conducted by

[152] ALLEN, J. & MCNAMARA, B. 2011. Reconsidering the value of consent in biobank research. *Bioethics,* 25**,** 155-66.

[153] BAC, Section 11.4 and 11.5.

institutions approved by the appropriate authorities and not by private individuals,[154] and institutions must have transparent and appropriate systems, and standards for the ethical, legal and operational governance of the research tissue banking.[155]

While recognizing the importance of informed consent,[156] the BAC is correct that this autonomy-based governance does not offer adequate protection of research participants from harm. Informed consent provides patients with a choice on whether or not to donate their HBMs unconditionally, but once the donation has been made, an effective system of governance on a biobank's operation must be in place to ensure accountability and transparency. Currently, the system of ethical governance of the use of residual HBMs in Singapore still lacks transparency and accountability. The BAC's recommendations on statutory regulations, governance and supervision are still not implemented. Contrary to BAC's recommendation, there is still no statutory authority being set up to regulate and supervise all human tissue research in Singapore. Further, institutions and companies that carry out human tissue research and banking are not transparent with their safeguards. There are also inadequate measures in place to ensure accountability in the collection, storage, distribution and use of donated HBMs. These issues will have implications for securing the public trust and long-term support that the success of biobanking depends on.[157] However, due to the absence of statutory authority, individual researchers in

---

[154] *Ibid*, Recommendation 2.

[155] *Ibid*, Recommendation 3.

[156] CAMBON-THOMSEN, A., RIAL-SEBBAG, E. & KNOPPERS, B. M. 2007. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J,* 30**,** 373-82.

[157] TUTTON, R., KAYE, J. & HOEYER, K. 2004. Governing UK Biobank: the importance of ensuring public trust. *Trends Biotechnol,* 22**,** 284-5.

institutions and private companies could still set up their own private collections of HBMs and storing HBMs in their own research laboratories for their own use, without any clear supervision or governance and control.

While the IRB is empowered by the institution and Ministry of Health to review all human subject research, it has the mandate from the institution to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving human subjects conducted by researchers of the institution,[158] and applying the guidelines of the BAC.[159] However, the role of the IRB in the monitoring of biobank governance and control is restricted since it is only mandated to receive annual continuing reports from approved projects.[160] McHale *et al.* mentioned that conventional research ethics committees or IRBs could not provide an effective solution to the legal and regulatory challenges arising from biobanks. They proposed the setting up of specialist ethics or biobank ethics and governance committee, with legislation, to focus on ethics and governance, and to provide oversight in relation to the operation of biobanks.[161] Properly situating informed consent within a system of research ethics governance is discussed in Chapter 4. In the Chapter that follows, empirical data is presented in support of the proposition that informed consent is in itself an inadequate safeguard of patient welfare and interests. The nature and content of

[158] MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.

[159] BAC, "Research Involving Human Subjects: Guidelines For IRBS", November 2004.

[160] MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.

[161] MCHALE, J. 2011. Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger? *Health Care Analysis,* 19**,** 231-246.

these welfare and interests are elucidated (in the context of Singapore), with a view to better inform ethical governance and policies with regards to HBMs.

Chapter 3. Research on donation of residual biological samples and consent given for secondary use

3.1 Background

The research value of residual HBMs in tissue repositories or biobanks has been earlier discussed in Chapter 1. However, the scientific potential of HBMs cannot be achieved unless ethical challenges can be effectively addressed. Of these challenges, there is still no clear consensus on an appropriate standard for informed consent, according to Budimir *et al* (2011) in their systematic review on the ethical aspects of human tissue repositories and biobanks.[162] As discussed in Chapter 2, the general requirement of informed consent is not disputed. However, it remains unclear how much information must be provided in order for consent to be sufficiently 'informed' and whether lack of sufficient information will render the consent invalid. This has been a subject of debate and some scholars have argued for 'fully' informed consent, which is equivalent to the model of specific consent within a classificatory system of consent-taking presented in Chapter 1. For instance, Tom Beauchamp argued that the pervasive view in U.S. bioethics is that if consent is taken, it should be an adequately informed consent and that a broad consent is not sufficiently

[162] BUDIMIR, D., POLASEK, O., MARUSIC, A., KOLCIC, I., ZEMUNIK, T., BORASKA, V., JERONCIC, A., BOBAN, M., CAMPBELL, H. & RUDAN, I. 2011b. Ethical aspects of human biobanks: a systematic review. *Croat Med J,* 52**,** 262 - 279.

"informed". [163] Others have criticised this proposition to be illusory, and have instead gone further to propose approaches in implied consent or general consent.[164]

In Chapter 2, it is argued that broad consent is to be preferred, provided that it is instituted within a broader system of governance that promotes accountability, transparency and trust. A further distinction has been made between the contribution of HBMs through broad consent and one that is essentially through donation. While there will be few practical differences between the two means of contribution, donation is arguably least restrictive in that the giving is predicated on purpose (typically altruistic) rather than on explicit informational specifications, no matter how general.

This chapter reports on a systematic literature review and two empirical studies that have been conducted to uncover the purposes and motivations that underscore the contributions of HBMs to NUHTR. The demographics, knowledge, attitudes, preferences and expectations of patients with NUH as contributors of their residual HBMs are documented, analysed and compared (at a thematic level) with corresponding published data from outside of Singapore. These preferences, experiences and expectations are also related to key themes that have been identified from a systematic literature review as: (1) Reasons for donation; (2) Degree of information to be provided in consent-taking; (3) Pre- or post-surgery consent (and when to take consent); (4) Right to withdraw; (5) Privacy and Confidentiality of Medical Information; (6) Governance, safeguards and controls; and (7) Access and uses of tissues. In addition, my empirical qualitative study shows that there is a statistically significant

---

[163] BEAUCHAMP, T. L. 2011. Informed consent: its history, meaning, and present challenges. Camb Q Healthc Ethics, 20, 515-23.

[164] WENDLER, D. 2013. Broad versus Blanket Consent for Research with Human Biological Samples. Hastings Center Report, 43, 3-4.

relationship between social demographics and the likelihood that a patient will contribute HBMs to research. Demographic differences among patients do matter, and these are often not accounted for in consent taking. For instance, a certain level of information associated with a specific consent regime is provided on the assumption that all patients recruited for the study have the same informational needs. Overall, this study shows that arguments in favour of 'specific informed consent' are misguided, as most patients are not concerned with being fully 'informed'. Depending on the situation, patients are more likely to get confused by practices necessitated by specific informed consent. If they are to be burdened with a high level of details in consent taking, such an approach is more likely to encourage distrust and limit meaningful participation.

This study has been designed as an explanatory mixed-method research that was implemented in three sequential phases. It began with a comprehensive systematic review (CSR) of the literature from 1990 to 2010, regarding donors' preferences and perceptions of tissue repositories and biobanking as Phase I. The CSR provided an overview of the published information concerning patients' experiences with, and expectations of tissue banks and biobanks internationally. This was followed by a quantitative analysis of the Surgical Consent Forms of NUH over a period of 10 years and a qualitative study involving 100 NUH patients, conducted as Phases II and III respectively. The findings in Phase III of the research study have been matched and contrasted with the key themes derived from the CSR in Phase I.

This mixed-methods research methodology was selected as it enabled in-depth exploration into the different purposes and motivations to tissue donation.[165] Both quantitative and qualitative methods are used, as neither is sufficient and comprehensive on its own to capture the trends and details of perceptions, preferences and expectations with regards to tissue banking.[166] By utilizing both quantitative and qualitative research, the strengths of both methodologies are incorporated by enabling triangulation, and providing a more comprehensive analysis and account.[167]

As a component of a sequential explanatory design, the qualitative findings serve to explain and interpret the quantitative results.[168] Initially the consent rate (numeric quantitative data) of NUH patients was analysed and derived through the quantitative study using statistical analysis. The quantitative study took into account certain demographic factors, including ethnicity, religions, age groups, genders and types of organs involved, while the qualitative interviews drew out the reasons underlying the patients' participation, their understanding of the risks and benefits of participation and their expectations and attitudes towards tissue banking research. Analysis of this quantitative data, in combination with results from the CSR, facilitated the formulation of research questions for the qualitative

[165] CRESWELL, J. W. & ZHANG, W. 2009. The application of mixed methods designs to trauma research. J Trauma Stress, 22, 612-21, IVANKOVA, N. V., CRESWELL, J. W. & STICK, S. L. 2006. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. Field Methods, 18, 3-20.

[166] CRESWELL, J. W. & PLANO CLARK, V. L. 2007. Designing and conducting mixed methods research, Thousand Oaks, Calif., SAGE Publications.

[167] CRESWELL, J. W. & CRESWELL, J. W. 2007. Qualitative inquiry & research design : choosing among five approaches, Thousand Oaks, Sage Publications.

[168] CRESWELL, J. W. 2003. Research design : qualitative, quantitative, and mixed method approaches, Thousand Oaks, Calif., Sage Publications.

study (in Phase III). Qualitative interviews (text data) of NUH HBMs donors were then analysed to help explain and elaborate on the consent rate obtained in Phase II.

The qualitative study thus built on the quantitative results, by explaining why patients donated their HBMs (and medical information) to NUHTR, and what their preferences, motivations and expectations were. [169] Combining quantitative and qualitative sets of information can produce insightful results to learn more about patients' opinions, preferences and attitudes in tissue donation [170] and provide a richer account of the study population.[171] They could also be useful in informing policy-makers in the formulation of future policies and good practices in tissue donation, as these findings are thematic-based and practice-oriented. This aspect is elaborated on in Chapter 4.

3.2 Research Objective

As an explanatory mixed-method research implemented in three sequential phases, the main objective of the study reported in this Chapter is to understand and present the best available empirical evidence on the perceptions, motivations, expectations and experiences with donating HBMs to NUH TR by patients of NUH.

---

[169] CRESWELL, J. W. 2009. Editorial: Mapping the Field of Mixed Methods Research. Journal of Mixed Methods Research, 3, 95-108.

[170] IVANKOVA, N. V., CRESWELL, J. W. & STICK, S. L. 2006. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. Field Methods, 18, 3-20.

[171] CRESWELL, J. W. 2003. Research design : qualitative, quantitative, and mixed method approaches, Thousand Oaks, Calif., Sage Publications.

3.3 Methodology

A mixed-methods design[172] was conducted in 3 sequential phases, comprising a systematic literature review, a quantitative analysis of NUH Surgical Consent Form over a period of 10 years and a qualitative study involving 100 patients who had donated residual HBMs to NUHTR.

A summary of each of the three phases is as follows:

- In the first phase, a comprehensive systematic review (literature review) was conducted using a standardized data extraction and analysis tool from the Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI) and the review was subsequently published in the *International Journal on Evidence Based Healthcare,* to ensure that it meets the standards of peer researchers.[173] A comprehensive systematic review was conducted on published literature that investigated patients' experiences on the donation of their residual tissues, patients' experiences with consent-taking for the use of residual tissues and the different types of consent which influenced their decision to donate.
- In the second phase, I conducted a quantitative analysis of the consent rate among 167,329 patients in NUH in relation to the donation of residual surgical HBMs for

---

[172] TASHAKKORI, A. & TEDDLIE, C. 2003. Handbook of mixed methods in social & behavioral research, Thousand Oaks, Calif., SAGE Publications.

[173] CHAN, T., MACKEY, S. & HEGNEY, D. 2012. Patients' experiences on donation of their residual biological samples and the impact of these experiences on the type of consent given for the future research use of the tissue: a systematic review. *Int J Evid Based Healthc,* 10**,** 9 - 26. This publication was accepted as the Best Practice: Evidence-based information sheets for health professional: "Donation of residual biological samples and consent given for secondary use." by The Joanna Briggs Institute Vol 15, No 9, Page 1-4, 09/12/2011

research, education or study. A detailed quantitative statistical analysis was carried out on filled Surgical Consent Forms over a period of ten years (from 2002 to 2011), and matched with the patients' demographics, including ethnicity, religion, age groups and type of surgery.

- The third phase encompasses a qualitative study involving 100 patients from NUH who had donated HBMs to NUHTR for research. The questionnaire was designed to further understand patients' preferences, experiences and attitudes in relation to their donation. The thematic results generated were then compared with qualitative research collected from elsewhere in the world (and through the CSR in Phase I of this study).

Ethical approvals for both the quantitative research of NUH consent forms and qualitative interviews have been obtained from the National University of Singapore – Institutional Review Board (NUS-IRB). Details on NUS-IRB application and approval are discussed below and enclosed in APPENDIX 5.

3.3.1 Overview of mixed method research design

Phase 1: Comprehensive Systematic Literature Review

A systematic literature review was carried out to critically appraise, synthesize and present the best available evidence related to the perceptions, experiences and knowledge of residual biological sample donors and the impact of this experience on the type of consent given for future use of these tissues. This systematic review was conducted in accordance

with the Joanna Briggs Institute (JBI) Evidence Based Systematic Review Methodology[174] and (as noted above) the full text of this systematic review report was published in 2011 in JBI Library of Systematic Reviews. Details of this systematic review are included as APPENDIX 4. The search strategy employed in this review was to identify qualitative research results in peer-reviewed published studies from 1990 to 2010, on tissue banking and patients' preferences. A three-step search strategy was utilized. An initial limited search of MEDLINE and CINAHL was first undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles were searched for additional studies. The databases searched included Pub Med (MEDLINE), CINAHL, SCOPUS, EMBASE and PsycINFO. The search for unpublished studies included Mednar and PROQUEST. Initial keywords used were: (i) "Tissues or Biological Samples or Blood or DNA or Bones and Human", (ii) Consent, (iii) Research or Medical research, and (iv) Qualitative studies or qualitative research.

A total of 153 published papers were initially identified following a search of the abstract, title, and references of all retrieved papers. Following a review of abstract and title by 2 independent reviewers using JBI-QARI assessment tools, 29 papers were deemed appropriate to this review topic based on their methodological quality. Any disagreements that arose between reviewers were resolved through discussion or with a third reviewer. Out of the 29 papers retrieved for detailed review and examination, seven were excluded, as they were not congruent with this review study. These were mixed method studies, that

[174] The Joanna Briggs Institute. Levels of evidence and Grades of Recommendations. http://www.joannabriggs.edu.au/About%20Us/JBI%20Approach

were primarily quantitative research with some sections on qualitative discussion, and either did not contain illustrations or subjects' quotation or did not have themes relevant for this systematic research. After applying the respective criteria in the JBI methodology, out of the 22 papers identified, 18 were included and four were excluded, as the latter were not congruent with the criteria for methodological quality of this review. A total of 131 findings were identified from the 18 eligible studies and included in this review. Qualitative data were extracted from these papers using the standardized data extraction tool from the JBI's Qualitative Assessment and Review Instrument (JBI-QARI).[175] The Grades of Recommendation have been based on the JBI-developed 2006 Grades of Meaningfulness: Grade A - Strong support that merits application; Grade B - Moderate support that warrants consideration; Grade C - Not supported. Only Grade A papers are selected for this review. Studies that focused on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research and feminist research, and qualitative data from mixed-method studies were selected. This review was not limited by any geographical or cultural settings. Further, this current systematic review provided an overview of the patients' experiences of donation of their residual tissues including patient's experiences with different types of consent for the collection and use of leftover tissues, as well as the different types of consent that influenced their decision to donate. From these data, we formulated our qualitative research questions to further explore patients' preferences and attitudes toward tissue donation in the Singapore context.

---

[175] Pearson A, Wiechula R, Court A and Lockwood C. 2005. The JBI model of evidence–based healthcare Int J Evid Based Healthc 3 (8): 207–215
The Joanna Briggs Institute Levels of evidence and Grades of Recommendations. These Grades of Recommendation have been based on the JBI-developed 2006 Grades of Meaningfulness: Grade A: Strong support that merits application, Grade B: Moderate support that warrants consideration, Grade C: Not supported

Phase 2: Quantitative Research on NUH tissues consent from 2002 to 2011

This quantitative research involved statistical analysis of the consent rates of patients at NUH, over a period of ten years (from 2002 to 2011), and are matched with patients' demographics which included gender, ethnicity, religion, age group, and type of surgery in 167,329 filled consent forms. The consent rates were obtained through monthly computer-generated reports with detailed breakdown on the number of patients who had either given or refused consent under the Surgical Consent Form for their surgically removed residual tissues to be used for medical research, education or study. The reports on consent rate and demographics of the patients were provided without any identifiable personal information of any individual patient, and were initially meant to be a quality assurance project. The reports were analysed and compiled for a period of 10 years (2002-2011) with ethical approval and permission from the hospital's administration. The data has been analysed using statistical p-value hypothesis test, to determine if the observed effect was statistically significant[176] (e.g. $p<0.05$) and not due to chance or sampling error. The null hypothesis is based on the proposition that the association between the consent rate and demographic factor(s) is not statistically significant. In statistical significance testing, the p-value is the probability of obtaining a test statistic result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. The null hypothesis is rejected when the p-value turns out to be less than a predetermined significance level, often 0.05.[177] In this study, all the null hypotheses have been rejected on the basis that the associations between the consent rate and various demographic factors are of statistical significance. The

[176] FISHER, R. A. 2010. Statistical methods in genetics. 1951. Int J Epidemiol, 39, 329-35.

[177] Goodman, SN (1999). "Toward Evidence-Based Medical Statistics. 1: The P Value Fallacy." Annals of Internal Medicine 130: 995–1004

quantitative research titled: “Consent for donating leftover tissues in Singapore” was approved by NUS-IRB (Reference code: 10-252E dated 9 June 2010). NUS-IRB application and approval are set out in APPENDIX 5.

Phase 3: Qualitative Study involving HBMs Donors

Qualitative interviews of 100 NUH patients who had donated HBMs for research were conducted with the aim to further understand their preference towards donation of residual tissues, the impact of these experiences on level of information required for consent purposes, as well as experiences and attitudes towards donation. The author and consent nurses of NUHTR conducted the 100 qualitative interviews from the period of 2011 to 2012. Open-ended questions were used during the interviews. This would allow respondents to answer in their own words and to avoid pre-judging responses. This methodology collects the opinion, reflection, knowledge, perception and attitude from participants who either have donated or have intentions to donate to NUHTR. With the permission of the interviewees, face-to-face interviews were voice-recorded and verbatim transcriptions were prepared by the interviewers and compiled in an MS Excel spreadsheet. The responses to all questions were then examined using Taylor’s (2006) qualitative thematic analysis method.[178] The initial thematic domains were also identified based on our systematic literature review, as well as essences or patterns within the text and key words. New themes were subsequently identified after analysing the responses. Thematic results generated were then compared with those collected from other qualitative research selected through the

[178] Taylor, Beverley J. 2006. Research in nursing and health care : evidence for practice 3rd Edition

CSR.[179] A relatively large number of interviews (100 in total) were conducted in order to ensure that saturation points were reached for each of the emergent themes. This was also considered to be necessary as patients were in different states of health during the interviews and some of them could be too tired to answer all the questions clearly.[180] The following open-ended questions under the following themes were included in the interview:

- Reason for Donation
- Degree of Information Needed for Consent-Taking
- Pre or Post surgery Consent (or When to Take Consent)
- Right to Withdraw
- Privacy and Confidentiality of Medical Information
- Governance, safeguards and controls
- Access and uses of tissues
- Recruitment of patients for interview

The qualitative study recruited English- speaking patients who have been asked to donate their leftover tissue. The NUHTR consent nurse routinely asked patients whether they wished to donate their leftover tissues before their scheduled surgery. After the nurses noted their decisions on the donation, the subjects were then invited to participate in the qualitative research. Participation was voluntary and the patients could withdraw and not answer any questions at any time. Subjects were approached visited by the research team only after their surgery, when they were comfortable enough for the interview. Verbal

[179] AL-BUSAIDI, Z. Q. 2008. Qualitative Research and its Uses in Health Care. Sultan Qaboos University Medical Journal, 8, 11-19.

[180] MASON, M. 2010. Sample Size and Saturation in PhD Studies Using Qualitative Interviews.

informed consent was sought before the interview begun, since many did not feel comfortable about signing a document. This waiver of written informed consent has been approved by the NUS-IRB and consent was voice recorded or documented in the field notes, for those who refused to have their interviewed recorded. Each patient participated in a 30-minute interview at a time convenient for him/her. The interviewers were the NUH tissue Consent Nurses together with myself, and the interviews were conducted at the NUH's wards. The interviews were conducted only in the English language and audio-recorded if consent was obtained. Personal information were not collected from the patients but demographic information, e.g., age, sex, religion, etc., would be transferred from the initial NUHTR Consent Form to the researchers' records. Subjects' identities have been coded on the questionnaire and the NUHTR Consent Form. The data collected, including transcripts and audio-recordings, have been stored in a password=protected personal computer at the NUHTR for a maximum period of seven years after the last publication. Thereafter, the data will be destroyed.

3.4 Ethics Approval for qualitative interview

The qualitative research entitled: "Patients' experiences towards the donation of their leftover tissues and the impact of these experiences on the types of consent given for secondary use" was approved on 8 August 2011 (NUS-IRB reference code: 11-234), Head of NUHTR and Pathology. The Head of NUS Department of Pathology and NUS-IRB approved the quantitative research on consent forms statistics of NUH patients, with assistance from the NUH TR team and NUH Computer Centre. Details on NUS-IRB application, approval documents, participant consent forms, recruitment materials (e.g. information sheet, approval form), and interview materials are enclosed in APPENDIX 5.

3.5 Review of Results and Findings

3.5.1 PHASE 1: Systematic Literature Review

131 findings were aggregated into 19 categories and grouped under four main findings using the meta-synthesis methodology established by JBI, from the 18 eligible studies (1990-2010) and included in this review.

The four main thematic findings were synthesized as:

1. Patients' contribution of their residual tissues is influenced by many and varied factors. Key factors are benefits to self and others and trust in research and researchers;
2. Patients expect strict safeguards and controls to maintain privacy and confidentiality of their data;
3. The views on ownership and rights to the tissues vary between individual patients;
4. Patients have different views on the commercial use of their tissues.

From here on, each of the four main synthesized thematic findings are elaborated on and discussed.

Finding 1: Patients' contribution of their residual tissues is influenced by many and varied factors. Key factors are benefits to self and others and trust in research and researchers. (See figure 2 for reasons why the donors contributed the HBMs for research.)

More than half of the findings from the review, which was 69 out of 131 sub-findings, explained the different reasons why patients were willing to donate their residual tissues for

research (Figure 2). This synthesized thematic finding was the dominant theme in the analysis and was therefore an important consideration for researchers and policy makers as all 18 selected studies did include findings, which supported the varied reasons that patients would consider when donating their biological samples for research. The qualitative evidences from the systematic literature review and its specific quotations are listed in APPENDIX 4.

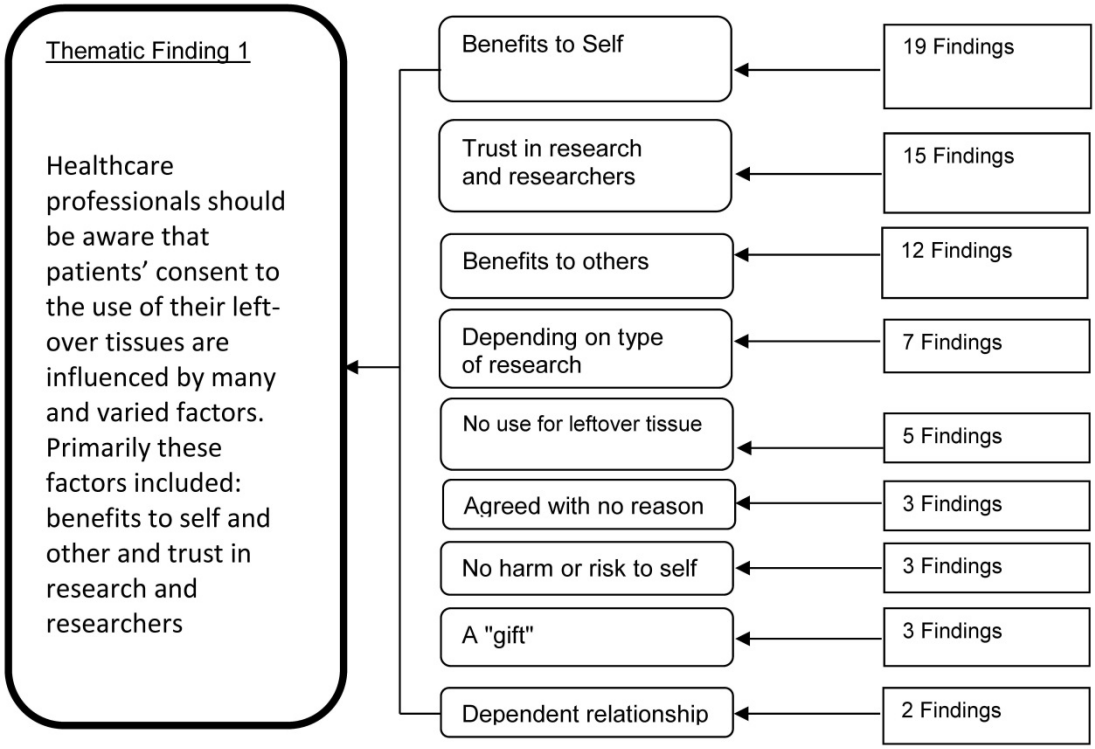


FIGURE 2: SYNTHESIZED THEMATIC FINDING 1 - CATEGORIES AND STUDY FINDINGS

The most common category of this group of findings was "benefits to self".[181] [182] [183] [184] [185] [186] [187] [188] In this category, some patients donated tissues because they

[181] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

believed there was either a direct or an indirect benefit to themselves. For example, they may have a medical condition for which further research may be of direct benefit, either presently or in the future. This group of patients would thus expect that the outcomes, conclusion and results of the research (whether accidental findings of a specific individual's tissue or an important finding on the medical condition) be communicated back to the participants in the future.[189]

Trust in research, medical researchers, research organization, and governance of the donated tissues was the next dominant category.[190] [191] [192] [193] [194][195] [196] [197] [198] [199] Patients

---

[182] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Social Science & Medicine, 65, 2212-2222.

[183] FELT, U., BISTER, M. D., STRASSNIG, M. & WAGNER, U. 2009. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health,* 13**,** 87-106.

[184] HADDOW, G., LAURIE, G., CUNNINGHAM-BURLEY, S. & HUNTER, K. G. 2007. Tackling community concerns about commercialisation and genetic research: a modest interdisciplinary proposal. *Soc Sci Med,* 64**,** 272-82.

[185] HAMILTON, S., HEPPER, J., HANBY, A. & HEWISON, J. 2007. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics,* 33**,** 229-33.

[186] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[187] HENS, K. & DIERICKX, K. 2010. Human tissue samples for research. A focus group study in adults and teenagers in Flanders. *Genet Couns,* 21**,** 157-68.

[188] ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. *Policy, Politics, & Nursing Practice,* 11**,** 5-12.

[189] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[190] *Ibid.*

claimed to have trust in the public good paradigm of research for societal progress,[200] and believed researchers were generating public good in the diagnosis and treatment of medical conditions. Patients trusted the professionals, who gained their consent to use their tissue samples for research.[201] They also trusted that their tissues would not be misused[202] and

---

[191] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Social Science & Medicine, 65, 2212-2222.

[192] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[193] HAMILTON, S., HEPPER, J., HANBY, A. & HEWISON, J. 2007. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics,* 33**,** 229-33.

[194] KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.

[195] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[196] LIND, U., MOSE, T. & KNUDSEN, L. E. 2007. Participation in environmental health research by placenta donation - a perception study. *Environmental Health,* 6**,** -.

[197] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[198] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[199] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[200] LIND, U., MOSE, T. & KNUDSEN, L. E. 2007. Participation in environmental health research by placenta donation - a perception study. *Environmental Health,* 6**,** -.

[201] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[202] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

exhibited confidence in the research process[203] and meaningfulness of the research[204] to generate new knowledge. Overall, trust was an important factor in the decision on whether they will donate their residual tissues.

A similar category is that of "Benefits to others," where participants believed that their donated tissues will benefit society.[205] [206] [207] [208] [209] [210] [211] [212] [213] [214] This category

---

[203] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Social Science & Medicine, 65, 2212-2222.

[204] LIND, U., MOSE, T. & KNUDSEN, L. E. 2007. Participation in environmental health research by placenta donation - a perception study. *Environmental Health,* 6**,** -.

[205] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[206] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Social Science & Medicine, 65, 2212-2222.

[207] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[208] FELT, U., BISTER, M. D., STRASSNIG, M. & WAGNER, U. 2009. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health,* 13**,** 87-106.

[209] KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.

[210] HENS, K. & DIERICKX, K. 2010. Human tissue samples for research. A focus group study in adults and teenagers in Flanders. *Genet Couns,* 21**,** 157-68.

[211] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[212] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[213] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

demonstrated the altruistic and solidaristic characteristics of society where patients donated their tissues out of their own kindness or gratitude. Through the donation of tissues for research, some patients wanted to contribute to the development of medical science and public good, and to promote a greater public interest.[215] Because of a "desire to do good"[216] or because of "seeing donation as an act of reciprocity for having received benefit from past research",[217] some patients were willing to donate their tissues in recognition of "the good" that the research could bring to others.[218] Exact quotes from the literatures are enclosed in APPENDIX 4 .

Some people believed that donating their tissues was one way to contribute to medical science[219] and medical education,[220] and considered the tissue donation as "a gift" to humanity. This line of evidence indicated an unconditional gratitude and reciprocity, with

---

[214] JENKINS, M. M., REED-GROSS, E., RASMUSSEN, S. A., BARFIELD, W. D., PRUE, C. E., GALLAGHER, M. L. & HONEIN, M. A. 2009. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A,* 149A**,** 2378-86.

[215] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[216] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Social Science & Medicine, 65, 2212-2222.

[217] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[218] *Ibid.*

[219] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[220] FELT, U., BISTER, M. D., STRASSNIG, M. & WAGNER, U. 2009. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health,* 13**,** 87-106.

some people not even having a specific reason[221] [222] [223] when donating their tissues. One group of patients based their decision to donate (or not to donate) their residual tissues on the type of research[224] [225] [226] [227] to be conducted. For example, some patients refused to donate for either cloning,[228] or non-therapeutic research[229] or research using stem cells[230] as they were viewed as "weird" research.[231]

Many patients felt that as there was "no risk and harm"[232] [233] [234] to the donor, they would donate their residual tissues which would otherwise be discarded or destroyed (as it was

---

[221] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[222] KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.

[223] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[224] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[225] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[226] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[227] ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. Policy, Politics, & Nursing Practice, 11, 5-12.

[228] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[229] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[230] Ibid.

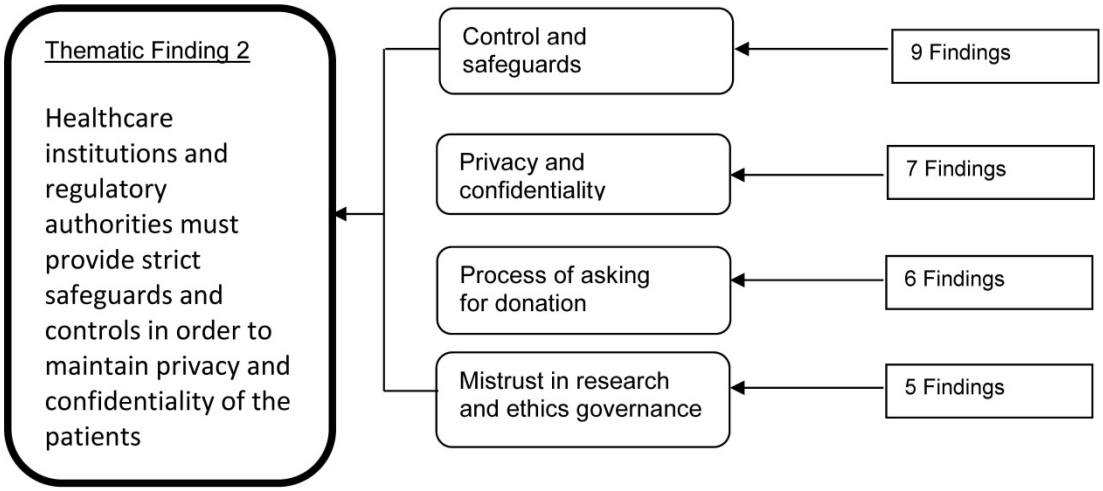
[231] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[232] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and

considered a “waste”[235] product of the surgery). However, some patients donated because they believed they had a “dependent relationship”[236] with the doctors requesting these tissues and consequently felt obliged to donate.

Finding 2: Patients expect strict safeguards and controls to maintain privacy and confidentiality.

The enclosed figure 3 shows a total of 27 sub-findings grouped into four categories to support this main finding.



---

samples without informed consent: preliminary findings based on focus group interviews. *BMC Med Ethics,* 3**,** E1.

[233] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. *Social Science & Medicine,* 65**,** 2212-2222.

[234] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[235] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[236] JENKINS, M. M., REED-GROSS, E., RASMUSSEN, S. A., BARFIELD, W. D., PRUE, C. E., GALLAGHER, M. L. & HONEIN, M. A. 2009. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A,* 149A**,** 2378-86.

FIGURE 3: SYNTHESIZED THEMATIC FINDING 2 - CATEGORIES AND STUDY FINDINGS

On the collection and storage of residual tissues, patients believed that research institutions should have strict controls and ethical safeguards on these HBMs and their related genetic and medical information.[237] [238] [239] Protection of privacy and maintaining confidentiality[240] [241] [242] [243] were two major concerns of patients. Patients were worried that private and confidential medical records and genetic information from tissue identification would be leaked into the hands of insurance agents and employers.[244] This could result in potential economic and financial loss to patients in the future. Further, they were concerned about social and financial discrimination once their medical confidentiality was

---

[237] HADDOW, G., LAURIE, G., CUNNINGHAM-BURLEY, S. & HUNTER, K. G. 2007. Tackling community concerns about commercialisation and genetic research: a modest interdisciplinary proposal. *Soc Sci Med,* 64**,** 272-82.

[238] LEVITT, M. & WELDON, S. 2005. A well placed trust? Public perceptions of the governance of DNA databases. Critical Public Health, 15, 311-321

[239] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[240] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[241] KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.

[242] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[243] ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. Policy, Politics, & Nursing Practice, 11, 5-12.

[244] KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.

breached and thus believed that there should be safeguards and controls on the medical or genetic information retained by researchers and their organizations.[245]

Mistrust in research organizations and their governance was one of the main reasons for the refusal to donate residual tissues for research.[246] [247] Others were also concerned about the method and timing in which patients were approached for donation.[248] [249] It was important that patients should not feel coerced to donate or be placed in a vulnerable position where they felt forced to donate.[250]

Finding 3: The views on ownership and rights to the tissues vary between individual patients.

On the storage and use of stored tissues, patients presented differing views on the ownership of donated tissues and their rights to use donated tissues for future research. A total of 29 sub-findings were grouped into four categories to derive this main finding (Figure 4).

---

[245] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[246] Ibid.

[247] JENKINS, M. M., REED-GROSS, E., RASMUSSEN, S. A., BARFIELD, W. D., PRUE, C. E., GALLAGHER, M. L. & HONEIN, M. A. 2009. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A,* 149A**,** 2378-86.

[248] HAMILTON, S., HEPPER, J., HANBY, A. & HEWISON, J. 2007. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics,* 33**,** 229-33.

[249] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010q. Cancer as rubbish: donation of tumor tissue for research. Qual Health Res, 21, 75 - 84.

[250] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

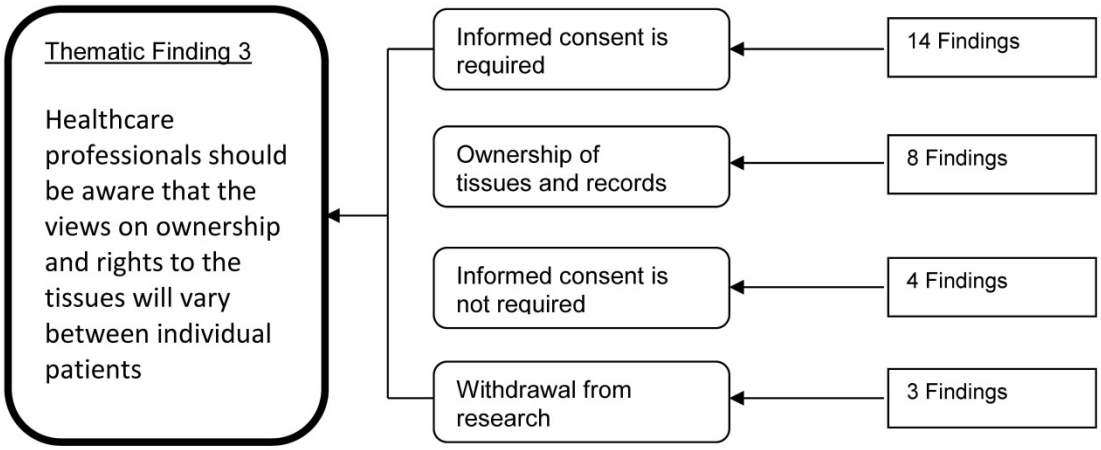


FIGURE 4: SYNTHESIZED THEMATIC FINDING 3 - CATEGORIES AND STUDY FINDINGS

Eighteen of the 29 sub-findings were related to the issue of informed consent. Most patients (14 out of 18 findings) agreed that residual tissues should not be collected, stored, distributed and used for research without the prior consent of patients.[251] [252] [253] [254] [255] [256] [257] [258] Other issues mentioned by patients include query of who

[251] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[252] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[253] LIND, U., MOSE, T. & KNUDSEN, L. E. 2007. Participation in environmental health research by placenta donation - a perception study. *Environmental Health,* 6**,** -.

[254] HENS, K. & DIERICKX, K. 2010. Human tissue samples for research. A focus group study in adults and teenagers in Flanders. *Genet Couns,* 21**,** 157-68.

[255] MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. *American Journal of Public Health,* 99**,** 2128-2134.

[256] ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. Policy, Politics, & Nursing Practice, 11, 5-12.

should give consent (especially in the case of minors),[259] use of the stored residual tissues for future research,[260] length of time of storage[261] [262] and the type of research carried out.[263] The types of consent models, whether broad or specific informed consent, were briefly discussed in two articles,[264] [265] although the authors did not conclude the type of consent models preferred by interviewed patients. Some patients considered that tissue samples as property that they owned[266] as these were once part of their own body[267] and

---

[257] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[258] SQUE, M., LONG, T., PAYNE, S., ROCHE, W. R. & SPECK, P. 2008. The UK postmortem organ retention crisis: a qualitative study of its impact on parents. *J R Soc Med,* 101**,** 71-7.

[259] WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

[260] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[261] MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. *American Journal of Public Health,* 99**,** 2128-2134.

[262] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[263] DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

[264] PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. Social Science & Medicine, 66, 2544-2554.

[265] MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. *American Journal of Public Health,* 99**,** 2128-2134.

[266] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[267] BRYANT, R. J., HARRISON, R. F., START, R. D., CHETWOOD, A. S. A., CHESSHIRE, A. M., REED, M. W. R. & CROSS, S. S. 2008. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *Journal of Clinical Pathology,* 61**,** 322-326.

these patients claimed that they have a right to know the fate of their tissues.[268] [269] These patients were not willing to give up the right of ownership of their tissues[270] [271] [272] [273] when donating to research institutions. In contrast, some patients said that informed consent was neither required nor necessary,[274] and thus informed consent was not an issue for them. Some patients preferred to be given an option to either opt-out of donation or the possibility of withdrawing their donated samples[275] from tissue repositories, even though they did not think that the materials would be misused.[276]

---

[268] FELT, U., BISTER, M. D., STRASSNIG, M. & WAGNER, U. 2009. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health,* 13**,** 87-106.

[269] ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. Policy, Politics, & Nursing Practice, 11, 5-12.

[270] ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. BMC Med Ethics, 3, E1.

[271] HAMILTON, S., HEPPER, J., HANBY, A. & HEWISON, J. 2007. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics,* 33**,** 229-33.

[272] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[273] WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

[274] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[275] LEVITT, M. & WELDON, S. Ibid.A well placed trust?: public perceptions of the governance of DNA databases. 311-321.

[276] HADDOW, G., LAURIE, G., CUNNINGHAM-BURLEY, S. & HUNTER, K. G. 2007. Tackling community concerns about commercialisation and genetic research: a modest interdisciplinary proposal. *Soc Sci Med,* 64**,** 272-82.

Finding 4: Patients have different views on the commercial use of their tissues.

(Figure 5 shows a total of six sub-findings grouped into two categories to derive this main finding.)

Patients were divided based on the use of their residual tissues by commercial companies to generate profit. While they were willing to donate for altruistic reasons to a government-funded institution for research of public benefit,[277] they cautioned that such donations should not be used for commercial purposes, because they distrusted 'for-profit' organizations.[278] They were generally suspicious[279] of the profiteering motive of private companies compared to the motives of either a government or public institution funded tissue bank. Some viewed the involvement of commercial companies and the access of third parties to the tissues as necessary[280] and considered this as part of the development of drugs, or a "necessary evil",[281] to advance technology for research. Such patients also cautioned that the use of tissues must be either closely monitored or regulated.[282]

---

[277] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[278] BRYANT, R. J., HARRISON, R. F., START, R. D., CHETWOOD, A. S. A., CHESSHIRE, A. M., REED, M. W. R. & CROSS, S. S. 2008. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *Journal of Clinical Pathology,* 61**,** 322-326.

[279] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.

[280] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.

[281] VERMEULEN, E., SCHMIDT, M. K., AARONSON, N. K., KUENEN, M., VAN DER VALK, P., SIETSES, C., VAN DEN TOL, P. & VAN LEEUWEN, F. E. 2009. Opt-out plus, the patients' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. *J Clin Pathol,* 62**,** 275-8.

[282] WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

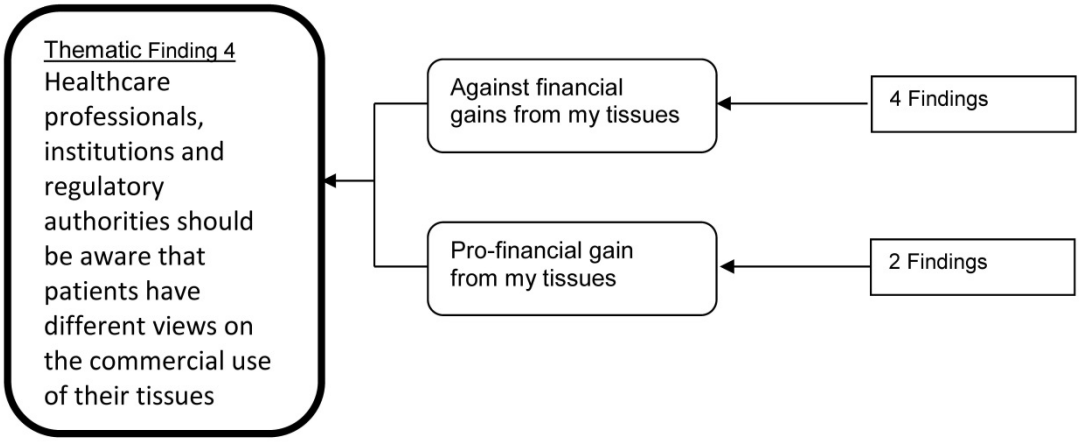


FIGURE 5: SYNTHESIZED THEMATIC FINDING 4, CATEGORIES AND STUDY FINDINGS

3.5.2 PHASE 2: Analysis of Consent for Residual Surgical HBMs from 2002 – 2011

In Phase 2 of the research, data was collected from Surgical Consent Forms of patients who either agreed to provide tissue for medical research, education or study (Patient's consent= Yes), or those who declined (Patient's consent= No). Forms that were left unfilled (Patient's consent= Null) were regarded as consent being refused, as their HBMs would not have been collected for these purposes.

An analysis of data on consent rates for the contribution of residual HBMs in NUH from 2002 to 2011 was conducted. The data is then stratified according to gender, ethnicity, religion, age groups, paying class and type of surgery performed. These data fields were existing demographics captured in the NUH administrative system for patients' admission.

Based on our detailed quantitative analysis of 167,329 Surgical Consent Forms of NUH spanning a period of ten years (from 2002 to 2011), it has been determined that 73.58 % of

all patients were willing to contribute their residual HBMs. The consent forms were originally collected for quality assurance purposes to ensure that the informed consent processes were properly administered. Subsequently, detailed quantitative statistical analysis was carried out on the completed Surgical Consent Forms, and matched with patients' demographics, including ethnicity, religion, age groups and type of surgery. The following demographics have been found to be relevant in considering if a person would agree to provide their residual HBMs for medical research, education or study:

Gender - Men were found to be more willing to contribute their residual HBMs than women.

Ethnicity - Chinese patients were more willing to provide consent under the Surgical Consent Form, followed by Malay and Indian patients.

Religion - Buddhists and Non-Denomination Christians were more willing to donate.

Age groups - Elderly patients of more than 50 years of age were more willing to donate.

Paying Class - Private patients were more willing to donate.

Different medical conditions - Patients' donation rate varied with their medical conditions.

Gender

Within the period of 10 years (from 2002 to 2011), a total of 167,329 patients admitted to NUH (Table 1) comprising 95,409 females, 71,916 males and 4 of unknown gender (foetuses). Comparisons on willingness to donate were then made between the two genders whereas samples of unknown gender were deemed as unclassified and omitted from analysis. The data suggested that there were significantly more men willing (at 78.00%) to donate their

tissues when compared to women (at 70.24%) with $p<0.05$ (using Fisher's exact test, two-sided).[283]

TABLE 1: SUMMARY OF GENDER AND CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	Gender			
Response	**Female (%)**	**Male (%)**	**Unknown (Fetus,%)**	**Total (%)**
No	28389 (29.76)	15819 (22.00)	1 (25.00)	44209 (26.42)
Yes	67020 (70.24)	56097 (78.00)	3 (75.00)	123120 (73.58)
Grand Total	95409	71916	4	167329

Ethnic Groups

Based on the sampled population, the willingness to donate appeared to be in the following order, from highest to lowest in consent rate: Chinese > Sikh[284] > Others > Eurasian > Malay > Indian (Table 2). The Chinese (74.78%) and Sikh (74.55%) had the two highest consent rates, above the total consent percentage (73.58%; Table 1), whereas the Malays (69.49%) and Indians (68.69%) had the lowest consent rates.

[283] In statistical significance testing, the p-value is the probability of obtaining a test statistic result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. Researchers will often "reject the null hypothesis" when the p-value turns out to be less than a predetermined significance level, often 0.05. Goodman, SN (1999). "Toward Evidence-Based Medical Statistics. 1: The P Value Fallacy." *Annals of Internal Medicine* **130**: 995–1004

[284] The Sikh community is one of the smallest ethnic groups in Singapore and is usually considered part of the larger North Indian community. According to the 2010 census, there are about 12,952 Sikhs in Singapore. Their Religion is Sikhism. Accessed on 1 May 2015 http://eresources.nlb.gov.sg/infopedia/articles/SIP_2013-07-29_174120.html

TABLE 2: SUMMARY OF ETHNIC GROUP AND CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	RACE						
Response	**CHINESE (%)[a]**	**EURASIAN (%)[a]**	**INDIAN (%)[a]**	**MALAY (%)[a]**	**SIKH (%)[a]**	**OTHERS (%)[a]**	**TOTAL**
No	29070 (25.22)	113 (26.7)	4362 (31.31)	5633 (30.51)	1287 (25.45)	3744 (26.41)	44209
Yes	86207 (74.78)	309 (73.22)	9570 (68.69)	12831 (69.49)	3770 (74.55)	10433 (73.59)	123120
Grand Total	115277	422	13932	18464	5057	2868	167329

[a] - % within ethnic group

Religion

From the sampled population in Table 3, the willingness to donate based on religion were in the following order, from highest to lowest consent rate: Non-denomination > Buddhism > Others > Christianity > Roman Catholics > Sikhism > Islam > Hinduism. Among the religions, Non-denomination (75.45%), Buddhism (74.42%), Others (74.15%) and Christianity (73.91%) had higher consent rates when compared to total consent percentage (73.58%; Table 1). The field 'Non-denomination' refers to patients who do not have a religion (or no religious affiliation) and the field "Others" refer to those who have a religion but not indicated as a selection option on the NUH admission form.

TABLE 3: SUMMARY OF RELIGION AND CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	Response		
RELIGION	**No**	**Yes**	**Total**
BUDDHISM (%)[a]	9907 (25.58)	28827 (74.42)	38734
CHRISTIANITY (%) [a]	3508 (26.09)	9937 (73.91)	13445
HINDUISM (%) [a]	2023 (31.03)	4497 (68.97)	6520
ISLAM (%) [a]	5551 (30.28)	12782 (69.72)	18333
ROMAN CATHOLICISM (%) [a]	68 (26.46)	189 (73.54)	257
SIKHISM (%) [a]	191 (29.98)	446 (70.02)	637
NON-DENOMINATION (%) [a]	2860 (24.55)	8790 (75.45)	11650
OTHERS (%) [a]	20101 (25.85)	57652 (74.15)	77753
Total	44209	123120	167329

[a] - % within religion

Age Group

Based on the sampled population, the willingness to donate based on age group were in the following order, from highest to lowest consent rate: 60-69 > 70-79 > 80-89 > 50-59 > 90-99 > below 10 > 10-19 > 20-29 > 40-49 > 30-39 > above 100 (Table 4). The results showed that patients between the age groups from 50 to 89 years had higher consent rates when compared to total consent percentage (73.58%; Table 1). The age group of between 50 to 59 years was especially notable as the results showed a steady downward trend from age groups 10-49 years and a steep increase from the age groups of 50 – 89 years.

TABLE 4: SUMMARY OF AGE GROUP AND CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	Response		
AGE GROUP, years	**No**	**Yes**	**Grand Total**
< 10 (%)[a]	741 (27.3)	1973 (72.7)	2714
10 to 19 (%)[a]	1475 (28.07)	3780 (71.93)	5255
20 to 29 (%)[a]	3528 (28.28)	8946 (71.72)	12474
30 to 39 (%)[a]	6066 (30.61)	13751 (69.39)	19817
40 to 49 (%)[a]	8176 (29.44)	19600 (70.56)	27776
50 to 59 (%)[a]	9478 (26.08)	26869 (73.92)	36347
60 to 69 (%)[a]	6681 (22.81)	22609 (77.19)	29290
70 to 79 (%)[a]	5027 (23.38)	16472 (76.62)	21499
80 to 89 (%)[a]	2479 (24.46)	7656 (75.54)	10135
90 to 99 (%)[a]	513 (27.11)	1379 (72.89)	1892
> 100 (%)[a]	45 (34.62)	85 (65.38)	130
Total	44209	123120	167329

[a] - % within age group

Fee Schedule

Based on the sampled population, a significantly higher percentage of private-paying patients donated their tissues when compared to patients who received subsidized care or had other forms of payment methods ($p<0.05$ using Fisher exact test, two-sided; Table 5). The field "Others" in the fee schedule database refers to patients who were treated free of charge.

TABLE 5: SUMMARY OF FEE SCHEDULE AND CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	FEE SCHEDULE			
Response	**Private (%)[a]**	**Subsidised (%)[a]**	**Others (%)[a]**	**Total**
No	14033 (24.02)	30150 (27.70)	26 (31.33)	44209
Yes	44378 (75.98)	78685 (72.30)	57 (68.67)	123120
Grand Total	58411	108835	83	167329

[a] - % within fee schedule

Annual Consent Rate

Results showed that there was an increasing trend of consent from 2002 (at 61.89%) to 2008 (at 83.15%) (Table 6). However, a decreasing trend of consent rate was seen from 2009 to 2011. The average consent rate over the 10=year period was 73.82%. There was an upward trend observed for positive consent, throughout the ten-year period based on the number of participants regardless of either positive or negative consent. The rate of participants increased by 1.76% per annum (95% CI 0.30% to 3.21%) and was found statistically significant with $p = 0.024$ (p-value<0.05).

TABLE 6: SUMMARY OF YEARLY ANNUAL CONSENT RATE FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

	Response		
YEAR	**No**	**Yes**	**Total**
2002 (%)[a]	4084 (38.11)	6633 (61.89)	10717
2003 (%)[a]	4531 (31.80)	9717 (68.2)	14248
2004(%)[a]	5345 (32.62)	11043 (67.38)	16388
2005(%)[a]	4292 (27.39)	11380 (72.61)	15672
2006(%)[a]	4106 (23.99)	13009 (76.01)	17115
2007(%)[a]	3933 (21.43)	14417 (78.57)	18350
2008(%)[a]	3147 (16.85)	15527 (83.15)	18674
2009(%)[a]	4206 (22.39)	14581 (77.61)	18787
2010(%)[a]	5152 (28.19)	13125 (71.81)	18277
2011(%)[a]	5413 (28.3)	13688 (71.66)	19101
Grand Total	44209	123120	167329

[a] - % within year

Departments

Results of consent for contribution of tissue based on department showed that out of the 24 departments within NUH, 18 had positive consent rate of higher than 50% (Table 7). Departments including Laboratory Medicine, Ambulatory Service, Urology, Neonatology and University Surgical Cluster were the top 5 in terms of positive consent. On the contrary, the lowest 5 included Clinical trial Unit, Diagnostic Imaging, Radiation Oncology, Psychological Medicine and Haematology Oncology. Different departments excise different types of tissues and thus provide an indication on the willingness to donate based on the type of surgeries, the types of tissues removed and the various medical departments involvement in the collection of residual HBMs. Further research is necessary to understand the inter-departmental differences in consent rate.

TABLE 7: SUMMARY CONSENT RATE STRATIFIED BY DEPARTMENT FOR THE DONATION OF RESIDUAL TISSUES IN NUH FROM 2002 TO 2011.

Department	No	Yes	Total	% No	%Yes
Clinical Trial Unit	218	72	290	75.17%	24.83%
Diagnostic Imaging	4113	2005	6118	67.23%	32.77%
Radiation Oncology	55	33	88	62.50%	37.50%
Psychological Medicine	29	18	47	61.70%	38.30%
Haematology Oncology	1273	1045	2318	54.92%	45.08%
Rehab Medicine	4	4	8	50.00%	50.00%
Cardiac	812	1080	1892	42.92%	57.08%
Obstetrics & Gynaecology	10620	17066	27686	38.36%	61.64%
Orthopaedic Surgery	2601	4222	6823	38.12%	61.88%
Paediatric Surgery	835	1538	2373	35.19%	64.81%
Emergency Medicine	588	1489	2077	28.31%	71.69%
Ophthalmology	521	1331	1852	28.13%	71.87%
Dentistry	302	857	1159	26.06%	73.94%
Otolaryngology - Head & Neck Surgery	3052	8841	11893	25.66%	74.34%
University Medicine Cluster	8992	29971	38963	23.08%	76.92%
Paediatrics	603	2101	2704	22.30%	77.70%
Anaesthesia	630	2221	2851	22.10%	77.90%
Hand & Reconstructive Microsurgery	758	2744	3502	21.64%	78.36%
Cardiac, Thoracic & Vascular Surgery	1067	3959	5026	21.23%	78.77%
University Surgical Cluster	6393	36639	43032	14.86%	85.14%
Neonatology	15	109	124	12.10%	87.90%
Urology	725	5578	6303	11.50%	88.50%
Ambulatory Service	2	113	115	1.74%	98.26%
Laboratory Medicine	1	84	85	1.18%	98.82%
GRAND TOTAL	44209	123120	167329	26.42%	73.58%

Keys:

"No" – Patient who refused consent for donation of residual tissues

"Yes" – Patient who consented for donation of residual tissues

"Null" – The consent form was not completed, i.e. neither Yes nor No

Statistical Analysis

Data collected on 167,329 potential donors including their age, gender, ethnicity, religious beliefs and fee schedule and statistical analysis were performed (using Odds ratio [OR] and 95% confidence interval [CI] on the data). The results are enclosed in Appendix 6 of this thesis.

Based on the multivariate statistical analysis,

1. On Gender, men were found to be more willing to contribute their residual HBMs than women. The odds of males in willing to donate the human biological materials is significantly higher compared with females (OR = 1.50, 95% CI = 1.47 to 1.54, $p < 0.001$).
2. On Ethnic groups, Chinese patients were more willing to provide consent under the Surgical Consent Form, followed by Malay and Indian patients.

   a) Chinese compared with Malay: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with Malay (OR = 1.30, 95% CI 1.25 to 1.36, $p < 0.001$).

   b) Chinese compared with Indian: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with Indian (OR = 1.35, 95% CI 1.29 to 1.42, $p < 0.001$).

   c) Chinese compared with Eurasian: OR = 1.08, 95% CI 0.82 to 1.44, $p = 1$

   d) Chinese compared with Sikh: OR = 1.01, 95% CI 0.93 to 1.10, $p = 1$

   e) Chinese compared with Other Races: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with other races (OR = 1.06, 95% CI 1.01 to 1.12, $p = 0.011$).

3. On religions, Buddhists and Non-Denomination Christians were more willing to donate.

    a) Buddhism compared with Christianity: OR = 1.03, 95% CI 0.97 to 1.09, p = 1

    b) Buddhism compared with Hinduism: The odds of Buddhism in willing to donate the human biological materials is significantly higher compared with Hinduism (OR = 1.31, 95% CI 1.21 to 1.42, p < 0.001).

    c) Buddhism compared with Islam: The odds of Buddhism in willing to donate the human biological materials is significantly higher compared with Islam (OR = 1.26, 95% CI 1.20 to 1.33, p < 0.001).

    d) Buddhism compared with Roman Catholicism: OR = 1.05, 95% CI 0.71 to 1.53, p = 1

    e) Buddhism compared with Sikhism: OR = 1.25, 95% CI 0.98 to 1.58, p = 0.082

    f) Buddhism compared with Non-Denomination: OR = 0.95, 95% CI 0.89 to 1.01, p = 0.178

    g) Buddhism compared with Other Religion: OR = 1.01, 95% CI 0.98 to 1.05, p = 1

4. On age groups, elderly patients of more than 50 years of age were more willing to donate. The odds of patients who were 50 and above 50 years old in willingness to donate the human biological materials were significantly higher compared with those who were below 50 years old (OR = 1.29, 95% CI = 1.26 to 1.32, p < 0.001).
5. On types of patients' payment scheme, private patients were more willing to donate.

    a) Private compared with Subsidised: The odds of those who had private fee schedule in willingness to donate the human biological materials were significantly higher compared with those who had subsidised fee schedule (OR = 1.21, 95% CI 1.18 to 1.24, p < 0.001).

b) Private compared with Other Fee Schedule: OR = 1.44, 95% CI 0.84 to 2.45, p = 0.244

Base on the analysis in Appendix 6, an elderly i.e., 60-69 years old, Chinese man, Buddhist who is in the private paying ward, would be most likely to donate his residual HBMs, as compared to a middle age i.e., 30-39 years old Indian lady, Hindu in the subsidized ward), who is least likely to donate her leftover HBMs for research. Further research must be conducted to conclude that demographic factors were significant predictors of attitudes toward donation of residual HBMs for research. Based on the annual report on the number of consent collected, we were only able to perform chi-square test as listed in Appendix 6. One limitation of this study is that we could not perform the multivariate analysis, as we could not direct access to the individual patient medical records for confidential reason.

The quantitative research (in Phase II) showed that a majority of the patients admitted to NUH (73.58%) was willing to provide their residual surgical HBMs without much information provided. The data also suggests that a decision to contribute residual HBMs from surgery was influenced by gender, ethnicity, religion, age groups, paying class and type of surgery performed. As explained in Chapter 2, the results indicate that this is also the pool of patients that can be approached to donate residual HBMs to NUHTR. In the description and analysis of Phase 3 of the research that follows, 100 patients have been interviewed to better understand their motivations and concerns in relation to informed consent and research governance.

3.5.3 PHASE 3: Qualitative Study involving NUH Patients

In this phase of research, interviews were conducted with 100 NUH patients who agreed to donate their residual HBMs to NUHTR. As these patients have all expressed agreement in the Surgical Consent Form, it was not possible to identify any patient who refused the proposed donation. Attempts were made to recruiting patients who refuse to contribute residual HBMs under the Surgical Consent Form, but these invitations to participate were declined. The demographics of the recruited participants (n=100) are described below.

Gender

Among the 100 donors interviewed, 58 of them were women and 42 were men (see Table 8).

Table 8: SUMMARY OF GENDER OF PARTICIPANTS (N=100)

GENDER OF PARTICIPANTS	NUMBER
Female donors	58
Male donors	42

Ethnic Group and Nationality

Table 9 provides the ethnicity of the participants. The largest ethnic group was Chinese (54%) followed by Malay (18%). Seventy-five are Singapore citizens of whom 18 were Malays, 9 were Indians and 48 were Chinese. The rest are foreigners, comprising 10 Indonesians, 6 Malaysians, 5 patients from Myanmar, 1 patient each from Bangladesh, Philippines, Canada and the UK.

Table 9: SUMMARY OF ETHNIC GROUPS OF PARTICIPANTS (N=100)

	RACE						
	CHINESE (%)[a]	EURASIAN	INDIAN (%)[a]	MALAY (%)[a]	SIKH	OTHERS (%)[a]	TOTAL
Grand Total	54 (54.00)	-	9 (9.00)	18 (18.00)	-	19 (19.00)	100

[a] **- % within ethnic group**

Religion

Table 10 provides the religion of the participants. The largest group was Buddhist (25%) followed by Islam (24%) and Christianity (18 %). The listing follows the existing fields in the NUH administrative system for patients' admission.

Table 10: SUMMARY OF RELIGION OF PARTICIPANTS (N=100).

RELIGION	Number of participants
BUDDHISM (%)[a]	26 (26.00)
CHRISTIANITY (%)[a]	18 (18.00)
HINDUISM (%)[a]	4 (4.00)
ISLAM (%)[a]	24 (24.00)
ROMAN CATHOLICISM (%)[a]	14 (14.00)
SIKHISM	-
NON-DENOMINATION	-
OTHERS (%)[a]	13 (13.00)
Total	100

[a] **- % within religion**

Age Group

Table 11 provides the age group of the participants. The largest group was at age 50-59 (28%) followed by 40-49 (21%) and 60-69 years(18 %). The participants were selected randomly and not based on age. NUS-IRB approval was granted for interview with adults

above 21 years and thus those below the age of 21 years were excluded from the study due to concerns with proper consent-taking (as they were considered legal minors). The age distribution amongst the population is listed below.

Table 11: SUMMARY OF PARTICIPANTS STRATIFIED BY AGE GROUP (N=100)

AGE GROUP, years	Number of participants
< 10	-
10 to 19	-
20 to 29 (%)[a]	7 (7.00)
30 to 39 (%)[a]	14 (14.00)
40 to 49 (%)[a]	21 (21.00)
50 to 59 (%)[a]	28 (28.00)
60 to 69 (%)[a]	18 (18.00)
70 to 79 (%)[a]	11 (11.00)
80 to 89 (%)[a]	1 (1.00)
90 to 99	-
> 100	-
Total	100
[a] - % within age group	

Key Findings from Qualitative Interviews

This study utilized an interpretive approach (as discussed in Schwandt, 2001) [285] to data collection and analysis with the aim of capturing the individual's constructed knowledge and meaning, through a close analysis of their actions and behaviour. Interpretive research denotes an approach to studying social life with the assumption "that the meaning of human

[285] Schwandt, T.A. (2000). Three Epistemological Stances for Qualitative Inquiry: Interpretivism, Hermeneutics and Social Constructionism. In: Denzin, N.K. & Lincoln, Y.S. (eds:) Handbook of Qualitative Research. (2nd ed.). Thousands Oaks: Sage Publications Schwandt, T. A. (2001). Dictionary of qualitative inquiry (2nd ed.). Thousand Oaks, CA: Sage.

action is inherent in that action" (p. 134. Schwandt, 2001) [286]. The results of the data analysis are presented as thematic analysis, under seven broad themes for each group of questions. The themes are: (1) Reasons for donation; (2) Degree of information to be provided in consent-taking; (3) Pre- or post-surgery consent (or when should consent be taken); (4) Right to withdraw; (5) Privacy and Confidentiality of Medical Information; (6) Governance, safeguards and controls; and (7) Access and uses of tissues. Key findings from the interviews, grouped in the sequence of these seven headings, are summarised below. The primary reason for tissue donation for a majority of the participants (92%) are altruism, for advancement of future research, helping other people and benefiting future generations. Some even donated to prevent waste, having the opinion thinking that HBMs were superfluous and of no use to them.

A majority of the participants (81%) did not think or did not know there was any risk involved in the donation of residual HBMs, and had implicit trust in researchers and the research governance system.

74% of the participants were satisfied with the short and brief NUHTR consent form, and indicated that they did not have time to go into the details or that they did not really care. Most of the participants (78%) did not think they would withdraw from research participation although a few participants indicated that they might do so under certain conditions such as unethical research, familial pressure or for religious reasons.

[286] Schwandt, T. A. (2001). Dictionary of qualitative inquiry (2nd ed.). Thousand Oaks, CA: Sage.

Most participants (85%) did not object that researchers accessed their personal and medical information, as long as the researchers were under obligation to keep these confidential. Most participants were not sure of the safeguards and controls that currently exist with regards to residual HBMs. However, a majority of the participants were of the view that IRBs or researchers should ensure responsible practices.

Some participants objected to their tissues being used by commercial companies and foreign institutions, mainly for the reason that subsequent benefits may not be equitably distributed.

Our qualitative research on 100 NUH patients showed that majority of the patients contributed their residual tissues for altruistic reasons, have trust in the institutions and researchers, preferred brief general consent to detailed informed consent with safeguards and control, were unaware of risks related to tissue bank research and objected to the use of the residual tissues by a commercial company.

Reasons for donation

Interview Question (1a): Why have you consented to tissue donation?

All participants interviewed consented to the donation of their residual surgical tissues (n=100), out of which 82 were repeated tissue donors and 18 were first time donors. When asked why they agreed to donate their residual HBMs, 56 participants gave one reason, 27 participants gave two reasons, 9 participants gave three reasons and 1 participant gave four reasons. The reasons were grouped into the following themes using thematic analysis by

using Taylor's (2006) qualitative thematic analysis method.[287] The themes from the analysis of the interviews were then compared with the findings from the CSR (see Table 12).

Table 12: SUMMARY ON REASONS GIVEN FOR DONATING HBMs

REASONS TO DONATE THEIR HBMs	NUMBER OF FINDINGS IN NUH PATIENTS
Trust in research and researchers	54 Findings
Benefits to others	38 Findings
No use for residual tissue	28 Findings
*Support education and training	8 Findings
Agreed to donate without any reason	7 Findings
No harm or risk to self	5 Findings
A "gift"	2 Findings
Benefits to Self	2 Findings
Reciprocate for benefits received from previous research contributions	2 Findings
Dependent relationship	1 Finding

The reasons participants gave for donating their residual HBMs were mainly that they trusted the researchers and they believed the research would benefit others, and that there was no other use for the residual HBMs. Only a few of the respondents believed that: donation supported education and training for medical staff; here was no harm to oneself by donating; it was seen as a gift; that there would be benefits to themselves; that findings

[287] Taylor, Beverley J. 2006. Research in nursing and health care : evidence for practice 3rd Edition

would inform other research; and that they donated because they believed that they should or there may be some negative outcomes to themselves (see Table 12).

TABLE 13: REASONS FOR DONATING HBMS IN CSR AND QUALITATIVE RESEARCH

REASONS TO DONATE THEIR HBMs	THEME FINDINGS IN CSR	THEME FINDINGS IN NUH PATIENTS
Benefits to Self	YES	YES
Trust in research and researchers	YES	YES
Benefits to others	YES	YES
Depending on type of research	YES	Not reported
No use for residual tissue	YES	YES
Agreed with no reason	YES	YES
No harm or risk to self	YES	YES
A "gift"	YES	YES
Dependent relationship	YES	YES
*Reciprocate for benefits received from previous research contributions	Not reported	YES
*Support education and training	Not reported	YES

Key: * = themes not reported in systematic literature review

There were 2 new findings from the qualitative data from NUH patients, which had not been reported in previous research (references) in any country nor was it found as a theme in the systematic review undertaken of the literature in this study. The first theme, 'support education and training' (8 findings) could be unique because NUH is a teaching hospital and patients assumed that their HBMs are used by students for their research and experiments.

The second theme, 'reciprocate for benefits received from previous research contributions', was, however, only reported by two participants and therefore should be viewed with caution until other studies confirm this theme.

In contrast, the CSR data suggested that the major reasons to donate would be for benefits to self. Additionally the CSR data suggested that the type of research that the tissue was going to be used would influence participants on whether they will donate their tissues. In the interviews however, only a few respondents raised this concern. This shows a lack of understanding (knowledge gap) of tissue banking and research in general among the local patient population. Apart from these, the other findings were similar between the CSS and the interviews conducted.

The reasons participants gave for donating their residual HBMs were mainly that they trusted the researchers and they believed the research would benefit others, and that there was no other use for the residual HBMs. In contrast, the CSR data suggested that the major reasons to donate would be for benefits to self. Additionally the CSR data suggested that the type of research that the tissue was going to be used would influence participants on whether they would donate their tissues. In the interviews however, only a few respondents raised this concern. This shows a lack of understanding (knowledge gap) of tissue banking and research in general among the local patient population. Apart from these, the other findings were similar between the CSS and the interviews conducted.

In addition to the themes already identified in the CSR, two new themes emerged from the interviews: "Reciprocate for benefits received from previous research contributions"; and

"Support education and training". The theme, "Reciprocate for benefits received from previous research contributions". was explained by Participant 8, who stated:

"I have given consent as I (am) also interested in research and it can help doctors to get advancement in this technology. Plus, it will be beneficial for the patient. This tissue is also of no use and I do not want to waste it. Hence, if somebody can use then let them use it."

Additionally Participant 12 noted:

"Yes I have given my consent. I believe that whatever advanced medication or treatment I'm getting now is the result of research from the past. In order for that to be done, there has to be people who need to volunteer themselves for research materials. Hence, I should also do my part."

It is clear from these findings that these two participants had agreed to donate based on reciprocity. They were grateful for the past contribution of others, and wanted to contribute their HBMs as research materials for medical progress that will benefit future patients.

Another new theme that emerged was "support education and training", since NUH was perceived as a teaching and training hospital, and affiliated with the university. Participant 22 stated:

"Because I pity the student, they want to study about it. So I give my permission."

Similarly Participant 74 also noted:

"Because of the students, they want to do their research. That's why I see… ok I give to University students."

Interview Question (1b): Do you know of any benefits and risk in this donation, and uses of your donated tissue/s?

More than half of the participants interviewed considered the use of their tissues in future research and discovery of new treatment as benefits. A few people did not answer and/or were unaware of the benefits or risks. A majority of the participants did not think there was any risk involved, except surgical risk, and they trusted that systemic safeguards were in place to ensure that they suffered no harm. Based on the results, 41 participants replied that there was no risk involved; 40 participants were unsure of the risk involved; 3 participants mentioned that they did not care about risk as long as there were benefits; 3 participants were concerned about whether their HBMs would be misused (although the participants described this as "abuse"); 2 participants claimed that they trusted the hospital to protect their HBMs; and only 1 participant was concerned about privacy issues. When asked if there was a risk of misuse, most were unsure the context in what misuse would be.

Quoting participant P10:

"I do not know much about the risks and benefits."

Participant 8 was similarly confident that there was little risk of misuse:

"Benefits are the reasons that I have stated before, which are for the medical research and diagnosis and treatment of the patient. I don't think that there is any risk as I believe that the people who are doing this research will keep and use the tissues properly."

Interview Question (1c): What would influence your decision?

Many decisions to donate were influenced by the knowledge that it would advance medical and scientific discoveries; help people with same disease in the future; and constitute sharing on the basis of religious belief.

Participant 36 stated:

“Because this sickness of mine is rare. According to Professor X, it is rarely happen like this. Sarcoma in the liver. Sarcoma usually doesn't make tumour… doesn't make our leukocyte increase. But this… we cannot get it in ordinary tumour. So maybe it will help other people if they have same disease like me.”

Participant 16 stated a similar intent to support scientific progress:

“I think that there are many things that we need to learn from the medical field. So by donating my specimen, I hope that they will be able to find something from it.”

Religious belief encouraged some participants to donate for the benefit of other, like Participant 98:

“It's because I'm a Buddhist, so the donation is a sense of from our entire experience. We're taught to donate each and everything. If we've extra, or even if we don't have extra, we have to share ... So I think because of our religions background. We're used to this...”

Some participants claimed that they would not donate if there were risks to one’s health. As Participant 79 said:

“Well, nothing really... I mean what. Like I've said earlier, if it's going to do good, let it be. It doesn't involve anything more from me. I don't have to cut off another limb or suffer or be deprived of some parts of my organ, just for the donation. Actually it doesn't have bearing whatsoever on my well-being so that's being the case, it seem no objection whatsoever, you know, to donate whatever has been removed from me and people need to use, go ahead. You know, I think it's the same principle as organ donation. If anything happen to me, if my organs are needed, so be it, you know. Same principle.”

Patients were willing to contribute their residual tissues for the purpose of scientific advancement and the benefit for future patients. Some cited religious practice and belief as an influence of their altruism to contribute without direct benefit.

Interview Question (1d): Would you have consented to donate a different organ/tissue than the current one?

For most participants, the type of HBM did not seem to matter if it had to be removed for therapeutic purposes. More than half of the participants would still donate if it were a different HBM. As Participant 100 said:

"Regardless of the organ, I would still have given, unless maybe it poses a risk to me, you know, more than what...I mean I've already contributed. You know, if I've contributed excess and it poses additional risk, then maybe I will start to consider. But if you… there's no risk, you know, then of course I'm happy actually in fact that they're using it for, you know, for improving science for expanding upon knowledge."

Participant 70 also expressed a similarly pragmatic viewpoint:

"Different organ? That's fine. Since it'll be removed from my body already, right?"

Some participants did indicate that they would rethink at some point in time in the future, as Participant 23 noted:

"That one I may have to think about it. (Why?) Because those are the things that are like different, you see. This is just the stomach that is given away."

Religious conviction would stop some Muslim participants from donating organs. Participant 40 said:

"I don't think so. Because as a Muslim if I die I want to have completed everything."

Participant 39 expressed a similar view: "Yes maybe. I would reconsider. (Why?) If it's a different organ I would reconsider because as a Muslim, and I'm being born with everything that was being given and if I were to go back to Him, I would want to be as one whole piece."

This finding reflects a rather more traditional thinking among some members of the Islamic community, as the Islamic Religious Council of Singapore has issued a religious ruling (or *fatwa*) that did not prohibit the donation of such HBMs.[288]

Degree of Information to be provided in Consent-Taking

Interview Question (2a): Do you remember that you have earlier agreed to donate your left over tissues in the surgical (brief) consent form?

Almost 95% of the participants remembered that they had agreed to contribute tissue in the Surgical Consent Form, but many regarded this as no different from the proposed donation to NUHTR. Some participants mentioned that they did not read the consent form fully or did not have time to read. Participant 29 explained:

"Yes I remember. Because I got no time to go through. I am very tired, (before the) operation. No time to read this."

Interview Question (2b): Do you think that the surgical consent form contain adequate information for you to be able to decide on left over tissue donation or would you want more detailed information, such as the one in the Tissue repository consent form? Why?

Only 26% of the participants said that they needed more detailed information, and they recalled being provided with the Participant information Sheet by the NUHTR 'consent' nurse. The main reason for requesting for more information was to have a better idea as to why, how and whom exactly were going to use their tissues. This view was not specific to

[288] ***Fatwa*** committee of the Islamic Religious Council of Singapore issued a ***fatwa***, a religious edict, allowing Muslims to come under Human Organ Transplant Act (HOTA) in Jul 2007. Accessed on Aug 13, 2014 http://www.muis.gov.sg/cms/oomweb/fatwa.aspx?id=14698

Hussain, Z. (2008, January 22). Muslims to be included in the Act from Aug 1. ***The Straits Times***. Retrieved Aug 13, 2014, from Factiva database.

any group of particular educational background or age. This study did not identify any shared characteristics among these participants who requested for more information.

The majority (or 74%) of the participants were, in some way or another, satisfied with the NUHTR consent form, and did not ask for the information sheet or otherwise refused when it was offered. A variety of reasons were given, ranging from "do not have time to go into the details", "cannot read", "have already decided to donate", "medical office explained well to me", "wanted it simple and basic", to "I do not care". A number of participants provided more reflective responses. Participant 6 said:

"I think it is sufficient if you ask for my permission in advance. I think the simplified form is better as when you are sick, you do not want anything complicated. You will want it to be simple and basic."

Participant 8 was somewhat more nonchalant:

"I have read through so many things but have not read this form. When you all came some time ago, I was still recovering from anaesthesia. I do not know what is written there but whatever is written in the form does not affect my decision to donate my leftover tissues."

Some participants appeared to have decided independently of information that was furnished. Participant 13 said:

"I have already made up my decision and I am very decisive about it. I am not bothered by the details in the form as long as the doctors and researchers do something good with the tissues."

Participants also mentioned that a detailed consent form could be confusing and that they were not in the right frame of mind to be bothered with the residual HBMs as they were worried about their medical conditions. Participant P33 candidly responded:
"I never read. Don't remember. Of course (I prefer) the shorter version. Shorter version, in the sense that just goes precisely to the point and let me know what is this. Right now with my sickness, I am not in the mood to go for details."

Pre or post-surgery consent (or When to Take Consent)

Interview Question (3a): When is the best time for someone to approach you to get your consent to donate leftover tissue?

The suggested choices for this question were: (A) Before admission; (B) On admission but just before surgery; (C) After the surgery; or (D) After your tissue has been fully analysed. Most participants (34%) preferred informed consent to be taken before admission (i.e. Choice A) and at the time when information on their surgery was provided. Around 25% of participants preferred Option B, or after admission but before surgery as the best time of taking consent. 15% of the participants preferred this to occur after surgery (i.e. Option C), and one participant preferred Option D, or only after the tissue had been fully analysed.

Most participants preferred consent to be taken before admission as the subjects felt that they would be in an anxious state during the admission and operative process. They were also concerned that if consent was taken just before or after surgery, effects like pain, anaesthetic or medication could affect their choice to donate. Quoting Participant 9:
"Before admission, as after operation I may be too tired. During the admission day, it may be too tough. Before going for the operation, patients may be mentally and physically stressed and might be emotional. If it was me, I do not want people to ask me questions."

Some participants preferred consent to be taken after surgery, as the subjects believed that they would be more relaxed and free of disease anxiety, post-surgery. Other participants were of the opinion that the types of surgery or disease could influence their choice on the different timings for consent taking. Take the view of Participant 85, for instance:

"Probably after the surgery because before the surgery, you will be very anxious over the surgery, and of course the result. You don't have actually any time for this consenting."

[CH: You have explained Options A and C. How about Options B and D? What reasons were given for these choices?]

Interview Question (3b): Who would be the most appropriate person to ask for this consent, and why?

Most of the participants preferred either researchers or doctors (almost equal percentages) to take consent. Participants who preferred researchers to take consent stated that they believed that researchers would know details of research to be carried out. However, participants who preferred doctors to do so indicated the reasons as trust and the doctors' knowledge of patients' disease and operative procedure. Participant 6 expressed this view:

"I think the doctors would be more appropriate as you are dealing with them and already have a personal relationship with them."

Only a few participants preferred nurses because of their friendly attitude. Participant 86 indicated:

"The consent nurse. Doctor might not free to, you know. Doctor shouldn't be the one to go for research consent. Yeah I still prefer nurses lah. Seem that nurses are approachable."

Right to Withdraw

Interview Question (4): If you change your mind to this donation, what do you think would be the best way to do this? Under what circumstances would you want to change your decision?

A majority of the donors would prefer to go back to their doctors and inform them about their decision to withdraw consent, if at all. Few participants said they would go back to NUHTR or use the contact number provided. A number of participants also mentioned that they would call, but did not indicate which telephone number. Others said they would go and inform the researchers about their decision if they changed their mind on the donation. A few participants said they had no idea whom to contact in the given situation (even though this information would have been provided in consent-taking).

Almost 90% of the patients interviewed said they would not change their minds under any situation. Those participants who said they would change their mind cited unethical research, media news on breach of trust, large number of follow up visits or interviews after donation, and tissue not being used for the purposes communicated. One subject also mentioned family pressure and religion (for Muslims) as a possible reason for withdrawing participation. However, almost all participants shared Participant 71's view:

"As long as the research projects have a good objective, I don't see why I should change my mind unless the research uses it for unethical whatever reason."

Privacy and Confidentiality of Medical Information

Interview Question (5): Would you object or not if researchers, carrying out research on your tissue, know about your personal and medical information with an undertaking that they would keep the information confidential? Why or why not?

A majority of the participants do not object if researchers, when conducting research on the HBMs, can access the personal and medical information with an undertaking that they will keep the information confidential. To quote Participant 40:

"I would prefer all details to be kept confidential. As long as it is not being passed on to others. I don't object but as long the researcher keep the information confidential and don't pass the personal information away."

Participant 21 expressed a more hesitant view:

"I would rather be kept anonymous. For instance, for one part that I understand is confidential but the researcher will know, is it? I think I'm a bit ambivalent I should be okay but my first preference will be anonymity. But if that's the way do it, I mean I'm fine as well, rather than… (pause). Why would there be a need for them to know the individual's particulars, except for the age, maybe the types of job they do to see the sort of stress result this kind of things?"

Generally speaking, most participants had difficulty understanding the exact nature and operation of privacy and confidentiality. However, it was a general expectation among participants that they should not be harmed or embarrassed through research participation. A summary of some pertinent comments are set out in Table 14.

TABLE 14: SUMMARY ON COMMENTS ON PRIVACY AND CONFIDENTIALITY

No objections (N= 85)	Mostly agreed, if confidentiality is maintained
	"Faith in researchers and system"
	"Personal and medical info are necessary for better research"
	"Ready to provide even more info if required"
	"Nothing to hide"
	"I am a commoner, not a celebrity"
Yes, with objections (N=15)	Confidentiality is not 100% fool proof
	Info may spill out and spoil some better chances in future life
	Inadvertent publicity
	Private person – don't want people to know personal information

Governance, safeguards and controls

Interview Question (6): Who should monitor use of your donated tissue? Are you aware of any safeguards and controls for this donation, and what governance would you expect?

A majority of the participants do not know what safeguards and controls in relation to their donated HBMs were, even though effective governance was uniformly emphasised. Some participants mentioned protecting confidentiality, proper documentation and audit with standard operational procedures as measures to prevent misuses. There was no agreement as to who should have greater responsibility in ensuring responsible conduct. For instance,

some felt that researchers should themselves be responsible. Participant 7 expressed this view:

"I think the researcher should definitely be the one who should monitor the use of the leftover tissues. I believe that when the tissues are handed over to the researchers, everything should be at the researchers' compound. Everything should be done by them. I am not aware of any safeguards. I believe that after the research, it should be handled properly as I do not know how deadly the tissue is. So they should dispose the tissue off in a good and rightful way, though I am not sure clinically how."

A majority of the participants did consider IRBs to shoulder most of the responsibility, although this point was already communicated in consent-taking. Table 15 provides a breakdown of views on who should ensure responsible conduct or prevent misuses of HBM.

TABLE 15: SUMMARY ON PERCEIVED GOVERNANCE

Types of Monitoring	**Number of responses**
Institutional Review Board	35
Researchers	18
Doctors	10
A government body	8
Hospital/institution	10
Combined	3
Not sure/doesn't matter	4

The questions were asked to understand patients' preference on who should monitor use of their donated tissue and during the questioning, we briefly explain the role of various choices given, to allow them gain a better understanding on the types of governance and control.

Access and uses of tissues

Interview Question (7): Would you object if following groups of researchers have access to your tissues for research, and why?

Most participants agreed that researchers, scientists and students should be allowed to use the residual HBMs for research. There was some resistance to access by commercial companies, as the motives of profit-driven enterprises were seen as incompatible with the more reciprocal or altruistic sentiments associated with the donation of HBMs for research. A summary of stakeholders that should be granted access to residual HBMs for research is set out in Table 16.

TABLE 16: SUMMARY ON "WHO CAN USE MY HBMS FOR RESEARCH?"

Would you object if following groups of researchers	**Responses (No = No Objection)**
Hospital researchers/University scientists and students	No – 100% Yes – 0%
Government funded agency	No – 98% Yes – 2% (government might make money; may tie with

	private company)
Commercial laboratories and drug companies	No – 69% Yes – 31% (profiteering; my tissue for students/government; doubt on confidentiality; not for free)
Overseas researchers & institutions	No – 89% (research is global; better facilities and technology overseas) Yes – 12% (tissue only for local benefit; overseas results may not benefit locals; difficult to monitor)

On TRUST in donating HBMs

Patients who have contributed the residual HBMs expressed the views that they trusted the doctors, consent nurses and researchers when they donated the HBMs. Although most of them do not know much about safeguards, controls and governance of research that use HBMs, they all said that they trust the institutions to have proper governance systems and to protect their privacy and the confidentiality of their medical information. Patients also expressed trust in healthcare institutions and researchers not to exploit their HBMs for unintended use, or sell them for commercial benefits.

It is unclear if the patients trust the system in a very general informed manner or if it was blind faith. This however could be mixed, as patients said they truly trusted, and have full faith that they will not be harmed by donating their residual HBMs otherwise they would not have donated their HBMs. Even when they did not know about the potential risk, they

trusted fully and gave their residual HBMs. The possibilities that their HBMs would generate potential public benefits were based on trust, when patients believed that their residual HBMs were only given to good researchers, who genuinely conducted scientifically grounded research for public benefits and not only for commercial patents or profits. Further research can be done to explore this issue on trust on donating HBMs for research.

Trust was often expressed in relation to privacy and confidentiality protection. For instance, patients were willing to trust medical professional on medical confidentiality and privacy, respect of their rights and proper handling of their HBMs. The following quotations from responses of participants are illustrative. Participant 21 said: “No, I don't object. Well I will trust our Singapore medical personnel to keep it confidential and I think that because, yeah, they're using it for research so it's nothing really secretive about it.”

A similar comment was also made by Participant 49: “No I do not object as they are supposed to keep it confidential. I trust them.” Participant 89 elaborated on what trust involved: “We are ok with doctor and the first one you said IRB, this two is fine. Doctors because he knows us well and we much trust our doctor. The IRB, that you have said, it takes care of the patient’s right. So I assume that it puts the patients’ health first. Not aware of safeguards. (On governance) The thing is that the tissue is something that we don't even need in the first place, so you can do pretty much whatever you want with it. Correct. So it’s up to you what governance you guys want to do with it.”

Some patients are willing to trust nurse on providing the relevant and concise information when taking their informed consent. Participant 27 said: “It looks like a lot of information. I trust the consent person will tell me everything because I really don't like to read, it's quite a lot of things. (Interviewer: "So in your own opinion, you prefer a short consent?”) Concise.

This one (Surgical consent form) looks simpler. That one a lot of words (TR consent form). This one (Surgical consent form) looks very simpler, look like sometimes...easily filled up. Really very easy to see & I can straight away see whether I will agree or not, then can cancel or not. The details are very concise, & I only need the nurse just to tell me what are the details; whether to donate or not to donate. If I'm to read myself, most probably I won't read." A similar trust was expressed by Participant 46: –"I don't mind. I think it can be anyone representing this Tissue Repository Centre. This is because I trust the person who is seeking for my consent."

Trust was also expressed in relation to researchers. In particular, patients are willing to trust researchers on the use of their HBMs for research. –For instance, Participant 41 said: "The researchers should monitor because I have already agreed to donate my tissues to them in the first place. Hence, I must be able to TRUST them. (On safeguards) I have no idea on any safeguards taken."

Even when they do not know the specific safeguards and control, patients are willing to trust that proper governance is in place on the use of their HBMs for research. This could be that the patients trusted the system in a very general informed manner or if it was blind faith, with no evidence that there were any knowledge on any prevailing system of governance in place. Participant 43 said: Yes I object as I am not sure what they are going to do with the tissues and it might be unethical. I "trust the governance." Participant 51 similarly indicated: "No need. I don't think so. I think if it's going to be donated, I think I will trust that whoever going to use is it is going to use it for research will be beneficial for future cases." Participant 72 expressed trust in relation to doctors: "I think the doctor. Because I trust him. I don't know (about safeguards and controls). It's hard to say because I really don't know the protocol but protocol about these (about governance)." While others (like Participant 4)

expressed a more general trust in the system: –"In my opinion, once you decide to donate your tissues then you should have trust in the system to protect your privacy."

Patients are willing to trust the institutions on the use of their HBMs for research. The reasons for trusting are different, as these quotes illustrate:

Participant 83: " I won't know. I won't change my mind. I trust this institution first and it's important to trust this institution because it's for university research. I'm confident to donate my tissue."

Participant 55: "Ok one thing, if in advance let's say - when I before admit to hospital, this kind of request is given to us. So at least we can look at it more thoroughly. But if you just before surgery, then actually you got no time to read it thoroughly. It will depend on the person explanation. I trust what's explanation is same as what on paper. I think if you're talking about reading it thoroughly, you got to be a few days before admission."

Participant 57: "As long as all trustworthy and ethically correct."

Interestingly, participants also expressed trust that the tissues would not be used for commercial purposes. Participant 13, for instance, said: "It should be fine, as long as they follow the guideline. I mean I'll trust you all will do a lot of screening that things are done in proper manner. I don't think you will just sell it away, you all won't, right? For purpose for advance our medical, you will look into that." In addition, Participant 13 indicated: "No I won't. I mean if they're doing the good job, why not. But somebody, as what you mention, must actually check on what they are actually doing…. (On governance) Something like that, that's what I said everyone have a part to play. I trust you all will do. I'll trust you will do that."

It is interesting to note that of the 100 participants involved in Phase III of this study, 81 patients did not consider compromises to privacy and confidentiality to be risks associated

with contributing their residual HBMs. However, they are willing to donate residual tissues for research when there are proper safeguards for privacy and confidentiality. In other words, most patients wanted safeguards and control, even without knowing the specifics of what constitutes sound governance. Hence, where biological materials are used for genetic research, confidentiality and privacy issues are clearly identified as risk to self and family, religious belief, and potential discrimination, especially in relation to employment and insurance coverage.

A key application of good governance relates to securing a participant's privacy and confidentiality interests. Protection of privacy and confidentiality of personal information were two main concerns of patients in terms of safeguards and control. From the research, patients were worried that their medical records (including genetic information) would be leaked to insurance agents and employers. They feared that this could result in future economic and financial loss. Further, they were concerned about social and financial discrimination once their medical confidentiality was breached. For patients who declined to donate, mistrust of research organisations in the handling of private and confidential information was a dominant reason. Others were also concerned about the manner and timing in which patients were approached for donation. It was important that they did not feel coerced to donate or were placed in a vulnerable position where they felt forced to donate.

3.6 SOME CONCLUSIONS FROM THE RESEARCH

3.6.1 Motivations, Attitudes and Perceptions of Singaporean in Tissue banking

From Phase II of the study, the consent rates among 167,329 patients at NUH for agreeing to contribute tissue for medical research, education and study over a period of 10 years was

73.58 %. The dataset on consent was matched with demographics data drawn from surgical consent forms and admission records, and more specifically, by gender, ethnic groups, religions, age groups, paying class and medical conditions. A statistically significant relationship was found between demographic characteristics (or factors) and the likelihood of consent. As noted above:

- Men were more willing to donate compared to women;
- Chinese patients were more willing to provide consent under the Surgical Consent Form, followed by Malay and Indian patients;
- Buddhists and Christians were more willing to donate;
- Elderly patients of more than 50 years of age were more willing to donate;
- Private paying patients were more willing to donate; and
- Patients' donation rate varied with their medical conditions.

The interviews conducted in Phase III of the study did provide some explanations for the findings from Phase II. The majority of the participants believed in altruistic donation, advancement of future research as a public good, helping other people and benefiting future generations being the prime reasons for donation. The high consent rate may be attributed to the reported motivation among most participants of altruism.

As one might expect, religious belief appears to have been an important influence over the decision to donate tissue for at least two reasons. First, participants who were Buddhists and Christians explicitly acknowledged the impact of their religious faiths in making the donation. For many Muslim patients, religious concern was a reason for declining the contribution of HBMs. Second, many participants did not consider the provision of detailed information in consent-taking to be the deciding factor on whether to donate. Risks of

harm were similarly not of special concern. Rather, sentiments of reciprocity and solidarity could often be traced to religious or civic mindedness. For this reason, some participants objected to their HBMs being used by commercial companies and foreign institutions, as they were concerned about inequitable distribution of benefits.

Where religion or civic consciousness has not been of influence, the donation may be simply attributed to pragmatism, as these participants do not have any use for the HBMs and do not think that there is any serious risk of harm. In fact, there was a high level of trust in systemic safeguards and sound governance was in place. A majority of the patients (81%) did not think that there was any risk involved in the donation, and clearly expressed faith and trust in researchers and the healthcare system (since NUHTR is associated with NUH and not an independent research setup). Perhaps most indicative of the low emphasis on the information aspect of consent is that a majority of the patients (74%) was satisfied with the short and brief Surgical Consent Form. As we have seen, some participants clearly indicated that they did not have time to go into the details, or that they honestly did not care. Interestingly, most participants (85%) did appreciate that there could be compromises to privacy and confidentiality, as researchers could access their personal and medical information. Nevertheless, they expressed confidence in the researchers as long as they kept the information confidential. Patients seemed to have found assurance in the high level of trust in the system of governance, but again not clearly distinguishing the healthcare setting from research. This is most evident as the participants did not seem to be well informed about existing safeguards and controls.

3.6.2 Altruism and Trust: Why patients donate their residual tissues

The most common reason for donating HBMs has been indicated as benefit either to the donors themselves or to others.[289] In my research, a majority of the participants reported the desire to help other people and to benefit future generations as the prime reason for donation. The dominant influence and intention should be noted by researchers and policy makers to secure and support altruism and being critical in maintaining trust. Our results showed that patients donated the residual HBMs with aspirations and intentions in contributing to public good, so that researchers could use their HBMs to find cure for diseases in the future. Thus, what happened are not a case of abandonment but an intentional contribution of residual HBMs for future research and an entrustment towards an altruistic cause.

Trust is often expressed as an expectation among donors that their HBMs will not be misused and applied for a good cause.[290] Trust is thus an important basis for patients to freely donate their residual HBMs for research,[291] and a betrayal of trust can lead to lower donation rates.[292] From our qualitative research, we found that patients who have contributed the residual HBMs expressed the view that they trusted the doctors, consent nurses and researchers and the institutions. They trusted the institutions collecting and using their HBMs to have proper governance systems and to be capable in protecting their

---

[289] DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. *Social Science & Medicine,* 65**,** 2212-2222.

[290] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[291] LEVITT, M. & WELDON, S. Ibid.A well placed trust?: public perceptions of the governance of DNA databases. 311-321.

[292] WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

privacy and confidentiality of their medical information. Patients also expressed trust in the institutions and researchers for not exploiting their HBMs for unintended use, or selling them for commercial benefits. The "betrayal of trust"[293] was described in some studies when the scandal of UK's Alder Hey Hospital came to light, [294] as described by some donors.[295] These research findings showed that patients contributed their residual HBMs for altruistic reasons and trusted the institutions, particularly since the ideals of informed consent are seldom met. Trust appears inevitable, as there is a "knowledge gap" between patient-donors and researchers. For example, patients would think that "there is no value" in their residual HBMs and consider them as surgically removed waste materials, while researchers know that such materials are extremely valuable. Most laypersons will not appreciate the value, or the risks and benefits associated with donating their residual HBMs.

As we considered in Chapter 2, some people believed that donating their tissues was one way to contribute to medical science and medical education, and they considered tissue donation as "a gift" to humanity. This act of giving could be considered as an expression of unconditional gratitude, and it was centred about trust. The strong association between altruism and trust has also been reported in two other research studies conducted in Singapore (between 2003 and 2004) on the donation of HBMs for research. In the first paper (which is included in the systematic review in Section 3.4.1 above), conducted a

---

[293] JENKINS, M. M., REED-GROSS, E., RASMUSSEN, S. A., BARFIELD, W. D., PRUE, C. E., GALLAGHER, M. L. & HONEIN, M. A. 2009. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A,* 149A**,** 2378-86.

[294] SQUE, M., LONG, T., PAYNE, S., ROCHE, W. R. & SPECK, P. 2008. The UK postmortem organ retention crisis: a qualitative study of its impact on parents. *J R Soc Med,* 101**,** 71-7.

[295] MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010a. Cancer as Rubbish: Donation of Tumor Tissue for Research. *Qual Health Res*.

qualitative research[296] interviewing 98 Singaporeans in 12 focus groups. The results from this study were used to formulate the second study – a quantitative survey[297] - involving 548 adult Singaporeans to examine their willingness to donate blood samples for research. They found that less than half of the sampled populations (49.3%) were willing to donate blood samples for genetic research. Among the willing donors, 84% were willing to have their blood stored for future research (49.3% for donating blood specimens and 41.4% for storage of the HBMs for future research). The authors attributed the observed low rates of willingness among the general population in Singapore to differences in religious and cultural beliefs. Additionally, participants of the survey also stated other reasons such as an apprehension about donating blood due to fear of pain and needles (38.1%), fear of finding out that they might have a disease (22.3%), no self-benefits (24.8%) and concern on discrimination (18.7%). Misconceptions such as weakness (15.4%) and weight gain (9.5%) from giving blood samples were reported by a small but significant proportion of respondents. Reasons reported for willingness to give blood were for medical progress (81.9%), to benefit future generations (81.1%) and for one's health concerns (66.6%).

In the qualitative focus group research session, the researchers also found differences in concerns and issues regarding the donation and storage of blood specimens for genetic research from their focus group sessions with the three major ethnic groups in Singapore: Malay-Muslim (n=35); Chinese (n=32) and Indian (n=31) Singaporeans. The participants

---

[296] WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

[297] WONG, M. L., CHIA, K. S., YAM, W. M., TEODORO, G. R. & LAU, K. W. 2004b. Willingness to donate blood samples for genetic research: a survey from a community in Singapore. *Clinical Genetics,* 65**,** 45-51.

(n=98) were recruited island-wide and stratified by gender, ethnicity and educational level (lower education defined as less than 10 years of schooling). There was a total of 12 focus group sessions with 7-9 participants in each group. From this research, some Malay-Muslims, regardless of their gender and educational level, said that it was against their religion to have their blood stored as the blood specimens would outlive the 'owner'. Some felt it was not right to test for genes to predict the future, just as it was not right to buy life insurance. They were also concerned about how and why they were selected for population-based genetic research and whether genetic tests would be used for discriminating conditions like intelligence. A few Malay males did not like the use of the word 'investigator' to denote the researcher in the consent form. They expressed that it had a negative connotation as if a police officer were investigating on the research participant like a 'criminal'. None of the abovementioned concerns was expressed by the other ethnic groups. These findings relate to our quantitative research where Malay patients are less willing to donate the HBMs due to lack of trust.

Chinese and Indians generally expressed concern about giving blood to strangers and being 'bothered often and inconvenienced' by participating in research that may require frequent follow-up visits. All groups expressed concerns about confidentiality; pain and needle pricks; finding out about disease and having no self-benefits.

The findings in these two studies complement my research findings, in the need to take serious account of ethnic-specific concerns, design ethnic-sensitive messages and involve the public and religious leaders in planning programs to promote community participation in research using HBMs. The centrality of trust and good governance is similarly evident in the two studies, and these are elaborated on in the next Chapter.

3.6.3 Lack of consensus on informed consent regime for Tissue banking

Traditional consent regimes vary from highly specific informed consent to broad consent for the use of HBMs. Consent norms and policies in ethics require that research participants be fully informed of the nature and risks involved in research. In Chapter 2, the impossibility of 'fully' informed consent was discussed at some length. Specifically in the case of tissue banking, where the sample population is diverse and a large number of samples are collected, mandating specific informed consent as a requirement can be an insurmountable challenge. In the ideal world, specific informed consent provides patients or donors with a specific choice on exactly how their HBMs will be collected, stored and used. Informed consent "allows individuals to exercise their fundamental right to decide the scenario on how their body, body parts and associated data will be used."[298] A broad consent is still informed and valid consent, if properly execute and that the patients know that the HBMs are used for research, even without knowing what types of research and when will it be used. The lack of specific information about particular uses of the samples does not imply that such consent cannot be fully autonomous and so is unethical.[299] My research shows that broad consent can also be informed consent and the patients knew what they are doing when they agreed to donate their residual HBMs.

Where HBMs are limited to specific uses in a research project, the researchers will have to discard the HBMs after the research in completed. Any future use of these HBMs will then

---

[298] GRUBB, A. 1995. The Nuffield Council report on human tissue. *Med Law Rev,* 3**,** 235-6.

[299] SHEEHAN, M. 2011. Can Broad Consent be Informed Consent? *Public Health Ethics,* 4**,** 226-235.

require re-consent from patients for new research use. However, this method was deemed not practicable or impossible, especially in a situation where the patient had died. In addition, it could trigger unnecessary emotional distress to patients and family (in the case of a deceased donor) to be contacted by researchers, particularly if the initial understanding was that the HBMs would be disposed of after use. Discarding residual HBMs may however not be in compliance with the requirements of certain scientific journal, as peer (or scientific) verification and data validation are sometimes required after the paper is published.[300] Limiting HBMs to a specific project at a time could also be a waste of valuable resources as time, money and effort have been expended in collecting and processing these HBMs as samples.[301] In addition, their valuable research potential will be lost.[302] For these reasons, most tissue banks favour the use of general or broad consent. This is the finding of Master *et al.* in their review of existing consent practices in the literature on tissue banking, even when they report that there is no consensus on consent regime amongst numerous scholars.[303] Phase I (or the CSR) of my research arrived at the same conclusion, in that there is no one superior consent regime. Based on patients' experiences and preferences alone, Phase III of this study suggests a clear preference for the broad consent approach over specific informed consent. However, there are too few studies to point to a clear and absolute choice.[304]

---

[300] 2009. Common consent. *Nature,* 460**,** 933-933.

[301] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[302] LEVITT, M. & WELDON, S. Ibid.A well placed trust?: public perceptions of the governance of DNA databases. 311-321.

[303] MASTER, Z., NELSON, E., MURDOCH, B. & CAULFIELD, T. 2012. Biobanks, consent and claims of consensus. *Nat Methods,* 9**,** 885-8.

[304] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7. SECKO, D. M., PRETO, N., NIEMEYER, S. & BURGESS, M. M. 2009. Informed consent in biobank research: a deliberative approach to the debate. *Soc Sci Med,* 68**,** 781-9. HOEYER, K., OLOFSSON, B. O.,

Other studies however are divided on the issue. For instance, Murphy noted that the patient "could be given a choice of either broad or study specific consent at the beginning of a research"[305] whereas Skolbekken[306] concluded that patients preferred "initial consent to be active, and the need for explicit and active consent for each new research project was perceived as unnecessary".[307] Depending on whether the tissues are identifiable, coded or anonymous (with no identifiable patient's information) at the point of collection and usage, preference for a particular consent model or approach may differ.[308] Some authors have indicated that, where coded and anonymous tissues were used, participants did not consider the stringent specific consent requirement to be necessary. In contrast, this requirement would be appropriate for identifiable tissues.[309] Due to limited qualitative studies on

---

MJORNDAL, T. & LYNOE, N. 2004. Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scand J Public Health,* 32**,** 224-9.

[305] MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. *American Journal of Public Health,* 99**,** 2128-2134.

[306] SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.

[307] ABOU-ZEID, A., SILVERMAN, H., SHEHATA, M., SHAMS, M., ELSHABRAWY, M., HIFNAWY, T., RAHMAN, S. A., GALAL, B., SLEEM, H., MIKHAIL, N. & MOHARRAM, N. 2010. Collection, storage and use of blood samples for future research: views of Egyptian patients expressed in a cross-sectional survey. *J Med Ethics*.

[308] LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.

[309] VAN VEEN, E. B., RIEGMAN, P. H., DINJENS, W. N., LAM, K. H., OOMEN, M. H., SPATZ, A., MAGER, R., RATCLIFFE, C., KNOX, K., KERR, D., VAN DAMME, B., VAN DE VIJVER, M., VAN BOVEN, H., MORENTE, M. M., ALONSO, S., KERJASCHKI, D., PAMMER, J., LOPEZ-GUERRERO, J. A., LLOMBART BOSCH, A., CARBONE, A., GLOGHINI, A., TEODOROVIC, I., ISABELLE, M., PASSIOUKOV, A., LEJEUNE, S., THERASSE, P. & OOSTERHUIS, J. W. 2006. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer,* 42**,** 2914-23. ROBERTSON, J. A. 1995. Ethical and legal issues in human embryo donation. *Fertil Steril,* 64**,** 885-94. GOODSON, M. L. & VERNON, B. G. 2004. A study of public

participant preferences, no conclusion could be made at this point and further research is thus necessary.[310]

3.6.4 Presupposition of Good Governance at various stages of tissue banking

From Phase III of this study involving NUH patients, different concerns were expressed at different stages of handling residual HBMs by researchers and research institutions. The stages of HBMs handling considered were collection, storage, distribution and future use of the HBMs, and related concerns that were reported are summarised as follows:

- During collection or donation of tissues, patients spoke mainly on the different reasons for donating their residual HBMs;
- During processing and storage of tissues in tissue banks or research institutions, patients expressed concerns about safeguards and controls on the collection and storage of residual HBMs; and
- Concerns over ownership and equitable distribution of benefits were reported in relation to the subsequent distribution, access to and use of tissues.

A common expectation that cuts across these different stages was the expectation of the existence of a good system of governance, as well as a system to protect the rights, privacy and confidentiality of patients. Most patients preferred an ethical and effective system to

---

opinion on the use of tissue samples from living subjects for clinical research. *J Clin Pathol,* 57**,** 135-8.

[310] OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.

decide on the future use of their donated HBMs. Institutions and research organisations were also expected to be responsible custodians in safeguarding where stored HBMs are not misused, and as stewardship in ensuring that research using HBMs are ethically conducted and for the public good. Good governance is hence a critical precondition to trust and sustains the willingness to donate. Higher patients' acceptance and greater positive donation rate are important because leftover or residual HBMs have no direct cost to patients and research institutions, as they will otherwise be surgical waste to be discarded. As a larger research enterprise, tissue banking can only survive if it is able to draw contributions of HBMs and related data on one hand, and allow reasonable access to researchers on the other.

Chapter 4. Discussions and Recommendations on Trust and Governance

Residual HBMs are usually stored in an institutional tissue repository for future research, or in the laboratories of individual researchers (as personal tissues banks) for their specific research. These are the two main types of biobanks for residual HBMs. As discussed in the earlier chapter, I argue that broad consent should be obtained from prospective contributors of HBMs as it is increasingly difficult to determine the types of research that would require the use of HBMs in the future.[311] Consent-taking will ensure that tissue contributors are aware that their HBMs will be banked in tissue repositories for future and unspecified research use.

While recognizing the importance of informed consent, I argue that this autonomy-based governance does not offer adequate protection of research participants from harm. Informed consent provides patients with a choice on whether or not to contribute their HBMs, but once the contribution has been made, an effective system of governance on a tissue bank's operation must be in place to ensure accountability and transparency. Currently, the system of ethical governance on the use of residual HBMs in Singapore still lacks transparency and accountability. The BAC's recommendations on statutory regulation, governance and supervision have yet to be implemented. More specifically, there is still no statutory authority being set up to regulate and supervise all the human tissue research in Singapore, and institutions and companies that carry out human tissue research and banking

[311] ALLEN, J. & MCNAMARA, B. 2011. Reconsidering the value of consent in biobank research. *Bioethics,* 25**,** 155-66.

are not transparent with their operational practices and safeguards. There are also inadequate measures in place to ensure accountability in the collection, storage, distribution and use of residual HBMs. These issues will have implications for securing the public trust and long-term support that the success of tissue banking depends on.

In this Chapter, I will elaborate on my support for broad consent (with a right to withdraw) that is supported by a system of governance that is transparent and accountable, and constitutes institutions that collect, store and use residual HBMs as stewards.

4.1 Broad Consent as the Preferred Choice in tissue banking

As discussed in Chapter 2, tissue banking of residual HBMs has added complexity to the regime of informed consent, which is an important ethical component in research. The current requirement of various levels (or models) of informed consent mainly emphasises the informational parameters deemed necessary for donors so that they can voluntarily determine whether to donate on their own free will or not. This ethical safeguard operates on the assumption that an individual will carefully deliberate on and assess the information provided, and then decide if s/he will voluntarily participate in the research based on an understanding of the risks and benefits of the research. Demographics (like gender, ethnic groups, religious belief and age) are accounted for in the informed consent process; ethnic group may be important because of the language used in the consent documents; age may be important to determine competence; religious belief may be important especially in cultural sensitivities study; gender may be of high importance in some male dominated community. However, it unclear if the motivation for contributing HBMs has been as closely scrutinized, particularly in relation to specific demographic features. As my study in Chapter 3 shows, such considerations are significant and important, if patients in Singapore act as a

useful point of reference. The requirement for 'specific' informed consent as an ethical safeguard will typically encompass a long and detailed informational process, depending on the complexity of the research envisaged. Based on a 'specific' informed consent regime, re-consent is necessary for every future unknown investigative use of collected HBMs (often construed as a form of respect for autonomy). Other forms of safeguards include privacy protection laws and anonymisation of personal information to protect privacy and confidentiality; ethical review by either a research ethics committee or an IRB represents different layers of protection and safeguard against potential misuses of collected HBMs. Some of these protections may not be as effective in protecting patients as research participants. For instance, the lack of privacy protection can be further aggravated by advanced data matching and re-identification techniques used by bio-informatics.[312] Recent studies have shown that tissue banks cannot guarantee absolute privacy due to advances in information technology processing and data mining tools.[313] The strategy to rely on specific informed consent (considered in Chapter 2) will either preclude a concerned patient from such research participation, or allow the participation at the patient's own risk since information on the possible privacy risk are normally not explicitly stated in the participants' information sheet and informed consent form. For this reason, specific informed consent taken at the time of contribution cannot be adequately applied, as a proper safeguard, to any future unknown use of HBMs in tissue banks research.

---

[312] GYMREK, M., MCGUIRE, A. L., GOLAN, D., HALPERIN, E. & ERLICH, Y. 2013. Identifying Personal Genomes by Surname Inference. *Science,* 339**,** 321-324.

[313] MALIN, B. & SWEENEY, L. 2004. How (not) to protect genomic data privacy in a distributed network: using trail re-identification to evaluate and design anonymity protection systems. *Journal of Biomedical Informatics,* 37**,** 179-192.

While specific informed consent can be, in theory, instructive for the potential research participant, it may impede the operation of tissue banks by creating unnecessary restrictions on the future use of collected HBMs and limiting their research application. It could even discourage an altruistic person from contributing HBMs to research, as my findings reported in Chapter 3 suggest. The requirement for a detailed and tedious informed consent process fails to give due recognition to the trust that is already manifested by HBM contributors, especially when it is presented in a legalistic format. This is more likely to arouse suspicion in patients, rather than to help patients realise that there is something important about the consent process and to enhance the trusting relationship. In the context of my research, such a tedious and long informed consent process also fails to acknowledge the emotional distress that patients are likely to be experiencing before surgery. The patients are willing to participate and contribute to tissue banks as long as they trust the researcher. In many cases, patients may also lack the sophistication or interest to understand a proposed research in its entire intricate details. For these reasons, as well as those set out and discussed in Chapter 3, tissue banks have generally preferred the use of general or broad consent for the contribution of residual HBMs for present and future research. This has been discussed in the case of NUHTR. In Chapter 2, it has been argued that there are clear justifications to obtain broad consent rather than specific consent. In fact, I have gone further to distinguish donation from contribution of tissue through broad consent, and to argue that the latter is to be preferred over the former. A reason for this is that contribution is more representative of the motivations of donors, and it need not necessarily (although it could) be limited by certain requirements. In other words, a conditional contribution to a public cause is not any less altruistic than a donation. Over emphasis on informed consent obscures important issues about the aims of assembling and using such collections, and the risk to contributors especially when the system of governance lacks rigour. Certain details may also be obscured in the process, such as allowing the use of HBMs for commercial

interests, which may not be consistent with the original altruistic motivation of donors, and could amount to a betrayal of trust that the contributors must invest.[314]

A donation has the character of what the BAC in Singapore has described as an 'outright gift', with no conditions attached. According to my research findings, altruistic motives are the main reasons for patients contributing their residual HBMs. They do it for the good of others with no expectation of direct self-benefit, as they want to help in search for better cure and treatments. Patients must weigh altruistic motives to advance research against personal risks of participation, since donating their residual HBMs do not directly benefit themselves. This finding is also discussed by Dr. Lynn A. Jansen, who mentioned that research participation can arise out of genuine altruistic motives to benefit others and these are different from decisions made as a product of confusion and misunderstanding.[315] Most patients are willing to contribute, based on a level of trust and the condition that this gift of residual HBMs will be applied to advance public good, and on the assumption that they will not suffer any harm as a consequence of making this 'conditional' gift. As a sign of respect for the trust manifested by the patients, it should not be necessary for the tissue bank to specify all possible future uses of the gift. The tissue bank should demonstrate that it is trustworthy to fulfil the donors' motives and conditions for contributing. A sound governance system should be directed at promoting and sustaining trust among contributors

[314] WILLIAMS, G. & SCHROEDER, D. 2004. Human genetic banking: altruism, benefit and consent. New Genet Soc, 23, 89-103.

[315] JANSEN, L. A. 2009. The ethics of altruism in clinical research. *Hastings Cent Rep,* 39**,** 26-36.

and trustworthiness on the part of tissue bank, by ensuring accountable and responsible handling and use of HBMs.[316] Trustworthiness is elaborated on later in this Chapter.

Within a framework of trust, the tissue bank serves as a public guardian of residual HBMs, and should be able to freely decide on the types of research that are in the public interest and can easily gain access to the stored HBMs. The constant need to re-contact contributors for re-consent on new research uses in the future does not show respect for the trust that has been given. Such a need should not arise if the purposes, goals and operating procedures of the tissue bank are clear to all parties involved. This is not to say that the tissue bank should discourage willing contributors to have greater participatory involvement in its work, however, where HBMs have been contributed pursuant to broad consent, the trust relationship is disregarded when re-consent is required. The application of broad consent does not require re-consent to be sought from contributors of HBMs. As discussed earlier, such re-contact for the purpose of re-consent would also be logistically burdensome and not practicable especially if the contributors have passed on.

My research data reported in Chapter 3 indicate that most patients did not want to know the specific details of the research that they were contributing to, nor the exact risks that were entailed, if there were effective safeguards in place to protect their interests. A general understanding that their HBMs would be used for research resulting in public benefits was sufficient for the patients, and many gave residual HBMs to NUHTR based on altruism and trust in the institutions and researchers. A similar outcome would have been achieved under a broad consent regime, where the consent sought was for the contribution of residual

[316] BAIER, A. 1986. Trust and Antitrust. *Ethics,* 96**,** 231-260.

HBMs for a broad range of activities, including research. Consider the Surgical Consent Form that was discussed in Chapter 2. By signing this broad consent form, donors agree that the future use of their HBMs in medical research, education and study is to be decided by NUHTR and the institution. A preoccupation with informed consent may even obscure other ethical issues about the proper use of the HBMs to reflect the original altruistic motivation of the patients and the trust they have invested in the system.[317] Decrease in the reliance on 'full' specific informed consent and the inability of researchers to ensure full privacy protection for instance would imply a greater need for better and more responsive system of tissue bank governance.[318]

Some authors prefer the use of tiered consent as they consider that, broad consent – although pragmatic – to be an unacceptable ethical compromise and not truly informed on the grounds of autonomy.[319] For instance, Steinsbekk *et al.* support the use of tiered or dynamic consent because they consider broad consent to be paternalistic and advocating of top-down governance. The intent is to give effect to the principle of autonomy, with the hope of also increasing user participation. The proposed 'dynamic consent' employs modern communication methods to inform, involve, offer choices and obtain re-consent for every research project based on available resources.[320] Several discussions on fine-tuning the tiered informed consent process by some authors have made it impracticable for tissue

---

[317] WILLIAMS, G. & SCHROEDER, D. 2004. Human genetic banking: altruism, benefit and consent. New Genet Soc, 23, 89-103.

[318] HAWKINS, A. K. & O'DOHERTY, K. 2010. Biobank governance: a lesson in trust. New Genetics and Society, 29, 311-327.

[319] MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. American Journal of Public Health, 99, 2128-2134.

[320] STEINSBEKK, K. S., KARE MYSKJA, B. & SOLBERG, B. 2013. Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem? *Eur J Hum Genet*.

repositories (and tissue banks) and researchers to execute this in practice.[321] Tiered (or dynamic) consent involves offering patients a variety of options about the use of HBMs. It is logistically difficult for both tissue banks and researchers to implement in consent-taking and could be difficult to honour as more complex conditions are added in the selection of the types of research to be undertaken. While sensible in theory, this approach to consent-taking is inconsistent with the expectations of HBM contributors or research participants. We know, from the results reported in Chapter 3, that the general preference of patients or research participants is for simplicity and ease of process. As an alternative to the 'full' informed consent regime, tiered dynamic consent is most unlikely to resolve important ethical issues surrounding tissue banking, the protection of patients' rights and general wellbeing, and it is inconsistent with the expectations of contributors; it can only add more barriers to the research.

By the analysis presented in this thesis, there appears to be a hierarchy of approaches to consent in terms of its informational component. In the order of highest to lowest priority, we have:

- Donation of HBMs, where the informational component is essentially purposive;
- Broad consent, where the contribution and use of HBMs are limited by minimal conditions;
- Tiered (or dynamic) consent, where the informational component can be onerous given that contributors of HBMs must make certain choices;
- Specific full consent, which is most onerous in terms of its informational requirements; and

[321] *Ibid.*

- Implied (or presumed) consent, which lacks sound ethical grounding and should not be implemented, unless supported by legislation or other forms public endorsement.

As argued in Chapters 2 and 3, the hierarchy proposed above is justified based on taking into serious account the perceptions, motivation and preferences of contributors of HBMs, at least in the Singaporean context. Practical concerns are also taken seriously for reasons that have already been discussed at some length. However, to properly secure public trust and safeguard the interests and well-being of donors, tissue repositories and tissue banks must themselves act as responsible stewards and are be supported by a system of good governance and control. These are elaborated on in the sections that follow.

4.2 Tissue Repository and its institution as Stewards of residual HBMs

The roles and functions of tissue repositories as research tissue banks have been discussed extensively. These repositories serve as collection centres of HBMs for researchers to tap as resources for their research. The primary objective of a tissue bank is to collect, process and store tissues and other residual HBMs for future research use. My research on the perceptions of contributors shows that their acceptance of tissue banks and their willingness to donate are influenced by several factors. These key factors include the understanding of the role of tissue banks and their purpose, trust in the institution and tissue bank administrators, equitable sharing of benefits, and privacy and confidentiality protection. These are consistent with existing requirements on tissue banks to protect the rights and respect the preferences of donors, and to minimise risks of harm to donors.

A person is more likely to contribute HBMs if s/he trusts that a tissue bank has a proper system of governance in place. Thus, tissue banks are entrusted with proper handling and

use of residual HBMs, including other services that the tissue bank may provide, such as extraction of DNA, RNA and/or proteins, which are often needed by researchers. However, the specific nature of a tissue bank's responsibilities may not always be easy to articulate clearly. From the CSR in Chapter 3, the literature points to a variety of relationships that can exist between contributors and tissue banks. For instance, this relationship could depend on the status of the HBMs, whether as 'outright' gifts, as abandoned 'waste' after surgery, or as 'conditional-use' research materials. The status of HBM contributors is also relevant, as they could be active participants or 'research subjects', 'donors' or 'patients' who may or may not be construed as having abandoned their 'waste' tissue (as we have considered in Chapter 2). In situations where residual HBMs are unconditional gifts, patients no longer possess ownership rights over them. Alternatively, if these residual HBMs are intentionally abandoned by patients after surgery, tissue banks should have the right to use them without having to obtain consent.[322] More often, patients are considered participants in research, especially if the HBMs are not anonymised. However, it is not always clear which patients are genuinely altruistic, which patients merely abandoned their HBMs, and which patients had a mixture of many motivations. My research demonstrated that most participants are aware that they are contributing their HBMs for research and thus, the rules of research ethics and human subjects protection apply. Patients may sometimes be considered as a 'partner' of a tissue bank, being party to a provider-researcher partnership for the advancement of medical research.[323] Whether patients contribute their residual HBMs in a donation (as donors), in a case of abandonment (as contributors), in research participation

---

[322] TUPASELA, A. 2011. From gift to waste: changing policies in biobanking practices. *Science and Public Policy,* 38**,** 510-520. ibid. ibid.

[323] KORT, E. J., CAMPBELL, B. & RESAU, J. H. 2003. A human tissue and data resource: an overview of opportunities, challenges, and development of a provider/researcher partnership model. Comput Methods Programs Biomed, 70, 137-50.

(as research participants) or in a partnership (as partners) for future research, published literature and opinion leaders have provided inconsistent descriptions and contrasting models of contribution leading to ambiguities in the examination of ethical, social and legal implications.[324] My research, as discussed in Chapter 3.5.3, demonstrates that these residual HBMs contributors care about what becomes of their tissue and expressed a continuing interest in the fate of their HBMs. They know that they have contributed their residual HBMs for research and hope that this research will result in future cure for other patients or even themselves. It is not intentional abandonment even though some have expressed that the HBMs are donated for good use rather than to simply discard them. Contributors expressed preference for a simple broad consent because they trusted the institutions, doctors and researchers and did not see the need for active control of the HBMs contributed, in a way that dynamic consent attempts to implement for instance.

I argue that as stewards of such tissue repository, trustworthy or moral institutions should proactively encourage responsible distribution and use of such collections, and sponsor research that reflects publicly agreed priorities and is likely to generate the greatest public benefits. The BAC in Singapore supports the notion of donation, that patients should willingly 'donate' their residual HBMs to tissue banks for the purpose of new research discoveries for the benefit of the community. Given the BAC emphasis on donation, the contribution of residual HBMs is to be regarded as a 'gift' to the tissue bank and patients should be considered as 'donors' or 'residual HBM contributors'. The recent draft revisions to the BAC's tissue research guidelines use the term 'custodianship' to refer to the

[324] WILLIAMS, P. H., SCHEPP, K., MCGRATH, B. & MITCHELL, P. 2010. The stewardship model: current viability for genetic biobank practice development. *ANS Adv Nurs Sci,* 33**,** E41-9.

relationship between tissue banks and the HBMs.[325] The term 'custodian' is also used in paragraph 2.1 of the UK's document on human tissue and biological samples for use in research. This model of custodianship, as a framework for tissue banking research is intended to promote fair research access and resolve issues of control and potential conflict between tissue banks, investigators, human research participants (human subjects), and sponsors.[326] From the initial collection of residual HBMs to the final dissemination of research findings, tissue banks have a moral obligation to ensure responsible oversight and use of residual HBMs collected for research. The custodial model attempts to ensure transparency in research, fairness to contributors of HBMs, and accountability shared by stakeholders and researchers involved in tissue bank research.[327]

Rather than to perceive the role of tissue banks as custodians of donated HBMs, a better view is to adopt a 'stewardship model'. This may be implemented in different ways, including the establishment of a tissue bank oversight committee in leading and taking responsibility for research projects that utilise residual HBMs provided by the tissue bank. Campbell (1998) stated that when patients donate their organs or tissues, the receiving organization has a duty and a responsibility to serve as a trustee of these HBMs and to

---

[325] Bioethics Advisory Committee, Draft Ethics Guidelines for Human Biomedical Research. Para 5.6. Accessed on 1 Aug 2014 https://www.bioethics-singapore.org/index.php/news/bac-news-press-releases/182-bioethics-advisory-committee-seeks-public-feedback-on-ethics-guidelines-for-human-biomedical-research

[326] YASSIN, R., LOCKHART, N., GONZÁLEZ DEL RIEGO, M., PITT, K., THOMAS, J. W., WEISS, L. & COMPTON, C. 2010. Custodianship as an Ethical Framework for Biospecimen-Based Research. *Cancer Epidemiology Biomarkers & Prevention,* 19**,** 1012-1015.

[327] MERZ, J. F., SANKAR, P., TAUBE, S. E. & LIVOLSI, V. 1997. Use of human tissues in research: clarifying clinician and researcher roles and information flows. *J Investig Med,* 45**,** 252-7.

ensure the protection of the contribution.[328] Stewardship embodies responsible planning and management of resources of others, which the stewards have been entrusted with.[329] The concept of stewardship is not new and it has been recognised as encapsulating duties and responsibilities to shepherd and safeguard these valuable resources. A conceptual framework of the 'stewardship model' is published and proposed by Jeffers in *Advances in Nursing Science*, and is substantively similar to the recommendations of the BAC.[330] Jeffers conceptualises the ethical responsibilities of a tissue bank and its governing institution, as managers acting as stewards who are responsible for the assets they receive and to manage them in the best interests of the intended beneficiaries.[331] When a person contributes his/her HBMs, s/he expects and trusts the tissue bank to ensure responsible use and in ways that maximise public good.

A stewardship model of governance also includes respect for human dignity, responsibility, accountability, service, cultivation, conservation, and protection of the preferences and needs of contributors of their residual HBMs.[332] Stewardship is a concept with deep roots in medical science, ethics and law, and in the practice of data and materials collection, sharing,

---

[328] CAMPBELL, C. S. 1998. Religion and the body in medical research. *Kennedy Inst Ethics J,* 8**,** 275-305.

[329] HRIPCSAK, G., BLOOMROSEN, M., FLATELYBRENNAN, P., CHUTE, C. G., CIMINO, J., DETMER, D. E., EDMUNDS, M., EMBI, P. J., GOLDSTEIN, M. M., HAMMOND, W. E., KEENAN, G. M., LABKOFF, S., MURPHY, S., SAFRAN, C., SPEEDIE, S., STRASBERG, H., TEMPLE, F. & WILCOX, A. B. 2014. Health data use, stewardship, and governance: ongoing gaps and challenges: a report from AMIA's 2012 Health Policy Meeting. *J Am Med Inform Assoc,* 21**,** 204-11.

[330] JEFFERS, B. R. 2001. Human biological materials in research: ethical issues and the role of stewardship in minimizing research risks. *ANS Adv Nurs Sci,* 24**,** 32-46.

[331] WILLIAMS, P. H., SCHEPP, K., MCGRATH, B. & MITCHELL, P. 2010. The stewardship model: current viability for genetic biobank practice development. Ibid.33**,** E41-9.

[332] *Ibid.*

and analysis.[333] Stewardship requires managers to act as trustees of the assets they control (in this case, residual HBMs) and they are held to high standards of conduct.[334] Where tissue banking could be conceived as a public enterprise, the HBMs and accompanying related health data should be viewed as public goods to be used for the benefit of patients or public causes.[335]

In the absence of a regulatory authority and legislation like the UK Human Tissue Act in Singapore, the role of stewardship falls upon the institution, the tissue bank administrators and researchers. Regardless of whether the residual HBMs were abandoned, donated or contributed by research participation, HBMs that NUHTR have received are akin to trust property and should be handled accordingly. As a practical measure, NUHTR could establish a committee to ensure that clear and transparent processes are in place for HBMs to be applied in ways that maximise public benefit. In other words, it is critical for the institution to assume the role of a moral institution to ensure good stewardship in governing the tissue bank for the public good.

4.3 Good Governance

---

[333] ROSENBAUM, S. 2010. Data governance and stewardship: designing data stewardship entities and advancing data access. *Health Serv Res,* 45**,** 1442-55.

[334] DONALDSON, L. & DAVIS, J. H. 1991. Stewardship Theory or Agency Theory: CEO Governance and Shareholder Returns. *Australian Journal of Management,* 16**,** 49-64.

[335] HRIPCSAK, G., BLOOMROSEN, M., FLATELYBRENNAN, P., CHUTE, C. G., CIMINO, J., DETMER, D. E., EDMUNDS, M., EMBI, P. J., GOLDSTEIN, M. M., HAMMOND, W. E., KEENAN, G. M., LABKOFF, S., MURPHY, S., SAFRAN, C., SPEEDIE, S., STRASBERG, H., TEMPLE, F. & WILCOX, A. B. 2014. Health data use, stewardship, and governance: ongoing gaps and challenges: a report from AMIA's 2012 Health Policy Meeting. *J Am Med Inform Assoc,* 21**,** 204-11.

As argued above, good governance at an institutional level is in essence good stewardship. Research using residual HBMs is different from other research activities because of the perpetuity of bio-specimens collected (most HBMs are kept forever by the tissue bank and some are immortalized as cell-lines), the emotional and personal factors associated with residual HBMs donation, and the uncertain future use of HBMs. Every future use of stored HBMs is equivalent to a new participation in a new research and unless a re-consent is given for every future use, it would seem that a one-time consent for collection will not suffice. Even if re-consent is done on each occasion, informed consent and discussion on privacy, ownership and rights do not answer all the ethical and social issues raised by such research without the implementation of proper governance of the HBMs. Governance of tissue banks and use of HBMs should take into consideration patients' concerns, motivations to donate and preferences, and protecting them from possible harm. Implicit to good governance is the need to give effect to the promise of anonymity, secure privacy and confidentiality and ensure that all research use would not lead to any harm to patients. The governance of tissue banks also includes institutional agreements that will meet the expectation of patients. Proper safeguards and controls on the use of HBMs by researchers form the foundation for the development of governance in tissue bank. Sustainable and effective governance of tissue banks is crucial in resolving some of the ethical problems in tissue banking. The principle of 'first do no harm to donors' should be of paramount importance of governance in tissue banks, based on the research ethical relationship between the researcher and the research participant.

As a trustworthy or moral institution, a tissue bank must fulfil its duty to safeguard the interests and rights of altruistic participants and ensure that research will be conducted with

the most efficient methodology benefitting society.[336] The use of HBMs ought to be maximized to avoid wastage and used in research to generate public good. An effective governing authority must best scrutinize resource allocation of HBMs to the qualified researchers to conduct research for public benefits. Optimized utilization of HBMs would uphold the intention and altruistic interests of donors and justify the funding spent on maintenance and operation of tissue banks. Tissue repositories require substantial investments in management and operations and lack of funding will thus affect its sustainability, as demonstrated by the closure of the Singapore Biobank in September 2011.[337]

TABLE 17: PROPOSED 'STEWARDSHIP' OF RESIDUAL HBMS

Proper **Governance** including • Ethical review on research and access requests • Biobanking only by institutions • Statutory regulation and supervision of bio banks	Moral institutions to ensure that clear and transparent processes are in place to ensure that for HBMs are to be applied in ways that maximises public benefit
Oversight committees in protecting and ensuring responsible use of HBMs.	• HBMs governance board or council, HBMs utilisation steering committee and

[336] DESCHENES, M. & SALLEE, C. 2005. Accountability in population biobanking: comparative approaches. *J Law Med Ethics,* 33**,** 40-53.

[337] CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.

• Biobank Governing Board • Biobank Tissues Allocation Committee • Biobank Ethics Committee	scientific advisory board with a view towards ensuring harmonization of its ethics governance with accepted international best practice. • Research ethics committee or an IRB represents different layers of protection and safeguard against potential misuses of collected HBMs.
Transparency and Mediated communication in Biobanking	• Biobanks are required to explain to patients the status of their HBMs to foster trust and enhance participation. • Mediated communication rather than close culture of communication to promote trust.

Accountability to participants and society remains the key principle underlying a moral institution, which oversees its tissue repository and proper conduct of research using HBMs.[338] A moral institution is a trustworthy organization which governs the moral behaviour of a set of individuals within a given community; in this case, tissue bank operators/administrators, researchers and everyone involved in the handling and use of residual HBMs. Institutions that collect HBMs from patients are responsible for the

[338] MCHALE, J. 2011. Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger? *Health Care Analysis,* 19**,** 231-246.

protection of patients and accountable to them for future use of stored HBMs. McHale *et al.* stated that "accountability of tissue banks and researchers should not be simply left to the individual researchers and organisational integrity, nor be dependent upon whether if something went wrong later or an aggrieved research subject decided to litigate" and sued the tissue bank. [339] He further cautioned, "Litigation (from the aggrieved subjects) was long, cumbersome and expensive, and could ultimately destroy a tissue bank through the resultant adverse publicity leading to participants withdrawing en masse." [340] McHale *et al.* concluded that tissue banks had the duty to establish a proper ethics system and governing bodies in order to be responsible and accountable to research subjects. Such governing bodies should be able to execute effective sanctions through good practice guidelines, policies and established laws that provided appropriate regulatory support. Gottweis *et al.* also stated that governance of tissue banks was a response to sociocultural challenges and required the building of trust, acceptance, and careful political and regulatory negotiation.[341] Due to the unique social and ethical challenges associated with implementation and operation of tissue banks, governance has become a complicated architecture and field of action involving a multitude of forces and rationalities.[342] Conception of accountability, usually reinforced with specific requirements for openness or transparency, is broadly management based.[343]

---

[339] *Ibid.* Page 236 Para 4.

[340] *Ibid.* Page 236 Para 4.

[341] GOTTWEIS, H. & ZATLOUKAL, K. 2007. Biobank governance: trends and perspectives. *Pathobiology,* 74**,** 206-11.

[342] *Ibid.*

[343] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.

Institutions that support and govern tissue banks need to establish stewardship and ethics systems to promote intelligent and appropriate governance through accountability, transparency and control. Onora O'Neill is against unintelligent views of accountability, which involves administrative bureaucracy and forms filling that have no meaning or purpose for research participants. To enable accountability to achieve its aims, one must look for intelligent and independent ways of holding professionals and institutions accountable.[344] She proposed the conception that good governance must include intelligent measurable accountability reinforced with specific requirements for openness or transparency.[345] Good governance would therefore include the forms of accountability that best support the relationship of trust allowing people to make intelligent and informed judgments about where to place their trust. O'Neill further stated that accountability depended on informed judgment and those lacking the relevant competence could not judge complex matters adequately. This is the case where research participants have a 'knowledge gap' in tissue banking when compared with the tissue bank researchers. Research participants are not familiar with tissue banking, or its risks and benefits, as shown in my empirical research. Hence, O'Neill suggested that accountability require independent judgment and that good accountability should not rely just on insiders to judge quality of performance. [346] By this analysis, it is not good enough for tissue banks to establish for themselves their own ethical review systems. There are limits to self-governance, and broader systemic safeguards should be introduced. This is consistent with the recommendations of the BAC, especially for the establishment of an independent regulatory

---

[344] *Ibid.*

[345] *Ibid*.

[346] *Ibid*.

authority. However, as we have noted in Chapter 2, this recommendation is yet to be implemented in Singapore.

The integrity of the institutional officials, tissue bank administrators and researchers is an important component of trust. Many practical considerations would follow, and some of these are discussed here. Researchers ought to agree to continue to protect the rights and privacy of patients and respect HBMs as a valuable research resource. Concurrently, a tissue bank has the duty to ensure that stewardship of HBMs is properly assigned and transferred, through material transfer agreements, to researchers. Maintaining a researcher utilization record and database will ensure the ethical use of HBMs through monitoring and reports.[347] Researchers using HBMs for research should be trained to handle HBMs as limited bio-samples and to properly dispose of them with respect after research completion. The risks of breach of confidentiality associated with HBMs research are tied to the confidentiality and sensitivity of requested personal identifiers and medical information. If such medical information were recorded with neither identifiers nor personal data, the sensitivity of information accompanying the HBMs would be less of a concern. But if the medical information collected and supplied with the HBMs were both identifiable and sensitive, then safeguards to protect confidentiality should be carefully considered by tissue banks, researchers and investigators and accompanied with proper ethical review by the IRB and other governing authority. When considering a research hypothesis, the investigator must first assess the importance of associating the participant with his/her medical information and identification. Some research may require continuous linkage with a patient's medical

[347] WHITLEY, E. A., KANELLOPOULOU, N. & KAYE, J. 2012. Consent and research governance in biobanks: evidence from focus groups with medical researchers. *Public Health Genomics,* 15**,** 232-42.

records to fulfil research criteria. For example, a breast cancer researcher may obtain breast cancer tissues from mastectomy, and continue to track the patient annually to carry out blood testing and review if there is either a relapse or slowing of efficiency of chemotherapy. Such a research will then require separate consent for every additional new blood donation and access of new medical information.

Tissue banks should have a thorough and effective policy for researchers to address and manage research incidental findings (IFs) and individual research results (IRRs) of either potential health, reproductive, or personal importance to individual donors.[348] It is commonly the duty of researchers and their affiliated research institutions to manage and decide on IFs and IRRs. However, there are on-going debates about the extent of researchers' responsibilities to inform research participants of IFs and IRRs generated in the course of their research. Research discoveries and information may or may not be diagnostically and analytically valid, since research laboratories are generally not accredited for clinical analysis and thus the IFs and IRRs may not always be clinically conclusive. In addition, releasing clinically un-confirmed research results may cause undue worry to patients. The worst-case scenario will be that the new research findings are not "clinically actionable", meaning that the findings do not allow either the patient or attending physician to prevent or alter the course of condition, or treatment of the condition. For example, the identification of new genetic markers associated with certain cancer types in HBMs will cause undue emotional distress and may be inconclusive for diagnosis. With the lack of regulation on return of IFs

[348] WOLF, S. M., CROCK, B. N., VAN NESS, B., LAWRENZ, F., KAHN, J. P., BESKOW, L. M., CHO, M. K., CHRISTMAN, M. F., GREEN, R. C., HALL, R., ILLES, J., KEANE, M., KNOPPERS, B. M., KOENIG, B. A., KOHANE, I. S., LEROY, B., MASCHKE, K. J., MCGEVERAN, W., OSSORIO, P., PARKER, L. S., PETERSEN, G. M., RICHARDSON, H. S., SCOTT, J. A., TERRY, S. F., WILFOND, B. S. & WOLF, W. A. 2012. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med,* 14**,** 361-84.

and IRRs to donors, the option of consenting to return these findings in the initial informed consent process must be requested and only released to patients who have earlier opted to receive them with the choice of a detailed counselling, on possible clinical implication of the research findings.[349] Some tissue banks may be designed to irretrievably de-link personal data and identifiers at the initial collection stage of HBMs to prevent future re-identification. By fully de-linking all personal data, these actions will conclusively hinder the return of IFs and IRRs to donors. In another design, tissue banks code the HBMs at time of collection and only provided with either de-identified or anonymous HBMs to researchers. A trusted third party (TTP) holds the code used to de-link personal data with HBMs. In such cases, the return of IFs and IRRs can only be done when re-identification of coded HBMs are re-linked back to patients' personal data.

As we have considered earlier on in this Chapter, proper discharge of an institution's stewardship responsibilities include the establishment of an ethics committee, HBMs governance board or council, HBMs utilisation steering committee and scientific advisory board with a view towards ensuring harmonization of its ethics governance with accepted international best practice. Central to good governance of tissue banks, is the requirement that confidentiality of donors is maintained throughout. Many of these measures will require investment in administrative, logistical and financial costs. For example, for the purpose of personal data protection, a moral institution should invest in a trusted third party computerized secure system to hold the link between donors' identities and tissue codes. The third party system will perform the necessary un-coding and re-coding allowing

[349] WOLF, S. M. 2013. Return of individual research results and incidental findings: facing the challenges of translational science. *Annu Rev Genomics Hum Genet,* 14**,** 557-77.

researchers access to de-identified medical information associated with the tissues.[350] Institutions should also allow results from research using HBMs to be disseminated to all participants and, where applicable, to the public, through mediated communication via newsletters and websites, which we will discuss in the next Section. Tissue repositories should communicate actively with their contributors when there is new information that may be of relevance to them, both through their websites and through regular e-bulletins, to promote transparency and accountability.

4.4 Transparency and Mediated Communication in tissue banking

Transparency is one of the crucial factors of a governance framework for tissue bank research, apart from accountability and control. O'Neill stated that accountability must be reinforced with requirements for openness or transparency. [351] Tissue repositories are required to explain to patients the status of their HBMs to foster trust and enhance participation. It is through this trust and continued participation that tissue banks can amass large numbers of HBMs for future research. Timothy Caulfield *et al.* have stated that "given the importance of public trust for the recruitment and continued involvement of much-needed participants, the obtainment and maintenance of public funding, and the implementation of any emerging health-related technologies, even a relatively small loss in

[350] EDER, J., GOTTWEIS, H. & ZATLOUKAL, K. 2012. IT solutions for privacy protection in biobanking. *Public Health Genomics,* 15**,** 254-62.

[351] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.

public trust could have substantial ramifications for the viability and utility of tissue bank initiatives."[352]

In Singapore, tissue banks are funded by public funds and governmental budgets, and are thus accountable to the funding agencies, taxpayers and contributors. Large substantial support from public funding entities has been channelled to set up and maintain these tissue banks, and long-term financial sustainability is one of the major concerns on the future of tissue banking.[353] There is a duty to respond to concerns of HBMs contributors in terms of good governance and accountability to foster continuous trust from patients and HBMs contributors. Onora O'Neill supports the view that trustworthy institutions will have to incorporate user-friendly ways, in which donors can check what is done to their HBMs, and whether they accord both with publicly agreed systems of protection and with the content of consent they have given.[354] Being accountable and transparent is thus a social responsibility of tissue banks.

However, tissue banks in general do not view providing transparency to the public as a priority over closed and restricted communications and discussions with scientific researchers, clinician scientists and surgeons, who have helped to build up and subsequently

---

[352] CAULFIELD, T., BORRY, P. & GOTTWEIS, H. 2014. Industry involvement in publicly funded biobanks. *Nat Rev Genet,* 15**,** 220.

[353] CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.

[354] O'NEILL, O. 2001. Informed Consent and Genetic Information. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 32**,** 689-704.

utilized the stored specimens.[355] The closed culture of communication was also described in Japan by Triendl and Gottweis,[356] who noted that the governance of Biobank Japan Inc. took the form of "governance by stealth". Most tissue banks adopted a closed culture of communications, which took place only amongst established players such as scientists, hospital administrators and clinicians, with no involvement of the public and thus the existing tissue banking framework lacked transparency to the public.

Presently, tissue banks resist engaging in open discussion with HBMs contributors and the public for fear that the communication could attract scrutiny and criticism resulting in the withdrawal of participation.[357] For the same reason, some opinion leaders even recommended that withdrawal of participation from tissue banks should not be allowed once a patient has agreed to donate or abandon tissues.[358] Where NUHTR is concerned, I am of the view that since patients may not have had the full information on the usage and risk of HBMs at point of consent and subsequently reconsidered and decided to change their minds, they should be allowed to withdraw their permission. This is especially relevant in cases when research participants do not agree that their stored residual HBMs can be used for certain types of research that are against their values - like cloning or genetic manipulation, which they would not have supported if they had known earlier. These contributors as research participants should be allowed to withdraw further participation

---

[355] WATANABE, M., INOUE, Y., CHANG, C., HONG, H., KOBAYASHI, I., SUZUKI, S. & MUTO, K. 2011. For what am I participating? The need for communication after receiving consent from biobanking project participants: experience in Japan. *J Hum Genet,* 56**,** 358-63.

[356] Gottweis, Herbert; Petersen, Alan, eds. Biobanks: Governance in Comparative Perspective. Abingdon, Oxon; New York, NY: Routledge, 2008: 123-140

[357] GOTTWEIS, H., CHEN, H. & STARKBAUM, J. 2011a. Biobanks and the phantom public. *Hum Genet,* 130**,** 433-40.

[358] HUG, K., HERMEREN, G. & JOHANSSON, M. 2012. Withdrawal from Biobank Research: Considerations and the Way Forward. *Stem Cell Rev*.

when they have been informed about research that are against deep-seated values or when the trust is broken.

The unused portion of stored HBMs should then be destroyed since it would not be feasible to physically return them to donors and no new research should be carried out. In research ethics documentation as stated in the Helsinki Declaration[359] and Nuremburg Code (principle 9), the research subject Nuremburg [360] should be at liberty to withdraw permission for the research or withdraw consent to participate at any time without reprisal.[361] Since no specific informed consent was given for any specific type of research and only generic consent was taken at the point of collection, patients should be allowed to withdraw permission for continual use of their samples at any time when they feel that their rights and motivations for donation were violated.[362] Thus, the refusal to allow donors to withdraw would create bad publicity for the tissue bank and erode public trust, even when it is legally justifiable to refuse such withdrawal. Further, some tissue banks felt that providing either too much or unnecessary information may cause scepticism and "disturb the water", thus creating greater confusion and suspicion.[363] Iwae reported that in her interview with people involved in Biobank Japan Inc., one interviewee commented that BioBank Japan Project could not have collected 287,929 specimens in 5 years if it had adopted open

---

[359] WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Para 26)

[360] 1996. *The Nuremberg Code (1947)*. BMJ 1996;313:1448

[361] GERTZ, R. 2008. Withdrawing from participating in a biobank--a comparative study. *Eur J Health Law,* 15**,** 381-9.

[362] HELGESSON, G. & JOHNSSON, L. 2005. The right to withdraw consent to research on biobank samples. *Med Health Care Philos,* 8**,** 315-21.

[363] IWAE, S. 2009. Attitude toward Public Trust; the Discourses of Accountability and Transparency in Biobank Japan. *Journal of International Biotechnology Law.*

communication, which would come with additional administrative complications and bureaucracy. This was one of the reasons given in justification of their "closed culture of communication" or "governance by stealth".[364] Some European authors, however, suggested that increased media attention and debate could contribute to greater public knowledge and interest in tissue banks.[365] Gaskell and Gottweis stated, "Controversies don't seem to lead people to reject the idea of tissue bank research *per se*. Instead they facilitate the spread of information, and improve understanding and sharing of views on what is appropriate and acceptable use of samples." They concluded that: "What is needed is a dialogue with the public, to explain the purposes of tissue banks and how they operate, and to give people an opportunity to voice their concerns and conditions for their support and participation."[366] There may be a difference in cultural preference in terms of open communication and determination of sufficient transparency and this requires further investigation.

According to Onora O'Neill, the need for transparency on performance information should not only be made available to stakeholders, government departments and auditors, funding agencies and governing boards, but also to the wider public.[367] Whilst it is important to increase awareness and utilization of the collected specimens to the research community for

---

[364] NISBET, M. C. & FAHY, D. 2013. Bioethics in popular science: evaluating the media impact of The Immortal Life of Henrietta Lacks on the biobank debate. *BMC Med Ethics,* 14**,** 10.

[365] *Ibid.*

[366] GASKELL, G. & GOTTWEIS, H. 2011. Biobanks need publicity. *Nature,* 471**,** 159-60. Page 160 Para 8

[367] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.

the survival of a tissue bank, [368] I am of the view that tissue banks should focus on communicating with the public and patients who have contributed their HBMs. In Singapore, there is neither public debate nor discussion on tissue banking, and Singapore's tissue banks do not provide information to update their HBMs contributors on the use of donated HBMs in research and the types of research involved.

Tissue repositories rely heavily on consent nurses to communicate with patients when requesting permission to collect their residual HBMs. After collection, there is either little or no communication between tissue banks and HBMs contributors, until the next collection of specimen from the same person subsequent to hospital admission. My research data (reported in Chapter 3) showed that most local patients were unaware of the existence, of tissue banks, the objectives of tissue banking, and the related risks (like implications on privacy and confidentiality), until they were approached by a consent nurse. Most participants donated their residual HBMs trusting that future research would generate public good and they were unaware of any risks associated with this donation. The patients' lack of awareness was also observed by Gaskell and Gottweis, who noted that "most Europeans haven't heard of their nation's repositories of human blood and tissue samples." [369] The European Commission reported that there was a low level of knowledge on tissue banks and genetic research in different countries,[370] and that the fact that most

---

[368] CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.

[369] GASKELL, G. & GOTTWEIS, H. 2011. Biobanks need publicity. *Nature,* 471**,** 159-60.

[370] European Commission (2010a) Europeans and biotechnology in 2010. Winds of change? In: Gaskell G, European Union (eds) Eurobarometer. European Commission, Brussels European Commission (2010b) Science and Technology. Special Eurobarometer 340. European Commission, Brussels European Commission (2010c) Public opinion in the European Union. Eurobarometer 72. European Commission, Brussels

people had not heard about tissue banks might make them suspicious of donating. My qualitative research showed that local patients, despite not understanding the nature of tissue banking and risks, 'trusted' the hospital and researchers, and had faith that research would generate future public good. However, this trust should be attributable to experiences so that one can form a judgment on trustworthiness to make a decision. Baroness O'Neill indicated: "To live our lives, we have to make decisions in the absence of full information or guarantees; it is pointless to sulk when the evidence is not perfect."[371] Trust, therefore, is not based on perfect knowledge and understanding of everything, and if we have complete proof or complete control of the variables, our decision will solely be based on facts, and trust will then be redundant.

O'Neill further stated that any "unscrupulous or unacceptable use of human tissue, even by a handful of researchers or doctors, might bring important medical and scientific activities into ill repute, and could lead to public demand for restrictions on less problematic uses of human tissue."[372] Thus, any misuse of human tissues would be considered a betrayal of trust given by the contributors and the general public. It is thus important to keep an active communication channel with HBMs contributors to maintain a balanced perspective of tissue banking and research, as opposed to hearing only bad news through the press when unscrupulous or unacceptable use of human tissue occurs.

---

[371] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76. Page 271 Para 4.

[372] O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7. Page 5 Para 2.

Both my qualitative and quantitative research showed that a huge proportion of patients (more than 70% of the 167329 patients in 10 years) were willing to donate their residual HBMs for research without the requirement of much information. Hence transparency should not be only about providing a lot of information, where the public have neither understanding nor interest in reading. Members of the public may lack the knowledge capacity to comprehend or time to understand "a cornucopia of disclosed documents".[373] Baroness Onora O'Neill supported genuine mediated communication that did not involve complicated scientific and technical terms and the provision of information specifically tailored for the public to understand; without deception, concealment and coercion.[374] The concept of mediated communication came from communication theories referring to communication carried out by the use of information communication technology, in contrast to face-to-face communication.[375] Mediated communication could be employed to maintain relationships with donors to allow transparency to be articulated in this connection. O'Neill further stated that providing more information during a face-to-face informed consent discussion would not necessarily improve accountability to patients and more disclosed information does not necessary fulfil obligations to be 'transparent' when compared to genuine communication.[376] Mediated communication in this case, refers to making information readily available for the patients when they needed it and allowing the donors access to the information at their own convenience, without emotional or physical duress. It engages the use of information communication technology such as websites, social media

---

[373] *Ibid.*

[374] O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.

[375] D. DAVID J. CROWLEY; DAVID MITCHELL. 1994. *Communication Theory Today*. Stanford University Press. p. 35. ISBN 978-0-8047-2347-3. Retrieved 4 June 2013.

[376] *Ibid.*

(e.g. Facebook and blogs), as well as mobile telephones or instant messaging, in place of conventional face-to-face communications.

Information that the tissue bank should make transparent includes future use of the stored residual HBMs, declaration of intellectual property, income generation and royalties, and conflict of interest, which must be transparent to all relevant parties, including research participants. Relevant information can be made available at their website or brochures for public access when required. Failure of transparency, through deception and concealment will be detrimental when the public discover such information via the press or other means.

In this thesis, I have argued for continuous mediated communication, as it is impossible for full information to be available at the point of requesting for permission to collect residual HBMs. To be transparent, communication should go beyond a one-off dissemination of information in a participation information sheet provided only at the point of consent. Mediated communication could act as a means of explaining the objectives of tissue banks and their operations, and providing an opportunity for people to voice their interests, concerns and promote transparency. Information should be made freely available as and when the patients need it and this could be done through the web portal. Transparency through mediated communication will shape the attitudes of potential donors and fosters support and trust in their future participation, together with a moral institution as stewardship for the collection, distribution and use of residual HBMs in Singapore.

Chapter 5. Conclusion

In Chapter 1, I set out the objectives of this thesis and outlined the value of tissue bank research. The thesis presented some definitions of the common terms used in tissue banking and the current consent paradigm used in tissue banking. I have also discussed BAC's guidelines on Human Tissues Research and the need for governance in Singapore.

In Chapter 2, I discussed the problems and inadequacies (even impossibility) of defining precise informational parameters in different informed consent regimes (set out in Chapter 1), and especially that of specific consent. Where residual HBMs are concerned, I have argued that there are clear justifications for the use of general or broad consent rather than specific consent. In fact, I have gone further to distinguish donation from a contribution of tissue through general (or broad) consent, and to argue that the former is to be preferred over the latter. Specific informed consent operates on the assumption that patients will understand and carefully deliberate on the information that is given to them, and then decide if they will participate in the tissue banking project. In consent taking generally, the focus is on keeping patients 'informed'. It is typically assumed that factors like demographics (like gender, religious belief and age), intention and purposes of research participation, and trust and governance, do not matter.

My empirical research reported in Chapter 3 shows that such assumptions are not empirically supported, and at least for patients in Singapore, demographics, preferences and trust do matter. While a long and detailed informational process could in theory be instructive for the potential research participant, this could discourage an altruistic person from contributing HBMs to research, as my empirical findings suggest. A detailed informed consent process does not enhance the trust manifested by HBMs contributors and actually

undermines that trust while showing disrespect for those contributors. Such a process fails to acknowledge the emotional distress that patients are likely to be experiencing before surgery. In many cases, patients interviewed are also likely to lack the sophistication or the interest to persist in understanding a proposed research in all its intricate details. Most patients did not want to know the specific details of the research, nor were they deterred by their failure to fully understand or anticipate the risks that were entailed, even with detailed explanation as part of the informed consent process. These patients knew there were risks that they did not understand fully, and yet are willing to participate in the research. A general understanding of 'use for research' was sufficient, and many donated HBMs to NUHTR based on altruism and trust. A similar outcome has been achieved in the Surgical Consent Form with general or broad consent, where the consent sought is for the contribution of residual HBMs for a broad range of activities, including research. By signing this broad consent form, patients agreed to the future use of their HBMs in medical research, education and study, as decided by NUH as a research institute. Decrease in the reliance on 'full' informed consent and the inability on the part of researchers to ensure full privacy protection for instance would imply a greater need for a more comprehensive and responsive system of tissue bank governance.[377]

In chapter 4, I also argued that good governance requires tissue banks to be more than mere custodians of HBMs. Instead, they must meet standards of accountability as stewards of HBMs that have been provided for the public good. At a minimum level, there must be mechanisms to ensure ethical review of research proposals, fair allocation and optimal use of HBMs, appropriate supervision or control over HBMs that have been provided to

[377] HAWKINS, A. K. & O'DOHERTY, K. 2010. Biobank governance: a lesson in trust. *New Genetics and Society,* 29**,** 311-327.

researchers (e.g. through material transfer agreements), effective safeguards through anonymisation of personal information, and transparency through mediated communication. I have also argued for all HBM contributors to have the right to withdraw participation at any time and without having to provide any reason.

Good governance should enable tissue banks to serve as good stewards, or more generally, as a moral institution. This is implicit in the altruistic nature of the donation of HBMs. In fact, the BAC in Singapore encourages donation of HBMs as an 'outright gift', with no conditions attached. However, a donation is predicated on a level of trust that the gift of HBMs will be applied to advance public good and that the donors will not suffer any harm as a consequence of making this gift. For trust to subsist, I agree with Onora O'Neill that it should not be necessary for the tissue bank to specify all possible applications of the gift. However, the tissue bank should demonstrate that it is trustworthy. A sound governance system should be directed at promoting and sustaining trust among donors and trustworthiness on the part of the tissue bank, by ensuring accountable and responsible handling and use of HBMs.[378] Annette Baier sets out that trust is the attempts by the more powerful entity to equalise differences in power through a variety of means, including being accountable for the use of discretionary power[379]. According to the result of my research, contributors of HBMs are often ignorant of the value of their contributions, as well as the risks entailed. In order to be trustworthy, tissue repositories and biobanks should ensure equalisation of power that arise from this asymmetric information and knowledge gaps. In

[378] BAIER, A. C. 1994. The possibility of sustaining trust. Norms, Values, and Society, 2, 245-259.

[379] ANNETTE C. BAIER. 1991. Trust, Tanner Lecture of page 67: http://tannerlectures.utah.edu/_documents/a-to-z/b/baier92.pdf

addition, they should demonstrate accountability for the discretion they have been entrusted with through broad consent that the contributors provided.

As the BAC has recommended, there are good reasons to include these values on trust through legislation, and to establish an independent body to oversee all tissue banks and tissue repositories in Singapore. Ultimately, tissue banking is an enterprise of trust. This is the ethical conclusion of this thesis, and is consistent with public perception and expectation, as the empirical evidence shows.

Tissue repository and tissue banks are controversial due to the ethical, legal, and social implications (ESLI) surrounding utilization of HBMs and related data.[380] These issues include: (i) Informed consent (e.g. how to inform participants about using banked samples for future research that has not yet been conceived), (ii) Confidentiality (e.g. increased risk of breaches owing to mandates of tissue banks to provide access to researchers and store samples and data for long periods of time), (iii) Secondary use of samples and data over time, (iv) Return of research results to donors, and (v) Data and Benefit sharing.

This thesis presented empirical data on public attitudes, values, concerns, and interests underlying the donation of residual HBMs to tissue banks. Policy makers, tissue bank operators and researchers who acknowledge the importance of public opinions will better able to maintain the trust of existing and new donors. This acknowledgement is of utmost importance to ensure the success and continuity of tissue banks. We have identified various themes underlying expressed objectives, preferences and concerns of patients regarding the

[380] HAGA, S. B. & BESKOW, L. M. 2008. Ethical, Legal, and Social Implications of Biobanks for Genetics Research. *In:* RAO, D. C. & GU, C. C. (eds.) *Advances in Genetics.* Academic Press.

collection, storage and use of tissues in tissue bank research. ESLI and associated challenges in tissue banking have been discussed extensively by lawyers and ethicists together with the scientific community. The use of expert opinions must be coupled with and supported by public engagement and opinion polls to gain public trust and support. Public opinion should matter in the sense that a tissue bank should be accountable and public transparency should be fostered. In addition, as a moral institution, the decisions and actions of a tissue repository should be able to withstand ethical scrutiny.

In the attempt to address these issues in tissue banks, we should take public perception and trust of tissue banks into consideration. Public opinions and perceptions of tissue banks are important and if they either do not trust the biobank, or are doubtful or suspicious of tissue banks and their governance structures, biobank collection and research may be significantly hindered. Understanding and considering public viewpoints and positions are thus a necessary component in ensuring public trust and support of biobank and its related research.[381] The current research shows that most donors of tissue banks contributed for altruistic reasons with good intentions despite lack of understanding of the risk and harm that donation poses. Even highly educated donors do not comprehend the privacy risk of their donation but yet are willing to contribute in good faith and for public good. Participants had donated based on trust in doctors, institutions and out of gratitude for their treatment. The trust given to institutions, tissue banks and researchers implied that they were given stewardship of HBMs and related data. Thus tissue banks and researchers must shoulder the duty to reduce risk to donors and protect them from harm. An effective biobank governance system could hence provide the needed safeguards and controls if

[381] HANSSON, M. G. 2005. Building on relationships of trust in biobank research. *J Med Ethics,* 31**,** 415-8.

executed with accountability and adequate transparency. Further, governance and control of tissue banks must be sustainable and practicable in biobank operations.

I have explained the value of public preferences, perceptions and expectations, which support my argument for relying on general (or broad) consent, and even outright donation, in obtaining HBMs for tissue banking and research purposes. My systematic literature review and empirical findings highlight that there is no clear consensus on the best ethical approach to consent taking. Furthermore, I have explained why other forms of consent taking are inadequate, inappropriate or ineffective. However, my argument for general consent or donation will be ethically effective and consistent with public expectations and requirements only when there is good governance to support tissue banks to act as stewards (and not as mere custodians) of retained HBMs. I have set out a number of requirements for good governance, which included accountability, responsible use, safeguards, transparency and mediated communication. Most importantly, I support the right to withdrawal of participation from the biobank and argue that failure to allow withdrawal will result in a betrayal of trust.

To conclude, I support the use of general (or broad) consent regime or for donation as 'outright gifts'. The same lexicon on 'donation' has also been proposed by the BAC, with recommendations to strengthen the governance and regulatory system in relation to tissue collections and uses. As discussed in Chapter 1 and 2, the BAC proposed legislation for management and use of legacy tissue and establishment of a regulatory body to oversee the collection, management and use of HBMs. The need for good governance was a reason that BAC considered research institutions, rather than individual researchers, to be appropriate custodians of HBMs.

My empirical findings in Chapter 3 are supportive of the BAC's recommendations to strengthen the governance framework, most likely through legislation. My findings give important content to the BAC's principle of 'respect for persons' and on the types of consent to be used to fulfil this principle; whether through general consent or as a donation and; whether they should take into account their preferences, social and economic status (i.e. demographics), gender, intentions and values. The proposed regulatory framework requires tissue banks to take these into account. However, broader public discussion on what should be taken into account should then be the subject of public discussion.

My empirical findings further support Onora O'Neill's argument that informed consent should be relied on as a means of promoting accountability and trust, rather than an end in itself or mere permission. In addition, donated residual HBMs should be taken to be like public goods as donors are often expected to give altruistically. I have argued in Chapter 4 for research institutions and tissue banks to be responsible, not as mere custodians, but as stewards of these public goods. I am also supportive of the Nuffield Council's view that stewardship will require a biobank to do all that is necessary to promote public health and to safeguard the well-being of donors. I understand that my position differs from the BAC in requiring tissue banks to be stewards, rather than just mere custodians, although my final proposal may not ultimately be so different from the BAC's, as the BAC may have meant stewardship, when it used the term 'custodian'.

For a system of governance that promotes trust, I have argued that tissue banks should respect the right of a contributor and allow donors' withdrawal from participation at any time. The biobank should be transparent and have continuous communication channels with the donors. This could be provided as a form of 'mediated' communications, so that the trust has some basis and continuously maintained. It is also a means of ensuring accountability

and to allow donors to appreciate the research use of their residual HBMs. Other forms of mechanisms to reinforce include HBMs research ethics and allocation committees; propose use of material transfer agreements, as well as mechanisms to ensure confidentiality and privacy safeguards (anonymisation and trusted third party) are in place.

I propose an ethical governance system that will protect the residual HBMs, respect the expectations and provide safeguards for the concerns of patients who have donated their residual HBMs. This supports my proposal on the use of broad consent, outright donation of residual HBMs for research (but with a continuing right to withdraw from participation at any time) and constituting the tissue repository and its moral institution as steward of residual HBMs. A moral institution's stewardship responsibilities will include the establishment of an ethics committee, HBMs governance board or council, HBMs utilisation steering committee and scientific advisory board with a view towards ensuring harmonization of its ethics governance with accepted international best practice. Central to good governance of tissue banks is the requirement that confidentiality of donors is maintained throughout.

Prologue

In order for my proposal of an effective biobank governance system to be implemented, additional manpower, effort and resources must be available to the research institutions and the tissue banks. This additional effort will involve a paradigm change in the current tissue banking culture and practices. Tissue banking is an expensive investment for research institutions, where funds are channelled to specific research projects rather than to building a central collection and core storage facility. Most research institutions are reluctant to bear the additional cost although they understand the need to encourage patients to continue donating their residual HBMs for research. The BAC's recommendations on statutory regulations on governance are still not implemented. My research supports the BAC's recommendation to strengthen the governance regime for tissue repositories and tissue banks through legislation, although my research at this stage does not provide guidance on how much effort and resources should be committed to developing tissue banks as moral institutions (or good stewards of public goods). In the absence of a regulatory framework, my proposals would also be limited in execution.

Implications for research

Another limitation of my thesis relates to the empirical aspect of my study, and I would like to suggest ways of addressing these limitations in future research. My quantitative research on the NUH Surgical Consent Form shows significant differences in consent rate, depending on demographics, religions, ethnics, etc. More in-depth research can be conducted using focus groups in relation to each one of these demographic factors to better understand these differences. In the qualitative research, we could only recruit patients who had donated their residual HBMs to NUH TR. Those patients who refused donating also refused

to participate in our qualitative research. We could only document their reasons informally. Future research may explore this group of patients to understand their concerns and preferences.

Implications for Practice

My paper on "Patients' consent and donation of their residual biological samples: A systematic review", published by International Journal of Evidence-Based Healthcare, was accepted by The Joanna Briggs Institute as "Best Practice: evidence-based information sheets for health professional". The Joanna Briggs Institute (JBI) Library is a repository for publications and information for policy makers, health professionals, health scientists and others with a practical or academic interest in evidence based healthcare. This evidence is collated and the results are appraised, synthesised and transferred to service delivery settings and health professionals who utilise it and evaluate its impact on health outcomes, health systems and professional practice.

Bibliography

1995. Nuffield Council on Bioethics. Human tissue: ethical and legal issues. London: Nuffield Council on Bioethics.

1996. *The Nuremberg Code (1947)*.

2003. Greenberg v. Miami Children's Hospital Research Institute. *Wests Fed Suppl,* 264**,** 1064-78.

2009. Common consent. *Nature,* 460**,** 933-933.

2010. After Havasupai litigation, Native Americans wary of genetic research. *Am J Med Genet A,* 152A**,** fmix.

ABOU-ZEID, A., SILVERMAN, H., SHEHATA, M., SHAMS, M., ELSHABRAWY, M., HIFNAWY, T., RAHMAN, S. A., GALAL, B., SLEEM, H., MIKHAIL, N. & MOHARRAM, N. 2010. Collection, storage and use of blood samples for future research: views of Egyptian patients expressed in a cross-sectional survey. *J Med Ethics*.

AL-BUSAIDI, Z. Q. 2008. Qualitative Research and its Uses in Health Care. *Sultan Qaboos University Medical Journal,* 8**,** 11-19.

ALLEN, J. & MCNAMARA, B. 2011. Reconsidering the value of consent in biobank research. *Bioethics,* 25**,** 155-66.

ALLEN, M. J., POWERS, M. L. E., GRONOWSKI, K. S. & GRONOWSKI, A. M. 2010. Human Tissue Ownership and Use in Research: What Laboratorians and Researchers Should Know. *Clin Chem,* 56**,** 1675-1682.

ANDERLIK, M. R. & ROTHSTEIN, M. A. 2003. Canavan decision favors researchers over families. *J Law Med Ethics,* 31**,** 450-4.

ASAI, A., OHNISHI, M., NISHIGAKI, E., SEKIMOTO, M., FUKUHARA, S. & FUKUI, T. 2002. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. *BMC Med Ethics,* 3**,** E1.

ASHBURN, T. T., WILSON, S. K. & EISENSTEIN, B. I. 2000. Human tissue research in the genomic era of medicine: balancing individual and societal interests. *Arch Intern Med,* 160**,** 3377-84.

AURAY-BLAIS, C. & PATENAUDE, J. 2006. A biobank management model applicable to biomedical research. *BMC Med Ethics,* 7**,** E4.

BAC, S. 2002. Human Tissue Research: A report by Bioethics Advisory Committee Singapore. November 2002.

BAIER, A. 1986. Trust and Antitrust. *Ethics,* 96**,** 231-260.

BAIER, A. C. 1994. The possibility of sustaining trust. *Norms, Values, and Society,* 2**,** 245-259.

BALKO, J. M., COOK, R. S., VAUGHT, D. B., KUBA, M. G., MILLER, T. W., BHOLA, N. E., SANDERS, M. E., GRANJA-INGRAM, N. M., SMITH, J. J., MESZOELY, I. M., SALTER, J., DOWSETT, M., STEMKE-HALE, K., GONZALEZ-ANGULO, A. M., MILLS, G. B., PINTO, J. A., GOMEZ, H. L. & ARTEAGA, C. L. 2012. Profiling of residual breast cancers after neoadjuvant chemotherapy identifies DUSP4 deficiency as a mechanism of drug resistance. *Nat Med,* 18**,** 1052-9.

BARNES, L., MATTHEWS, F. E., BARBER, B., DAVIES, L., LLOYD, D., BRAYNE, C. & PARRY, B. 2005. Brain donation for research: consent and re-consent post Alder Hey. *Bull Med Ethics***,** 17-21.

BEAUCHAMP, T. L. 2011. Informed consent: its history, meaning, and present challenges. *Camb Q Healthc Ethics,* 20**,** 515-23.

BERGMAN, H. R. 1992. Case comment: Moore v. Regents of the University of California. *Am J Law Med,* 18**,** 127-45.

BERUBE, K. A. 2013. Medical waste tissues - breathing life back into respiratory research. *Altern Lab Anim,* 41**,** 429-34.
BIAGI, K. G. 1991. Moore v. Regents of the University of California: patients, property rights, and public policy. *St Louis Univ Law J,* 35**,** 433-62.
BROCHHAUSEN, C., ROSSRICKER, N. & KIRKPATRICK, C. J. 2007. Biological waste, ownership and personality - future perspectives for the secondary use of human tissue in the view of national and international regulations. *Pathology Research and Practice,* 203**,** 404-404.
BROTHERS, K. B., MORRISON, D. R. & CLAYTON, E. W. 2011. Two large-scale surveys on community attitudes toward an opt-out biobank. *Am J Med Genet A,* 155A**,** 2982-90.
BRYANT, R. J., HARRISON, R. F., START, R. D., CHETWOOD, A. S. A., CHESSHIRE, A. M., REED, M. W. R. & CROSS, S. S. 2008. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *Journal of Clinical Pathology,* 61**,** 322-326.
BUDIMIR, D., POLASEK, O., MARUSIC, A., KOLCIC, I., ZEMUNIK, T., BORASKA, V., JERONCIC, A., BOBAN, M., CAMPBELL, H. & RUDAN, I. 2011a. Ethical aspects of human biobanks: a systematic review. *Croat Med J,* 52**,** 262-79.
BUDIMIR, D., POLASEK, O., MARUSIC, A., KOLCIC, I., ZEMUNIK, T., BORASKA, V., JERONCIC, A., BOBAN, M., CAMPBELL, H. & RUDAN, I. 2011b. Ethical aspects of human biobanks: a systematic review. *Croat Med J,* 52**,** 262 - 279.
CAENAZZO, L., TOZZO, P. & PEGORARO, R. 2013. Biobanking research on oncological residual material: a framework between the rights of the individual and the interest of society. *BMC Medical Ethics,* 14**,** 17.
CAMBON-THOMSEN, A., RIAL-SEBBAG, E. & KNOPPERS, B. M. 2007. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J,* 30**,** 373-82.
CAMPBELL, C. S. 1998. Religion and the body in medical research. *Kennedy Inst Ethics J,* 8**,** 275-305.
CAULFIELD, T., BORRY, P. & GOTTWEIS, H. 2014. Industry involvement in publicly funded biobanks. *Nat Rev Genet,* 15**,** 220.
CHAN, T. 2012. The Closure of the National Bio-bank in Singapore. *Asia-Pacific Biotech News Journal.,* 16**,** 40-43.
CHAN, T., MACKEY, S. & HEGNEY, D. 2012. Patients' experiences on donation of their residual biological samples and the impact of these experiences on the type of consent given for the future research use of the tissue: a systematic review. *Int J Evid Based Healthc,* 10**,** 9 - 26.
COHEN, B. 1990. The ethics of using medical data from Nazi experiments. *J Halacha Contemporary Society,* No. 19**,** 103-26.
CRESWELL, J. W. 2003. *Research design : qualitative, quantitative, and mixed method approaches,* Thousand Oaks, Calif., Sage Publications.
CRESWELL, J. W. 2009. Editorial: Mapping the Field of Mixed Methods Research. *Journal of Mixed Methods Research,* 3**,** 95-108.
CRESWELL, J. W. & CRESWELL, J. W. 2007. *Qualitative inquiry & research design : choosing among five approaches,* Thousand Oaks, Sage Publications.
CRESWELL, J. W. & PLANO CLARK, V. L. 2007. *Designing and conducting mixed methods research,* Thousand Oaks, Calif., SAGE Publications.
CRESWELL, J. W. & ZHANG, W. 2009. The application of mixed methods designs to trauma research. *J Trauma Stress,* 22**,** 612-21.
CURTIS, H. 2004. Getting ethics into practice: Tuskegee was bad enough. *BMJ,* 329**,** 513; author reply 513.
DESCHENES, M. & SALLEE, C. 2005. Accountability in population biobanking: comparative approaches. *J Law Med Ethics,* 33**,** 40-53.

DIXON-WOODS, M., ASHCROFT, R. E., JACKSON, C. J., TOBIN, M. D., KIVITS, J., BURTON, P. R. & SAMANI, N. J. 2007. Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. *Social Science & Medicine,* 65**,** 2212-2222.

DIXON-WOODS, M., CAVERS, D., JACKSON, C. J., YOUNG, B., FORSTER, J., HENEY, D. & PRITCHARD-JONES, K. 2008. Tissue samples as 'gifts' for research: A qualitative study of families and professionals. *Medical Law International,* 9**,** 131-150.

DONALDSON, L. & DAVIS, J. H. 1991. Stewardship Theory or Agency Theory: CEO Governance and Shareholder Returns. *Australian Journal of Management,* 16**,** 49-64.

EDER, J., GOTTWEIS, H. & ZATLOUKAL, K. 2012. IT solutions for privacy protection in biobanking. *Public Health Genomics,* 15**,** 254-62.

ENGLISH, V. & SOMMERVILLE, A. 2003. Presumed consent for transplantation: a dead issue after Alder Hey? *J Med Ethics,* 29**,** 147-52.

FADEN, R. R. & BEAUCHAMP, T. L. 1980. Decision-making and informed consent: a study of the impact of disclosed information. *Soc Indic Res,* 7**,** 313-36.

FELT, U., BISTER, M. D., STRASSNIG, M. & WAGNER, U. 2009. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health,* 13**,** 87-106.

FISHER, R. A. 2010. Statistical methods in genetics. 1951. *Int J Epidemiol,* 39**,** 329-35.

FITZGIBBONS, P. L. 2011. Are there barriers to the release of paraffin blocks for clinical research trials? A College of American Pathologists survey of 609 laboratories. *Arch Pathol Lab Med,* 135**,** 870-3.

FORSBERG, J. S., ERIKSSON, S. & HANSSON, M. G. 2010. Changing defaults in biobank research could save lives too. *Eur J Epidemiol,* 25**,** 65-8.

GARRISON, N. A. & CHO, M. K. 2013. Awareness and Acceptable Practices: IRB and Researcher Reflections on the Havasupai Lawsuit. *AJOB Prim Res,* 4**,** 55-63.

GASKELL, G. & GOTTWEIS, H. 2011. Biobanks need publicity. *Nature,* 471**,** 159-60.

GEFENAS, E., DRANSEIKA, V., SEREPKAITE, J., CEKANAUSKAITE, A., CAENAZZO, L., GORDIJN, B., PEGORARO, R. & YUKO, E. 2012. Turning residual human biological materials into research collections: playing with consent. *J Med Ethics,* 38**,** 351-5.

GERTZ, R. 2008. Withdrawing from participating in a biobank--a comparative study. *Eur J Health Law,* 15**,** 381-9.

GIESBERTZ, N. A., BREDENOORD, A. L. & VAN DELDEN, J. J. 2012. Inclusion of residual tissue in biobanks: opt-in or opt-out? *PLoS Biol,* 10**,** e1001373.

GLANTZ, L. H., ROCHE, P. & ANNAS, G. J. 2010. Gift giving to biobanks. *Am J Bioeth,* 10**,** 33-4.

GODARD, B., SCHMIDTKE, J., CASSIMAN, J. J. & AYME, S. 2003. Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. *Eur J Hum Genet,* 11 Suppl 2**,** S88-122.

GOODSON, M. L. & VERNON, B. G. 2004. A study of public opinion on the use of tissue samples from living subjects for clinical research. *J Clin Pathol,* 57**,** 135-8.

GOTTWEIS, H., CHEN, H. & STARKBAUM, J. 2011a. Biobanks and the phantom public. *Hum Genet,* 130**,** 433-40.

GOTTWEIS, H., CHEN, H. & STARKBAUM, J. 2011b. Biobanks and the phantom public. *Human Genetics,* 130**,** 433-440.

GOTTWEIS, H., GASKELL, G. & STARKBAUM, J. 2011c. Connecting the public with biobank research: reciprocity matters. *Nat Rev Genet,* 12**,** 738-9.

GOTTWEIS, H. & ZATLOUKAL, K. 2007. Biobank governance: trends and perspectives. *Pathobiology,* 74**,** 206-11.

GRUBB, A. 1995. The Nuffield Council report on human tissue. *Med Law Rev,* 3**,** 235-6.

GYMREK, M., MCGUIRE, A. L., GOLAN, D., HALPERIN, E. & ERLICH, Y. 2013. Identifying Personal Genomes by Surname Inference. *Science,* 339**,** 321-324.
HADDOW, G., LAURIE, G., CUNNINGHAM-BURLEY, S. & HUNTER, K. G. 2007. Tackling community concerns about commercialisation and genetic research: a modest interdisciplinary proposal. *Soc Sci Med,* 64**,** 272-82.
HAGA, S. B. & BESKOW, L. M. 2008. Ethical, Legal, and Social Implications of Biobanks for Genetics Research. *In:* RAO, D. C. & GU, C. C. (eds.) *Advances in Genetics.* Academic Press.
HAMILTON, S., HEPPER, J., HANBY, A. & HEWISON, J. 2007. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics,* 33**,** 229-33.
HANSSON, M. G. 2005. Building on relationships of trust in biobank research. *J Med Ethics,* 31**,** 415-8.
HANSSON, M. G., DILLNER, J., BARTRAM, C. R., CARLSON, J. A. & HELGESSON, G. 2006. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol,* 7**,** 266-9.
HAWKINS, A. K. 2010. Biobanks: importance, implications and opportunities for genetic counselors. *J Genet Couns,* 19**,** 423-9.
HAWKINS, A. K. & O'DOHERTY, K. 2010. Biobank governance: a lesson in trust. *New Genetics and Society,* 29**,** 311-327.
HELFT, P. R., CHAMPION, V. L., ECKLES, R., JOHNSON, C. S. & MESLIN, E. M. 2007. Cancer patients' attitudes toward future research uses of stored human biological materials. *J Empir Res Hum Res Ethics,* 2**,** 15-22.
HELGESSON, G. & JOHNSSON, L. 2005. The right to withdraw consent to research on biobank samples. *Med Health Care Philos,* 8**,** 315-21.
HENS, K. & DIERICKX, K. 2010. Human tissue samples for research. A focus group study in adults and teenagers in Flanders. *Genet Couns,* 21**,** 157-68.
HENS, K., NYS, H., CASSIMAN, J. J. & DIERICKX, K. 2011. Risks, benefits, solidarity: a framework for the participation of children in genetic biobank research. *J Pediatr,* 158**,** 842-8.
HEWITT, R., WATSON, P. H., DHIR, R., AAMODT, R., THOMAS, G., MERCOLA, D., GRIZZLE, W. E. & MORENTE, M. M. 2009. Timing of consent for the research use of surgically removed tissue: is postoperative consenting acceptable? *Cancer,* 115**,** 4-9.
HEWITT, R. E. 2011. Biobanking: the foundation of personalized medicine. *Current Opinion in Oncology,* 23**,** 112-119 10.1097/CCO.0b013e32834161b8.
HOEYER, K. 2008. The ethics of research biobanking: a critical review of the literature. *Biotechnol Genet Eng Rev,* 25**,** 429-52.
HOEYER, K., OLOFSSON, B. O., MJORNDAL, T. & LYNOE, N. 2004. Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scand J Public Health,* 32**,** 224-9.
HOEYER, K., OLOFSSON, B. O., MJORNDAL, T. & LYNOE, N. 2005. The ethics of research using biobanks: reason to question the importance attributed to informed consent. *Arch Intern Med,* 165**,** 97-100.
HOFMANN, B. 2009. Broadening consent--and diluting ethics? *J Med Ethics,* 35**,** 125-9.
HRIPCSAK, G., BLOOMROSEN, M., FLATELYBRENNAN, P., CHUTE, C. G., CIMINO, J., DETMER, D. E., EDMUNDS, M., EMBI, P. J., GOLDSTEIN, M. M., HAMMOND, W. E., KEENAN, G. M., LABKOFF, S., MURPHY, S., SAFRAN, C., SPEEDIE, S., STRASBERG, H., TEMPLE, F. & WILCOX, A. B. 2014. Health data use, stewardship, and governance: ongoing gaps and challenges: a report from AMIA's 2012 Health Policy Meeting. *J Am Med Inform Assoc,* 21**,** 204-11.

HUG, K., HERMEREN, G. & JOHANSSON, M. 2012. Withdrawal from Biobank Research: Considerations and the Way Forward. *Stem Cell Rev*.
IVANKOVA, N. V., CRESWELL, J. W. & STICK, S. L. 2006. Using Mixed-Methods Sequential Explanatory Design: From Theory to Practice. *Field Methods,* 18**,** 3-20.
IWAE, S. 2009. Attitude toward Public Trust; the Discourses of Accountability and Transparency in Biobank Japan. *Journal of International Biotechnology Law.*
JANSEN, L. A. 2009. The ethics of altruism in clinical research. *Hastings Cent Rep,* 39**,** 26-36.
JEFFERS, B. R. 2001. Human biological materials in research: ethical issues and the role of stewardship in minimizing research risks. *ANS Adv Nurs Sci,* 24**,** 32-46.
JENKINS, M. M., REED-GROSS, E., RASMUSSEN, S. A., BARFIELD, W. D., PRUE, C. E., GALLAGHER, M. L. & HONEIN, M. A. 2009. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A,* 149A**,** 2378-86.
KAPHINGST, K. A., JANOFF, J. M., HARRIS, L. N. & EMMONS, K. M. 2006. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet,* 69**,** 393-8.
KORT, E. J., CAMPBELL, B. & RESAU, J. H. 2003. A human tissue and data resource: an overview of opportunities, challenges, and development of a provider/researcher partnership model. *Comput Methods Programs Biomed,* 70**,** 137-50.
LEVITT, M. & WELDON, S. 2005. A well placed trust?: public perceptions of the governance of DNA databases. *Critical Public Health,* 15**,** 311-321.
LEWIS, M. H., GOLDENBERG, A., ANDERSON, R., ROTHWELL, E. & BOTKIN, J. 2011. State laws regarding the retention and use of residual newborn screening blood samples. *Pediatrics,* 127**,** 703-12.
LIND, U., MOSE, T. & KNUDSEN, L. E. 2007. Participation in environmental health research by placenta donation - a perception study. *Environmental Health,* 6**,** -.
MALIN, B. & SWEENEY, L. 2004. How (not) to protect genomic data privacy in a distributed network: using trail re-identification to evaluate and design anonymity protection systems. *Journal of Biomedical Informatics,* 37**,** 179-192.
MASON, M. 2010. *Sample Size and Saturation in PhD Studies Using Qualitative Interviews*.
MASTER, Z., NELSON, E., MURDOCH, B. & CAULFIELD, T. 2012. Biobanks, consent and claims of consensus. *Nat Methods,* 9**,** 885-8.
MASTER, Z. & RESNIK, D. B. 2013. Incorporating exclusion clauses into informed consent for biobanking. *Camb Q Healthc Ethics,* 22**,** 203-12.
MAVROFOROU, A., GIANNOUKAS, A. & MICHALODIMITRAKIS, E. 2006. Consent for organ and tissue retention in British law in the light of the Human Tissue Act 2004. *Med Law,* 25**,** 427-34.
MCGUIRE, A. L. & BESKOW, L. M. 2010. Informed consent in genomics and genetic research. *Annu Rev Genomics Hum Genet,* 11**,** 361-81.
MCHALE, J. 2011. Accountability, Governance and Biobanks: The Ethics and Governance Committee as Guardian or as Toothless Tiger? *Health Care Analysis,* 19**,** 231-246.
MELLO, M. M. & WOLF, L. E. 2010. The Havasupai Indian tribe case--lessons for research involving stored biologic samples. *N Engl J Med,* 363**,** 204-7.
MERZ, J. F., LEONARD, D. G. & MILLER, E. R. 1999. IRB review and consent in human tissue research. *Science,* 283**,** 1647-8.
MERZ, J. F., SANKAR, P., TAUBE, S. E. & LIVOLSI, V. 1997. Use of human tissues in research: clarifying clinician and researcher roles and information flows. *J Investig Med,* 45**,** 252-7.
MESLIN, E. M. & QUAID, K. A. 2004. Ethical issues in the collection, storage, and research use of human biological materials. *J Lab Clin Med,* 144**,** 229-34; discussion 226.

MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010a. Cancer as Rubbish: Donation of Tumor Tissue for Research. *Qual Health Res*.
MORRELL, B., LIPWORTH, W., AXLER, R., KERRIDGE, I. & LITTLE, M. 2010b. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res,* 21**,** 75 - 84.
MOUTEL, G., DE MONTGOLFIER, S., DUCHANGE, N., SHARARA, L., BEAUMONT, C. & HERVE, C. 2004. Study of the involvement of research ethics committees in the constitution and use of biobanks in France. *Pharmacogenetics,* 14**,** 195-8.
MURPHY, J., SCOTT, J., KAUFMAN, D., GELLER, G., LEROY, L. & HUDSON, K. 2009. Public perspectives on informed consent for biobanking. *American Journal of Public Health,* 99**,** 2128-2134.
NISBET, M. C. & FAHY, D. 2013. Bioethics in popular science: evaluating the media impact of The Immortal Life of Henrietta Lacks on the biobank debate. *BMC Med Ethics,* 14**,** 10.
O'NEILL, O. 1996. Medical and scientific uses of human tissue. *J Med Ethics,* 22**,** 5-7.
O'NEILL, O. 2001. Informed Consent and Genetic Information. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences,* 32**,** 689-704.
O'NEILL, O. 2003. Some limits of informed consent. *J Med Ethics,* 29**,** 4-7.
O'NEILL, O. 2004. Accountability, trust and informed consent in medical practice and research. *Clin Med,* 4**,** 269-76.
OECD 2009. The Organisation for Economic Co-operation and Development: Guidelines on Human Biobanks and Genetic Research Databases.
OOSTERHUIS, J. W., COEBERGH, J. W. & VAN VEEN, E. B. 2003. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer,* 3**,** 73-7.
PARK, A. 2009. 10 Ideas Changing the World Right Now. *Time*.
PARKINSON, D., DRACOPOLI, N., PETTY, B., COMPTON, C., CRISTOFANILLI, M., DEISSEROTH, A., HAYES, D., KAPKE, G., KUMAR, P., LEE, J., LIU, M., MCCORMACK, R., MIKULSKI, S., NAGAHARA, L., PANTEL, K., PEARSON-WHITE, S., PUNNOOSE, E., ROADCAP, L., SCHADE, A., SCHER, H., SIGMAN, C. & KELLOFF, G. 2012. Considerations in the development of circulating tumor cell technology for clinical use. *Journal of Translational Medicine,* 10**,** 138.
PFEFFER, N. 2008. What British women say matters to them about donating an aborted fetus to stem cell research: A focus group study. *Social Science & Medicine,* 66**,** 2544-2554.
PORTER, R. C. 2002. *The Economics of Waste*, Resources for the Future.
POST, S. G. 1991. The echo of Nuremberg: Nazi data and ethics. *J Med Ethics,* 17**,** 42-4.
PULLEY, J., CLAYTON, E., BERNARD, G. R., RODEN, D. M. & MASYS, D. R. 2010. Principles of human subjects protections applied in an opt-out, de-identified biobank. *Clin Transl Sci,* 3**,** 42-8.
RIEGMAN, P. H. & VAN VEEN, E. B. 2011. Biobanking residual tissues. *Hum Genet,* 130**,** 357-68.
RISCH, N. J. 2000. Searching for genetic determinants in the new millennium. *Nature,* 405**,** 847-56.
ROBERTSON, J. A. 1995. Ethical and legal issues in human embryo donation. *Fertil Steril,* 64**,** 885-94.
ROSENBAUM, S. 2010. Data governance and stewardship: designing data stewardship entities and advancing data access. *Health Serv Res,* 45**,** 1442-55.
ROTHSTEIN, M. A. 2002. The role of IRBs in research involving commercial biobanks. *J Law Med Ethics,* 30**,** 105-8.
ROTHWELL, E., ANDERSON, R. & BOTKIN, J. 2010. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. *Policy, Politics, & Nursing Practice,* 11**,** 5-12.

ROY, B. 1995. The Tuskegee syphilis experiment: medical ethics, constitutionalism, and property in the body. *Harv J Minor Public Health,* 1**,** 11-5.
SCHMIDT, C. 2006. Tissue banks trigger worry about ownership issues. *Journal of the National Cancer Institute,* 98**,** 1174-1175.
SECKO, D. M., PRETO, N., NIEMEYER, S. & BURGESS, M. M. 2009. Informed consent in biobank research: a deliberative approach to the debate. *Soc Sci Med,* 68**,** 781-9.
SHANKS, N., GREEK, R. & GREEK, J. 2009. Are animal models predictive for humans? *Philosophy, Ethics, and Humanities in Medicine,* 4**,** 2.
SHEEHAN, M. 2011. Can Broad Consent be Informed Consent? *Public Health Ethics,* 4**,** 226-235.
SHICKLE, D. 2006. The consent problem within DNA biobanks. *Stud Hist Philos Biol Biomed Sci,* 37**,** 503-19.
SKOLBEKKEN, J.-A., URSIN, L. Ø., SOLBERG, B., CHRISTENSEN, E. & YTTERHUS, B. 2005. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Critical Public Health,* 15**,** 335-347.
SQUE, M., LONG, T., PAYNE, S., ROCHE, W. R. & SPECK, P. 2008. The UK postmortem organ retention crisis: a qualitative study of its impact on parents. *J R Soc Med,* 101**,** 71-7.
STEIN, R. 2009. Newborns' Blood Samples Are Used for Research Without Parents' Consent. *Washington Post*
STEINSBEKK, K. S., KARE MYSKJA, B. & SOLBERG, B. 2013. Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem? *Eur J Hum Genet*.
STJERNSCHANTZ FORSBERG, J., HANSSON, M. G. & ERIKSSON, S. 2011. Biobank research: who benefits from individual consent? *BMJ,* 343**,** d5647.
TASHAKKORI, A. & TEDDLIE, C. 2003. *Handbook of mixed methods in social & behavioral research,* Thousand Oaks, Calif., SAGE Publications.
TUPASELA, A. 2011. From gift to waste: changing policies in biobanking practices. *Science and Public Policy,* 38**,** 510-520.
TUTTON, R., KAYE, J. & HOEYER, K. 2004. Governing UK Biobank: the importance of ensuring public trust. *Trends Biotechnol,* 22**,** 284-5.
VAN DIEST, P. J. 2002. No consent should be needed for using leftover body material for scientific purposes. For. *BMJ: British Medical Journal,* 325**,** 648-651.
VAN VEEN, E. B., RIEGMAN, P. H., DINJENS, W. N., LAM, K. H., OOMEN, M. H., SPATZ, A., MAGER, R., RATCLIFFE, C., KNOX, K., KERR, D., VAN DAMME, B., VAN DE VIJVER, M., VAN BOVEN, H., MORENTE, M. M., ALONSO, S., KERJASCHKI, D., PAMMER, J., LOPEZ-GUERRERO, J. A., LLOMBART BOSCH, A., CARBONE, A., GLOGHINI, A., TEODOROVIC, I., ISABELLE, M., PASSIOUKOV, A., LEJEUNE, S., THERASSE, P. & OOSTERHUIS, J. W. 2006. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer,* 42**,** 2914-23.
VERHEIJDE, J. L., RADY, M. Y. & MCGREGOR, J. 2009. Presumed consent for organ preservation in uncontrolled donation after cardiac death in the United States: a public policy with serious consequences. *Philos Ethics Humanit Med,* 4**,** 15.
VERMEULEN, E., SCHMIDT, M. K., AARONSON, N. K., KUENEN, M., VAN DER VALK, P., SIETSES, C., VAN DEN TOL, P. & VAN LEEUWEN, F. E. 2009. Opt-out plus, the patients' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. *J Clin Pathol,* 62**,** 275-8.
VOIDONIKOLAS, G., GINGRAS, M. C., HODGES, S., MCGUIRE, A. L., CHEN, C., GIBBS, R. A., BRUNICARDI, F. C. & FISHER, W. E. 2009. Developing a tissue resource to characterize the genome of pancreatic cancer. *World J Surg,* 33**,** 723-31.

WATANABE, M., INOUE, Y., CHANG, C., HONG, H., KOBAYASHI, I., SUZUKI, S. & MUTO, K. 2011. For what am I participating? The need for communication after receiving consent from biobanking project participants: experience in Japan. *J Hum Genet,* 56**,** 358-63.

WAUGH, P. J. 2004. Getting ethics into practice: comparing Alder Hey with Tuskegee is not helpful. *BMJ,* 329**,** 513; author reply 513.

WEATHERALL, D. J. 2003. Genomics and global health: time for a reappraisal. *Science,* 302**,** 597-9.

WENDLER, D. 2013. Broad versus Blanket Consent for Research with Human Biological Samples. *Hastings Center Report,* 43**,** 3-4.

WHITLEY, E. A., KANELLOPOULOU, N. & KAYE, J. 2012. Consent and research governance in biobanks: evidence from focus groups with medical researchers. *Public Health Genomics,* 15**,** 232-42.

WILLIAMS, G. & SCHROEDER, D. 2004. Human genetic banking: altruism, benefit and consent. *New Genet Soc,* 23**,** 89-103.

WILLIAMS, P. H., SCHEPP, K., MCGRATH, B. & MITCHELL, P. 2010. The stewardship model: current viability for genetic biobank practice development. *ANS Adv Nurs Sci,* 33**,** E41-9.

WOLF, S. M. 2013. Return of individual research results and incidental findings: facing the challenges of translational science. *Annu Rev Genomics Hum Genet,* 14**,** 557-77.

WOLF, S. M., CROCK, B. N., VAN NESS, B., LAWRENZ, F., KAHN, J. P., BESKOW, L. M., CHO, M. K., CHRISTMAN, M. F., GREEN, R. C., HALL, R., ILLES, J., KEANE, M., KNOPPERS, B. M., KOENIG, B. A., KOHANE, I. S., LEROY, B., MASCHKE, K. J., MCGEVERAN, W., OSSORIO, P., PARKER, L. S., PETERSEN, G. M., RICHARDSON, H. S., SCOTT, J. A., TERRY, S. F., WILFOND, B. S. & WOLF, W. A. 2012. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med,* 14**,** 361-84.

WOLFF, C., SCHOTT, C., MALINOWSKY, K., BERG, D. & BECKER, K.-F. 2011. Producing Reverse Phase Protein Microarrays from Formalin-Fixed Tissues. *In:* KORF, U. (ed.) *Protein Microarrays.* Humana Press.

WONG, M. L., CHIA, K. S., WEE, S., CHIA, S. E., LEE, J., KOH, W. P., SHEN, H. M., THUMBOO, J. & SOFJAN, D. 2004a. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet,* 7**,** 44-54.

WONG, M. L., CHIA, K. S., YAM, W. M., TEODORO, G. R. & LAU, K. W. 2004b. Willingness to donate blood samples for genetic research: a survey from a community in Singapore. *Clinical Genetics,* 65**,** 45-51.

YASSIN, R., LOCKHART, N., GONZÁLEZ DEL RIEGO, M., PITT, K., THOMAS, J. W., WEISS, L. & COMPTON, C. 2010. Custodianship as an Ethical Framework for Biospecimen-Based Research. *Cancer Epidemiology Biomarkers & Prevention,* 19**,** 1012-1015.

ZATLOUKAL, K. & HAINAUT, P. 2010. Human tissue biobanks as instruments for drug discovery and development: impact on personalized medicine. *Biomark Med,* 4**,** 895-903.

LIST OF APPENDICES

CONSENT FOR OPERATION / PROCEDURE BY PATIENT

(For competent patients above 21 years of age or patients below 21 years who are assessed to have capacity to provide valid consent)

PART I – To be Filled by Patient

1. I, _____ (NRIC/Passport No. _____),
   (Name of patient)

   hereby consent to undergo the operation / procedure of _____
   (State nature of operation / procedure)

   _____ the nature, effect and purpose, as well as benefits of the above proposed

   operation / procedure and risks involved have been explained to me by Dr/Mr _____
   (Name of medical practitioner)

   I confirm that the potential risks of not carrying out the procedure, and alternative modalities have been discussed with me.

2. I also consent to:
   (a) The administration of sedation, general, local or other forms of anaesthesia for this operation / procedure. The potential risks involved are illustrated overleaf.
   (b) The use of drugs and medicines as may be deemed advisable or necessary for the said operation / procedure.
   (c) Such further or alternative operative measures or procedures as may be found to be necessary during the course of the operation / procedure.
   (d) The transfusion of blood, blood components and other blood derived products as may be deemed necessary.
   (e) The taking of photographs / videographs for education /academic / research purposes, where my identity will not be revealed, if used.

3. I acknowledge that no assurance has been given to me that the operation / procedure will be performed by any particular medical practitioner. (*to delete if not applicable*)

4. ***Note: This clause is only applicable if tissue is to be removed.*** *Please tick here if it is not applicable* ☐ Not applicable

   I understand that in the course of the operation / procedure, tissues (which includes skin, bones, organs, blood and other body fluids) may be removed as part of the surgical procedure, and the remainder which otherwise be discarded, may prove valuable for medical research, education and study purposes.

   I ***agree / *do not agree** to allow the remainder of any tissue removed not required for my medical management, to be used for medical research, education and study purposes. I understand that only excess tissue that remains after all the necessary medical tests are completed will be used, and no extra tissue will be taken for these purposes.

5. I acknowledge that the following have been explained to me –
   (a) The potential risks involved with the administration of anaesthesia and sedation as illustrated overleaf, but not limited to the list.
   (b) The potential risks involved with blood transfusion as illustrated overleaf, but not limited to the list.
   (c) No guarantee has been made to me about the outcome of the blood transfusion.
   (d) The alternatives to the use of community blood supply which include pre-donation of my own blood (autologous blood donation).
   (e) The consequences of refusing to accept transfusion of blood or blood components, that include seriously jeopardizing my health or resulting in death.

_____ _____
(Signature of patient) *(Date)*

PART II – To be Filled by Medical Practitioner

I, _____ confirm that I have explained to the patient the
(Name of medical practitioner)

nature, effect and purpose, as well as benefits of the proposed operation / procedure and risks involved.

_____ _____ _____
(Signature of medical practitioner) *(Proceduralist's discipline)* *(Date)*

**Delete accordingly*

PART III – To be Filled by Interpreter (if applicable)

By Interpreter

* I, _____ confirm that I have explained to the patient the nature, effect and
(Name of Interpreter)

purpose, as well as benefits of the operation / procedure and risks involved, in _____
(Language / Dialect)

_____ _____
(Signature of Interpreter) *(Date)*

By Patient

* I, _____ the abovenamed patient, confirm that the nature, effect and
(Name of patient)

purpose, as well as benefits of the proposed operation / procedure and risks involved were explained to me by

Dr / Mr / Ms _____ in _____.
(Name of Interpreter) *(Language / Dialect)*

_____ _____
(Signature of patient) *(Date)*

Risks of Anaesthesia and Sedation

Note: There may be other risks (depending on your medical condition and type of surgery) that have not been listed here. Please ask your DOCTOR IN CHARGE OF SEDATION OR ANAESTHETIST if you have any general or specific concerns.	
Anaesthesia (including Deep Sedation)	**Moderate Sedation**
Common (1:10 to 1:100) Giddiness, nausea and/or vomiting, sore throat and hoarse voice, physical trauma including eye abrasions, damage to teeth or dental work, lips or tongue, pain and inflammation of injection site, headache, muscle ache and/or backache, postural headache related to a spinal or epidural injection	**Common (1:10 to 1:100)** Hypotension i.e. low blood pressure
Uncommon (1:1000 to 1:10 000) Respiratory depression, which may require ventilatory support, chest infection, awareness despite anaesthesia, serious allergy to drugs	**Uncommon (1:1000 to 1:10 000)** Allergic reactions, inflammation of veins (phlebitis), respiratory depression
Rare (1:10 000 to 1: 100 000) Permanent damage to the eyes (which may result in blindness), persistent nerve damage, resulting in transient / permanent numbness or weakness, cardiorespiratory arrest and death, equipment failure and related consequences	**Rare (1:10 000 to 1: 100 000)** Cardiorespiratory arrest and death

Risks of Various Potential Complication of Transfusion

Common Skin reactions and rashes (1-2%), Fever (0.5-1%)
Uncommon Bacterial contamination (platelet transfusion) (0.01-0.1%)
Rare Mistransfusion (0.008%), viral transmission (Hepatitis B, C, HIV) (0.0001-0.001%), ABO related acute hemolytic reaction (0.0002%), bacterial contamination (TBC transfusion) (0.0001%)

Consent to Donate Clinical Samples for Research to the NUH Tissue Repository

The National University Hospital (NUH) Tissue Repository request your kind consideration to donate clinical samples, blood and leftover tissues removed during your surgery for use in research. These leftover tissues, if not donated, will be discarded. If you consent, the blood would be drawn additionally and exclusively for this donation.

A detailed information pamphlet has been given and the nature of the donation explained to you. Your medical treatment will NOT be affected in any way by your decision.

You will be given a copy of this signed consent form.

I acknowledge that I have been given the Patient Information Pamphlet and the nature of this donation has been explained to me in the _____ language/ dialect* that I understand. I have had the opportunity to ask questions and have received satisfactory answers and information.

I voluntarily consent to donate my clinical samples for future research: (Please tick (√) as appropriate)

(i)	My left over tissue and blood* (both)	Yes ☐	No ☐
(ii)	My left over tissue (only)	Yes ☐	No ☐
(iii)	My blood* (only)	Yes ☐	No ☐

(**I consent to a maximum amount of 30 ml of blood to be drawn based on the Duty Anaesthetist's evaluation of my clinical condition and I consent to it being drawn during my surgery.)* Yes ☐ No ☐

(iv) Other clinical samples (viz, hair, nails, effusions, urine, faeces, saliva, left over blood), if applicable {Refer to para 2 of Patient Information Pamphlet) Yes ☐ No ☐

(a)	Hair	Yes ☐	No ☐
(b)	Nails	Yes ☐	No ☐
(c)	Effusions	Yes ☐	No ☐
(d)	Urine	Yes ☐	No ☐
(e)	Faeces	Yes ☐	No ☐
(f)	Saliva	Yes ☐	No ☐
(g)	Left over blood[@]	Yes ☐	No ☐

([@]left over from my routine blood examination in Dept of Lab Medicine)

Please continue only if patient has ticked any of the **'Yes'** box.

I also give permission for information in my medical records to be used for research. I understand that this information will not bear my name or other identifiers and that due care will be taken to preserve the confidentiality of this information.

I understand and acknowledge that the donated clinical samples as well as any substance or material derived from it, or modified versions of it, may be used for purposes relating to research and development, medical education, teaching, publications, diagnosis and possibly the treatment of medical conditions on a commercial basis or otherwise. I also understand that my samples and medical data will only be made available for future research studies, if those studies have first been approved by an Institutional Review Board to make sure they are ethical and scientifically sound.

I agree that, as a voluntary donor, neither I nor my estate will receive any benefits, commercial or otherwise, from the use of my clinical samples or any substance or material derived from them, or modified versions thereof.

My signature / thumbprint* below indicates my consent to the donation of clinical samples on the understanding indicated above.

	Name	Signature	Date
Patient			
Parent / Legal Guardian*, if appropriate[(1)]			
Witness / Translators*			
Consenting Nurse/ Staff			

**** Delete whichever is not applicable.***

[(1)] Signature of the parent or legal guardian is *required* if patient is under 21 years old or is incapable of understanding the nature of the donation as judged by the consenting nurse/staff.

For any further assistance/ queries regarding this donation, you may contact : Administrator, NUH Tissue Repository at tel 6772 2310

For an independent opinion regarding the research and the rights of research participants, you may contact a staff member of the National University of Singapore Institutional Review Board (Attn: Mr Chan Tuck Wai, at telephone 6516 1234 or email at irb@nus.edu.sg).

Donating Clinical Samples for Research Through
The NUH Tissue Repository

Patient Information Pamphlet

This pamphlet provides information on the use of clinical samples in research and development and what it means to be a donor of tissue and other patient samples.

Where do left-over clinical samples (tissues and other patient samples) come from?
During your surgery, some tissues may be removed from your body to help in the diagnosis and/or treatment of your condition. This tissue may be solid, semi-fluid (eg. bone marrow) or fluid (eg. blood left over from routine tests). Any such tissue removed from your body will always be used first and foremost to determine your medical condition, and how you can best be treated. Sometimes, not all the tissue removed from you is needed to diagnose and/or treat your condition. Leftover tissues, that are normally discarded or destroyed, are often useful material for research. Other clinical samples which may be useful for research include body fluids (eg. effusions), secretions (eg. saliva), excretions (eg. urine, faeces), hair, toenails, fingernails etc. Choosing to donate any such samples WILL NOT require removal of any extra tissue or change the care you will receive in any way.

How would blood for research be collected from cancer patients?
Blood, another important material for biomedical research, can be obtained from patients undergoing cancer surgery. If you consent to donating blood, a maximum amount of 30 ml of blood may be drawn. The amount of blood drawn would be decided by the Anaesthetist drawing blood, depending on your age, sex and your clinical condition but would not exceed 30 ml, at any cost. This amount of blood is quickly replenished by human body. This blood would be drawn during your surgical procedure by a qualified Anaesthetist in operating theatre. The blood would be drawn when venous line is being inserted for inducing anaesthesia during the surgical process and you would not have to undergo any additional pricks for donating blood. Drawing of this blood would not entail any additional health risk to you, apart from those associated with your surgery and have already been explained to you by your consulting surgeon.

Why should I donate clinical samples?
Researchers at the National University Hospital (NUH) and National University of Singapore (NUS) or other institutions are trying to learn more about diseases. Clinical samples provide the materials for researchers to study different diseases. Your samples will be used together with samples from many other donors, in research studies related to your condition or to other conditions. Some of the research findings may help doctors and scientists develop new products, such as drugs and diagnostic tests leading to better prevention and treatment of diseases.

Who can donate clinical samples?
Anyone undergoing treatment at the NUH can donate patient samples. You will be asked to consider donation only if it can be done without affecting your health.

What will happen if I agree to donate clinical samples?
Left-over clinical samples will be transferred to the NUH Tissue Repository where they will be processed and stored until they are needed for a study.

Who gets to use the donated clinical samples?
Researchers at the NUH, NUS and other Singapore institutes and organizations must apply for formal approval from the NUH Tissue Repository to use clinical samples for research. Your samples will only be made available for future research studies, if those studies have been approved by an Institutional Review Board to make sure they are ethical and scientifically sound. They will ask for a certain number of samples from a particular group of people (for example, for research study on diabetes, researchers may ask for research samples from men over age 65 who were diagnosed with diabetes). Samples that meet such requirements will be provided to the researchers. Researchers will not be able to ask for tissue samples from a specific person.

Do commercial companies have access to my clinical samples?
In addition to not-for-profit institutions, your donated clinical samples may also be provided to commercial organizations for their research and development purposes. It is also possible that your donated tissues might be used for commercial development, in ethically approved projects by the collecting agency. The approval process takes into consideration the expected future benefits of the proposed tissue usage, whether these be scientific, medical, or economic benefits, to Singapore as a whole. The process and criteria for approving requests from commercial companies will be at least as careful as for not-for-profit research.

Will I find out results of the research?
Neither you nor your doctor will receive the results of research done with your donated clinical samples. This is because research can take a long time and requires samples from many people before results are known. Results from research using your samples may not be ready for many years and will probably not affect your care right now.

Are there any risks to me from donating?
There is no additional risk to you during your operative procedure. As the study results will not be entered into your medical records, your health insurance will not be affected in any way.

Will researchers have access to my medical records?
Certain information that forms part of your medical record may be required for interpreting research results. Some examples include your age, gender, past health history, details of your present illness and family history of illnesses. Such information will be stored in tissue repository databases, and only approved researchers will be allowed access to the information. Your medical data will only be made available for future research studies, if those studies have been approved by an Institutional Review Board to make sure they are ethical and scientifically sound. Rigorous measures have been introduced to protect your privacy and none of your personal identifiers (like your name, address and NRIC number) will be stored with the information or made available to the researchers.

How will my privacy be protected?
To ensure that your samples and medical information cannot be linked to you, the samples and medical information received by the tissue repository will not contain your identifiable personal data. Instead, these will be replaced by code numbers. It will only be possible to retrace the link between the personal data and the codes by a decoding step. This decoding only takes place under special circumstances and approval needs to be given by an official ethics committee or institutional review board that oversees the ethical aspects of the research.

Does the donation cost me anything?
There will be no cost to you if you agree to donate your clinical samples for research.

Will I benefit from research done on my clinical samples?
Your donation of clinical samples is regarded as wholly voluntary and is treated as an outright gift. There will be no medical or personal benefit to you arising from the donation of your tissue or from the results of the research conducted using such samples. You will not have access to the results of the research conducted on your tissue. The results of research may be beneficial to future patients.

Can I change my mind if I do not want to donate my tissue after I have signed or donated?
Yes. You can notify the hospital and it will terminate your donation process or contact the repository to destroy any unused clinical samples that you have already donated.

What happens next?
Once you have read this pamphlet, you will have an opportunity to speak with your doctor or nurse before/after your operative procedure to make sure that all your questions are answered. Your signature on a Consent Form is required if you agree to donate your clinical samples. The choice of whether or not to donate is up to you. Refusal to participate or withdrawal from participation will not affect your medical management or cause loss of benefits to which you are otherwise entitled. Whatever you choose to do, your medical care will not be affected.

Can I contact anyone if I have further questions?
You may call the NUH Tissue Repository (6772-2310) and ask for the Repository Administrator who will be able to assist you with further questions.

For an independent opinion regarding research and the rights of research participants, you may contact a staff member of the National University of Singapore Institutional Review Board (Attn: Mr Chan Tuck Wai, at tel 6516 1234 or email at irb@nus.edu.sg).

Thank you for your kind consideration.

International Journal of
Evidence-Based Healthcare
The Joanna Briggs Institute

doi:10.1111/j.1744-1609.2011.00251.x Int J Evid Based Healthc 2012; **10:** 9–26

EVIDENCE SYNTHESIS

Patients' experiences on donation of their residual biological samples and the impact of these experiences on the type of consent given for the future research use of the tissue: a systematic review

Tuck Wai Chan BSc(Pharmacy) MBA,[1] Sandra Mackey RN BN(Hons) PhD[2] and Desley Gail Hegney RN BA(Hons) DNE PhD[3]

[1]Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore and [2]Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; and [3]School of Population Health and Sir Charles Gairdner Hospital, The University of Western Australia, Perth, Western Australia, Australia

Abstract

Aim This review aimed to critically appraise, synthesise and present the best available evidence related to the experiences of patients who have donated their residual biological samples and the impact of this experience on the type of consent given for future research use of these tissues.

Method The three-step search strategy aimed to find both published and unpublished studies published in English between 1990 and 2010 in electronic databases (PubMed, CINAHL, Scopus, Embase, PsycINFO, Mednar, PROQUEST).

Using the standardised data extraction tool from the Joanna Briggs Institute, the Qualitative Assessment and Review Instrument, 131 findings were extracted from the 18 papers included in this review. These findings generated 19 categories and four synthesised findings.

Results The synthesised findings generated were related to the different stages of the handling of leftover tissue. The first synthesised finding: patient consent to the use of leftover tissue is a complex interaction between many factors and not solely driven by perceptions of benefits to self or others, relates to the collection of the leftover tissue – the initial consent process. The second synthesised finding: healthcare institutions and regulatory authorities must provide clear and transparent safeguards and controls, and communicate these to the patient prior to the consenting process, outlines the issues affecting consent during the processing and storage of the tissues in biobanks or research institutions. The third synthesised finding: views on ownership and rights to the further use of the leftover tissue varies between individual patients and influences their willingness to consent to further use, demonstrates the concerns relating to the safeguards on the collection and storage of leftover tissue. The fourth synthesised finding: patients have opposing views on the use of their leftover tissue for commercial purposes, reflecting the differing community beliefs around using leftover tissue for research which may provide a commercial benefit to some, but not all, the community.

Conclusion For leftover tissues to be used, patients must clearly understand: the type of consent they are providing (opt in or opt out); the parameters for the future research use of their leftover tissues; the safeguards put into place to protect the individual and the donated tissue from unethical use; and the commercial implications of their consent.

Implications for practice This review provides information on patient's experiences on the collection, storage, distribution and future use of leftover tissue. These preferences need to be understood when designing a prospective model of consent regimen which respects patient's confidentiality and wishes. The information in this review is especially important for policy-makers designing a prospective model of consent regimen for the use of existing and previously collected biological samples with no consent taken.

Implications for research Further research is needed to ascertain what factors specifically influence patient's willingness to consent for the use of leftover tissue. Factors for further exploration include the effects of culture,

Correspondence: Mr Tuck Wai CHAN, Clinical Research Centre, National University of Singapore, Block MD 11, #03-02, 10 Medical Drive, Singapore 117597. Email: dprctw@nus.edu.sg

religion and age. Additionally, further research is required to inform the development of specific consent regimes for the use of leftover tissue for commercial, stem cell and genetic research.

Key words: ethics, leftover tissues, patient informed consent, residual tissues, tissue bank.

Background

During a patient's surgery, some biological samples may be removed from the body to aid in the diagnosis and/or treatment of their medical condition. In a majority of these cases, not all the tissues removed are needed for the primary use of clinical diagnosis and treatment of the condition. These leftover human biological materials, which are normally discarded or destroyed, are useful samples for secondary uses such as biomedical research, education and training.[1,2]

Current international statutory laws recognise the autonomy of a patient's decision over their body including leftover or residual biological samples.[3] Furthermore, it is agreed that a patient's informed consent should be obtained for the secondary use of these leftover or residual biological samples for research.[4] However, many countries do not have a standard procedure for obtaining a patient's consent for donating leftover biological samples.[5] Additionally, the international regulatory regimes for research using residual tissue differ widely between countries.[6,7] Even where regulations exist, consent regimens may range from highly project-specific consent to 'opt-out' presumed consent or even no consent at all.[8] For example, the Dutch Medical Treatment Act allows anonymous tissue samples obtained during medical treatment to be used for medical research if the patient has not previously objected. The United Kingdom Human Tissue Act, however, requires the need to obtain prior informed consent for the removal, storage and use of tissues for scheduled purposes.[6] Many countries in Asia, including Singapore, do not have any regulation on this issue.[9]

Current established informed consent regimens[8,10] include the following:

- Specific consent (where tissues requested are only used for that specific project)
- Tiered consent (patients are presented with a menu of options in their consent documents from which they can choose the future use of tissue, time of storage, types of research and whether the tissue can be commercialised)
- Open or blanket consent (a general consent for all future use of tissues)
- Presumed consent or implicit consent (an implied consent requiring patients to opt out if they do not wish to donate their tissues)

There is ongoing discussion about which consent regimens stated above will best comply with the patient's preference.[11] Some authors argue that presumed consent with opt-out is sufficient,[1,11,12] while others claim that 'one-time general' consent for all future research will suffice.[4,13] Additionally, some authors believe that a specific consent must be requested from patients for any future use of each and every sample as it provides more control over its use.[14,15] The implications for this latter model are that it can restrict research,[16] and will not be practicable in actual clinical practice, because of the additional resources such a consent requires.[17] Others claim that specific informed consent cannot be obtained on the type of future research as patients cannot be truly informed,[13] because science advances with time and the type of tissue research may also vary. Hence, it is impossible for a patient to give informed consent for future use, which may or may not eventuate. For example, 20 years ago, no scientist would mention the use of tissues for genetic sequencing and cloning nor were they able to predict the future use of such tissues due to the advancement in science.

For the purpose of this review, the following definitions were used.

Specific consent[10,15,18]

Specific consent is also known as Project Specific Consent, where patients are asked to consent to donate for one specific research project and are re-contacted for each new use of their specimens that is out of the scope of their original consent.

Tiered consent[8,9]

Tiered consent is also known as broad consent (as compared to specific consent), where patients agree to a menu of options, which may include general or specific consent for future use, whether related or non-related disease, time period, commercial uses, genetic conditions and so on.

Open consent[4,19]

Open consent is also known as one-time general consent, generic or blanket consent, where patients consent to an unlimited range of options such as the types of future research and time period/s. Patients are given the explicit choice to opt out during the initial consent process or to withdraw anytime after they have consented.

Presumed consent[1,11]

Presumed consent is also known as opt-out or implicit consent, where patients are informed that their specimens will be used for future research unless they deny permission by opting out.

Human biological samples[3,9]

Human biological samples refer to all kinds of human tissues derived from living or cadaveric patients, including solid body tissue, organs, fetuses, blood and other body fluids and

their derivatives, cord blood, embryos, gametes (sperm or eggs) or any part or derivatives including DNA and cells.

Tissues research[3,20]
The types of research requiring the used tissues include drug or clinical trials, cancer research, genetic research, general knowledge of the body tissue, testing medicine and genetic cloning.

Aim

The aim of this review was to critically appraise, synthesise and present the best available evidence related to the experiences of patients who have donated their residual biological samples and the impact of this experience on the type of consent given for the future research use of these tissues.

Search strategy

The search strategy employed in this review was to identify both published and unpublished studies published between 1990 and 2010 in the English language. These years were chosen as informed consent for leftover tissues was not reported earlier than 1990. The databases searched were PubMed (MEDLINE), CINAHL, SCOPUS, EMBASE, PsycINFO, Mednar and PROQUEST. The keywords used were: 'tissue+', 'tissues', 'biological material', 'DNA', 'blood', 'bone', 'consent', 'opt-in', 'opt-out', 'presumed consent', 'informed consent', 'research', 'biomedical research', 'qualitative research', 'empirical research', 'biological Samples', 'biological material', 'specimen', presumed', 'samples', 'tissue banking' and 'tissue bank'.

The Joanna Briggs Institute's three-step search strategy was utilised. An initial limited search of MEDLINE and CINAHL was undertaken to identify previous systematic reviews in this area, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases. Third, the reference lists of all identified reports and articles were searched for additional studies. The titles and abstracts of all papers identified were reviewed independently by two of the reviewers against the inclusion criteria. When the titles and abstracts were inconclusive, the full papers were retrieved and reviewed. Articles that met the inclusion criteria were then reviewed independently by two reviewers.

Inclusion criteria

This systematic review considered qualitative publications and the qualitative mixed-method publications that included patients, regardless of age or sex, who were involved in the donation of their residual biological samples for research. Specific inclusion criteria were: (i) all types of tissues (namely cancer tissues, reproductive tissues, adult stem cells, cord blood, gamete, eggs and sperm donation, embryo and fetal tissue) that were donated or not donated and were residual/leftover tissues after surgery, removed as part of a treatment of an illness or were collected for a medical diagnosis; (ii) tissue collected for research, education and teaching; and (iii) tissues stored or used in biological specimen banks, tissue banks and biobanking.

Exclusion criteria

As this review only focused on leftover tissues to be stored for future research use, it excluded research focusing on organ transplant and tissues collection for therapeutic purposes.

Review method

This systematic review was carried out between September 2010 and March 2011 using the guidelines provided by the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information.

The review considered all published and unpublished qualitative studies. It did not include opinion pieces or the grey literature. Studies that focused on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research and feminist research, and the qualitative data from mixed method studies were considered. This review was not limited by any geographical or cultural settings.

Qualitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardised critical appraisal instruments from the Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI). Any disagreements that arose between the reviewers were resolved through discussion, or with the assistance of the third reviewer. As there were 10 criteria for assessment in JBI-QARI, a cut-off point of 6/10 was set for inclusion of the studies in this review.

Qualitative research findings from each included paper were pooled using the JBI-QARI. This involved the extraction of findings, followed by an aggregation or synthesis of findings on the basis of similarity in meaning (categories). These categories were then subjected to a meta-synthesis to produce a comprehensive set of synthesised findings (Level 3 findings), which may be used as the basis for evidence-based practice.

Study characteristics

The review of initial potential papers (from abstracts and titles and reference lists of retrieved papers) resulted in a total of 153 papers. One hundred thirty-one papers were then excluded following a review of the abstract, or full text if an abstract was not available, against the inclusion criteria. The twenty-two remaining papers were then assessed with four papers excluded for the following reasons: (i) one of the studies recruited their participants from organ transplants, which was one of the exclusion criteria for this research[21]; and (ii) either the two studies had not discussed the

themes[22] or the themes were not confirmed by the presented data in the paper.[23] One of these latter papers used the computer program NVivo computer program for analysis[23] and did not include any actual textual data from the participants; thus, the findings were not able to be confirmed. The fourth study was not research, as it was a report of a public consultation conducted by the researchers.[24] A total of 18 papers were included in the review.

Methodological quality

A description of the included studies is provided in Table 1.

In summary, the 18 papers comprised 10 studies[25,29,31,32,34,37–40,42] that used focus group methods to collect the different views and attitudes of patients who had donated or were considering donating leftover clinical tissues for research; five studies[26–28,30,35,36] that conducted semi-structured in-depth interviews with individual patients or potential donors; two studies[33,41] which used both focus groups and semi-structured interviews; and one study which used interviews and observational techniques[35] for collecting their research data. Among the 18 papers in this review, eight papers scored 8/10, seven scored 7/10 and three scored 6/10.

Congruity between research objectives, methods used to collect data, representation, analysis and interpretation of data were high in these 18 studies. However, based on JBI-QARI evaluation methods for qualitative research analysis, all of the authors failed to clearly describe the methodology and paradigm used in their research. All authors, rather than describing the research paradigm and methodology, commenced their manuscript with an explanation of the data collection methods (focus groups, open-ended questions, semi-structured questions). This limitation was apparent in both 'qualitative' and the 'qualitative component of mixed methods' papers included in this review. Thus, it was not possible to assess the methodological quality of the papers for paradigm and methodology, based on the JBI-QARI criteria, as the reviewers were unable to assess the congruity (or otherwise) between the stated philosophical perspectives and the research methodology and the research objectives. Nevertheless, studies that demonstrated congruity between the research method, research questions, objectives, data collection and analysis were included.

These 18 studies covered the collection of a variety of different types of human biological samples and tissues from the patients. These included blood,[40,42] DNA,[27,29,32,34] cancer tissue samples,[26,36] aborted fetus,[38] residual newborn dried blood,[39] skin tissues,[28] placental tissues,[35] breast cancer and normal tissues,[30,33] post-mortem organs and tissues,[41] non-specific adults' human biological samples for biobanking,[25,37] and biological samples from children (non specific).[31] Ethnic groups included in these 18 studies included Chinese, Malays, Indians,[42] Japanese,[25] Non-Hispanics Afro and Afro Americans,[32] Caucasians, English and Irish.[26] The age groups of the study participants ranged from teenagers (15 to 19 years old)[31] to the elderly (65–69 years old).[41]

Results

The findings in the 18 studies were examined using the three JBI levels of credibility (unequivocal [E], Credible [C] or Unsupported [U]) (see Appendix I). The findings which did not have any textual data to support them were considered to be unsupported and were therefore excluded from the study. The remaining 131 credible and unequivocal findings were then clustered into 19 categories and further grouped into four synthesised findings.

Synthesised finding 1: Patient consent to the use of leftover tissue is a complex interaction between many factors and not solely driven by perceptions of benefits of self or others

More than half of the findings from the review, that is, 69 out of 131 findings explained the different reasons why patients were willing to donate their leftover tissues for research (Synthesised finding 1) (Table 2). This theme was the dominant theme in the analysis and is, therefore, an important consideration for researchers and policy-makers as all 18 selected studies included some findings to support the varied reasons that patients would consider when donating their biological samples for research.

The most common category of this group of findings was 'benefits to self'.[23,25,27–30,33,36,39] In this category, some patients donated tissues because they believed that there was a direct or indirect benefit to themselves. For example, they may have a medical condition for which further research may be of direct benefit, either presently or in the future. This group of patients would thus expect the outcomes, conclusion and results of the research (whether accidental findings of a specific individual's tissue or an important finding on the medical condition) to be communicated back to the participants[25] in the future.

Trust in research, the medical researchers, the research organisation and the governance of the donated tissues was the next dominant category.[25–27,30,33–36,38,40] Patients claimed to have trust in the public good paradigm of research for societal progress,[35] and believed that researchers were generating public good in the diagnosis and treatment of medical conditions. Patients trusted the professionals, who gained their consent to use the tissue samples for research.[26] They also trusted that their tissues would not be misused.[40] Patients exhibited confidence in the research process[27] and the meaningfulness of the research[35] to generate new knowledge. Overall, trust is an important factor in the decision on whether they will donate their leftover tissues.

A similar category is that of 'Benefits to others', where participants believed that their donated tissues would benefit society.[23,25–28,32,33,36,38,40] This category demonstrated the altruistic and utilitarian characteristics of society where patients decided to donate their tissues out of their own kindness or gratitude. By donating their tissues to research, some patients believed that they were contributing to the development of medical science, contributing to the public good and promoting public interest in the future.[25]

Table 1 Description of the included studies

Citation	Geographical setting	Design	Method	Analysis
Asai *et al.*[25]	Japan Osaka	No specified theoretical framework/philosophical perspective.	Qualitative focus groups	Thematic analysis
Dixon-Woods *et al.*[26]	United Kingdom	No specified theoretical framework/philosophical perspective.	Semi-structured interviews	Constant comparative method
Dixon-Woods *et al.*[27]	Leicestershire, United Kingdom	No specified theoretical framework/philosophical perspective.	Semi-structured interviews	A systematic and iterative method based on Constant comparative method
Felt *et al.*[28]	Austria	No specified theoretical framework/philosophical perspective.	Semi-structured interviews	Coded into categories for thematic analysis
Haddow *et al.*[29]	Scotland	No specified theoretical framework/philosophical perspective	Focus groups	Thematic analysis
Hamilton *et al.*[30]	United Kingdom	Mixed method	Qualitative interviews	Thematic analysis
Hens *et al.*[31]	Belgium	No specified theoretical framework/philosophical perspective.	Focus groups	Thematic analysis using NVivo
Jenkins *et al.*[32]	Atlanta, USA	No specified theoretical framework/philosophical perspective.	Focus groups	Visual qualitative data analysis
Kaphingst *et al.*[33]	Boston, USA	No specified theoretical framework/philosophical perspective	Focus group and interviews	Based on a grounded theory approach
Levitt & Weldon[34]	Great Britian	No specified theoretical framework/philosophical perspective	Focus groups	Thematic analysis
Lind *et al.*[35]	Denmark	No specified theoretical framework/philosophical perspective	Semi-structured interviews and observation	Interactionist method of analysis
Morrell *et al.*[36]	New South Wales, Australia	No specified theoretical framework/philosophical perspective	Interviews	Morse's description of the generic cognitive underpinnings of qualitative research
Murphy *et al.*[37]	USA	Mixed method	Qualitative focus groups	Thematic analysis using Nvivo
Pfeffer[38]	United Kingdom	No specified theoretical framework/philosophical perspective	Focus groups	Thematic analysis
Rothwell *et al.*[39]	USA	No specified theoretical framework/philosophical perspective	Focus groups	Content analysis
Skolbekken *et al.*[40]	Norway	No specified theoretical framework/philosophical perspective	Focus groups	Meaning condensation (Kvale, 1996)[44] for each focus
Sque *et al.*[41]	United Kingdom	No specified theoretical framework/philosophical perspective	Interviews and focus groups	Thematic analysis
Wong *et al.*[42]	Singapore	No specified theoretical framework/philosophical perspective	Focus groups	Constant comparison

Table 2 Synthesised finding 1: Patient consent to the use of leftover tissue is a complex interaction between many factors and not solely driven by perceptions of benefits to self and others

Category	Finding	Illustration from study
A 'gift'	Negative towards use of the term 'gift' (Dixon-Woods *et al.*)[26] (U)	Anything like a brain tumour any type of thing like that, it is not a gift – it is something you want out of you. If someone said to me when you know they said by donating your tissue you know it is a gift to research it would have held me back, I would have thought. You have got to sympathise with the patient that you know they have been through it and what it is, it is not a gift. [. . .] By donating your tissue it is like an aid to research again, it will help other people, it is not that it is a gift, cos it is like a bad thing is not it, it is nothing good. (Child 42, male aged 15) page 7
	Positive use of the term 'gift' to describe tissue samples for research (Dixon-Woods *et al.*)[26] (U)	I would say that it is probably that it is probably the greatest gift I can give, but the term 'gift' yes I think because that 'gift' conjures up something that is very precious and very special. (Mother 43). page 6
	They saw themselves as engaged in reciprocity (Dixon-Woods *et al.*)[26] (U)	We felt that we have not done anything to help so if we are being told that our consenting to samples being used as a gift, then perhaps that is our gift of giving something back and therefore in a round about way sort of thanking them for treating her and saving her and also helping [. . .] It is not a gift to us, it is not having a direct impact upon life but we feel that we are giving something back and saying thank you. (Mother 32) page 5
Agreed with no reason	Broadly approving about use of tissues for research (Dixon-Woods *et al.*)[26] (U)	I got asked then if I did mind donating any tissue. And I thought – well, oh well, I not really bothered where it goes after this and we could throw it in the bin for all I care- but I would do it, it did not bother me. (Child 51, 16 year old male) page 4
	Donation appeared to be a more-or-less automatic response (Morrell *et al.*)[36] (U)	No worries. I just told them take whatever and do whatever. page 3
	Positive aspect of having donated samples. (Kaphingst *et al.*)[33] (U)	The more research we can get out of all these little tissue samples the better. (Participant 6) page 395
Benefits to others	A desire to do good (Dixon-Woods *et al.*)[27] (U)	As much as we did not have a reason not to take part I suppose, just to be helpful and you know and anything that encourages medical progress you know I think has got to be advantageous to people. (Participant 24) page 2217
	Altruistic (Jenkins *et al.*)[32] (U)	That was one of the hardest things I have ever gone through in my life. Somebody telling me that my baby might not make it and there is nothing they could do. That was like so hard for me and if I can help somebody else not go through that, I am more than willing to do it. (Biologics Participant, Non-Hispanic Black Case Mother) Page 2381
	An example of the staunchly utilitarian position (Pfeffer)[38] (U)	I personally think it would be nice to have something, well, not nice, but something good comes out of it. It is an unfortunate situation but something that you might be able to help someone else, and that is, you know, if that is the only way you can do this sort of research. FG6F7 page 2549
	Burden and Benefit (Hens *et al.*)[31] (U)	If there is no fuss, if it happens, for example, at school and it is no burden for the child (for example through a mouth swab), if we know the benefit of the research, then I would probably not mind. (Table 1, FG8P2, female, 28). page 4
	Develop medical science . . . contributing to the public good. (Asai *et al.*)[25] (U)	As a matter of fact permission has never been asked, but I think that they have been using our medical charts and blood samples. Such behavior brings about medical progress, so I think that there exists tacit agreement between the researchers and patients for the good of all of us. (48-year-old female) page 4
	Education of researchers appeared to be central to the progress of medical science (Felt *et al.*)[28] (U)	Maybe one can learn from it [the donated tissue] in research and science, and a good student can become a rather good doctor, maybe. (P3). page 97
	Participants wanted to help others (Kaphingst *et al.*)[33] (U)	For generations that are coming up, that people have been diagnosed with it, that maybe something from us will be able to help them. (Participant 2) page 395
	Potential use of the biobank material (Skolbekken *et al.*)[40] (U)	My expectations are that the researchers will use these samples in a manner that will serve the health sciences. Maybe both we and the coming generations may benefit from it. (Man, 48) page 340
	Promoting the public interest (Asai *et al.*)[25] (U)	It would be fine if the research served the interests of all and confidentiality was maintained. (55-year-old male) page 5
	Pursuit of a common goal (Dixon-Woods *et al.*)[26] (U)	We talked it through and it comes back to if it is gonna be of help then it is not a problem. And without us doing, without people like us beforehand, we still be back in the sixties and people not understanding what they can and cannot do. (Father 56) page 5
	The need for promoting science and research (Felt *et al.*)[28] (U)	If it is not done, then there is no research because . . . it stagnates; then nothing goes on. And generally, if it was not done in the past . . . we would not be here now . . . with all the technologies and the possibilities . . . If you look today at what kinds of operations are done . . . you didn't even dream of them years ago. (P23) page 97
	Willingness to donate leftover tumor tissue for research because of the good that it might bring to others (Morrell *et al.*)[36] (U)	I think a lot of people will quite happily do it because it may not benefit them, but people have got kids and things like that so there could be a benefit, not to them at this particular time, but also to their family or friends and other people. page 3

Benefits to self	Absence of self-benefits (Wong *et al.*)[42] (U)	I do not see why I should give my blood to complete strangers. I do not even know you. How do I know what you will do with the results? What if the information leaks out to my employer or the insurance company? The insurance company will ask me to pay higher premiums or worse I am not eligible to buy insurance. (Chinese female clerk) page 49.
	Communicating the outcomes of studies to research subjects (Asai *et al.*)[25] (U)	I want to be privately or publicly told the results of studies in which the researchers used our information or blood. (43-year-old-male) page 5
	Hoped to learn more about their own cancer (Kaphingst *et al.*)[33] (U)	I thought it would be great if I could delve into the relationship between my . . . genealogy and my cancer. (Participant 1) page 395
	Imagined more direct relationships between themselves and other patients, both in the present and future (Felt *et al.*)[28] (U)	Maybe in 30 years . . . because I have psoriasis. I [will] need a piece [of skin] myself. And then somebody else [will] help me (P6) page 97
	Importance of individual benefit to motivate people (Haddow *et al.*)[29] (U)	I think it is something that is very easy to do, giving human blood or giving a genetic blood group for genetic study. But people probably won't get off their backsides to do it unless there is a direct benefit to them (FG3 R3). page 273
	Informed of the results of the genetic tests (Wong *et al.*)[42] (U)	What happens if you find something wrong with me? Will you let me know? Will you give me free treatment? What happens if information about my disease leaks out? Can I sue the research body or the government? (Chinese male technician)
	Interested in learning about research studies performed with the donated samples (Kaphingst *et al.*)[33] (U)	I would be interested in this, but what is the cost to keep informing us of all of these things and would it detract from the actual research itself, in other words, take away funds from the actual research? . . . I do not want to be asking for too much, eat up the funds. (Participant 12) page 395
	Interested in receiving aggregate results if individual results were not available (Kaphingst *et al.*)[33] (U)	I mean, I would prefer linked because obviously there is personal interest there, but if it is done without that then I still be interested in the overall results. (Participant 14) page 396
	Lack of perceived individual benefits of anonymous research (Rothwell *et al.*)[39] (U)	If you find something that is significant that is going to affect them you should let them know. (P).page 9
	Not to give them individual results if the implications for patients were unclear (Kaphingst *et al.*)[33] (U)	Because it would be too confusing for me then. Or maybe even scary. (Participant 15) Page 396
	Participants for giving their consent was to feel valued and respected by the hospital (Hamilton *et al.*)[30] staff (U)	So I had probably an understanding and I know it was the Registrar that he asked me and then he popped in at night and I think he said thank you for letting them use it. page 231
	Personal benefit, largely in the form of increased knowledge about ones own health (Morrell *et al.*)[36] (U)	Being asked I thought was good in that it made me feel involved in it, and I was contributing something to research by being the mother of a daughter with cancer. I could say, Yes, you can use this for research, whereas everything else, I was passive in a sense. page 3
	Possibility of some form of personal gain (Dixon-Woods *et al.*)[27] (U)	I embraced it, I thought it was a wonderful opportunity for my family to have a health check so it would benefit both the research programme and my family [y] I could not wait to do it, I was so, I just thought this was like manna from heaven, this was just what I had been looking for, for my family. (Participant 26) page 2218
	Possible benefits to subjects in the distant future (Asai *et al.*)[25] (U)	Using medical charts for research purposes would not offend me as long as my privacy was protected and it would be acceptable if it was likely that I might benefit from the results of the research. (44-year-old female) page 5
	Preference for individual results (Kaphingst *et al.*)[33] (U)	To participate in a study where you get specific results would be very, for me, very positive. It would make me feel that I'm contributing more instead of being lumped into this mass of people. (Participant 8) page 395
	Religious reasons (against donation) (Wong *et al.*)[42] (U)	It is against our religion to predict our future. Just like we should not buy life insurance, we should not undergo genetic tests to predict our future. Everything in this world is the will of Allah and we should not go against his will. (Malay male photographer) page 49
	Religious reasons against long-term storage (Wong *et al.*)[42] (U)	It is not right to store our blood as this is against our religion. We could have left this world before you do further tests. I think you should consult our religious leaders on this. (Malay male technician) PAGE 49
	Research on the disease the children had themselves was preferred (Hens *et al.*)[31] (U)	No, but J would like to find out first whether this can be used for . . . [the medical condition of her child] (FG8P2, female, 28) page 4
	Results may show they have an incurable disease (Wong *et al.*)[42] (U)	Take my blood once and for all and after that I do not want to be bothered again. I can do without the fear and stress of knowing that I have a faulty gene and not having the cure available for it' (Chinese male clerk).
Dependent relationship	Influence of interviewers (Jenkins *et al.*)[32] (U)	I started speaking with the interviewer . . . Then I think it helped me to understand better what the study was about and the purpose and benefit. At that point, once the kit came, it sat on the counter for maybe a couple of weeks, and then I was like okay, let's go ahead and do this. (Biologics Participant, Non-Hispanic Black Case Mother) Page 2381
	Unequal relationships between patient and researchers (Asai *et al.*)[25] (U)	I cannot help but accept researchers using my medical chart without my permission because I feel that the relationship between medical doctors and patients are socially unequal, with patients belonging to the lower rank. (52-year-old female) page 4

Table 2 *Continued*

Category	Finding	Illustration from study
Depending on type of research	Cloning were considered science fiction-y examples of weird research (Morrell *et al.*)[36] (U)	But I could not imagine them cloning, I think that might have even crossed my mind at the time, and I just thought no one is going to clone something from a tumor cell that I can imagine. page 4
	Excluded research and applications to do with cloning, stem cells, sex selection, designer babies and genes for intelligence and criminality (Levitt & Weldon)[34] (U)	. . . this cell stem things they are doing at the moment on cloning and that sort of thing, I be against it. But for medical research, yeah, fair enough. (FG1) page 316
	Genetic tests should not be used for conditions such as intelligence that might discriminate one ethnic group from another (Wong *et al.*)[42] (U)	It is OK to test our blood for genes for chronic diseases like heart disease, diabetes, cancers and even AIDS (if there is a gene for AIDS susceptibility) but I think it should not be used to test for conditions such as intelligence that might discriminate one race from another or to show that one race is superior to another. (Malay female medical student) page 47
	Lack of awareness about the NBS program itself (Rothwell *et al.*)[39] (U)	I think that is everybody job to educate everybody. (M).page 9
	Refuse to donate these fetuses for non-therapeutic research (Pfeffer)[38] (U)	No, not if the baby died in me or whatever, or something was wrong with it or, no I could not. I could not do it. I would be too upset. (FG4F6) page 2549
	Specific fields of research where they would refuse to donate an aborted fetus (Pfeffer)[38] (U)	Cosmetics – the thought of actually putting your lipstick on and things . . . biological weapons . . . sticking an ear on a mouse (mentioned in every group), and reproductive cloning where a participant envisaged you open the door and you are looking at a duplicate of yourself. (FG3F8). page 2549
	Stem cell research is associated with renewal, regeneration, and immortality. (Pfeffer)[38] (U)	Just the thought of it, I do not know, now telling me that, you know, how, stem lines, cell lines, it makes you think that they are keeping it somewhere for years, and I do not know. I think I have this vision of like, you donate, they do what they do and then, then that is it. Not that its kept around possibly for years. (FG6F4) page 2550
No harm or risk to self	Families willingness to consent was conditional on there being no risk to the child (Dixon-Woods *et al.*)[26] (U)	I imagine as a rational person you are not gonna sort of harm [childs] chances of recovery by doing anything and as long as you are not doing that then you add to the body of knowledge. I think it's your responsibility to do it cos we're already sitting here today [. . .] but they are still learning from so many years of treating other children with this, so you know I think you gotta duty to sort of put something back. (Father 7) page 5
	Non detrimental nature of the research (Asai *et al.*)[25] (U)	Using medical charts for research purposes would not offend me as long as my privacy was protected and it would be acceptable if it was likely that I might benefit from the results of the research. (44-year-old female) page 5
	perception of low risk (Dixon-Woods *et al.*)[27] (U)	you might find out that you are about to fluff it or you might find out that there is something seriously wrong with you, but then it is probably better to know that, but as far as negatives go, generally, no, none. Participant 27) page 2218
No use for leftover tissue	giving consent as secondary to their experience of the illness or the surgery they were to undergo. (Hamilton *et al.*)[30] (U)	I cannot imagine how anybody would be affected by it really, if it is helping somebody else then why worry. page 232
	Low value of the tissue to the donors (Dixon-Woods *et al.*)[26] (U)	Tumours and things that are like well I would call waste products. I mean, what use is a tumour to anybody? Unless you can do something good with it. [. . .] I could name statistics you know. Neuroblastoma accounts for over 20, 25% deaths of children but it's only 7% of [cancers]. So we have to improve this and we have to somehow do it [. . .] I don't think that it is fair of anybody to say, 'No I want the tumour just destroyed.' (Father 12) page 6
	Mishandling of aborted fetuses as 'waste' (Pfeffer)[38] (U)	I was a bit, it did bother me for a while, I just kept imagining like this big bag of fetuses and getting really upset about it. So in a way I do not really know if I want to know or, I do not know. (FG6F2) page 2549
	Permission to use tissue that would only go to waste otherwise (Morrell *et al.*)[36] (U)	It would not have worried me, would not have cared. When you are going through that process there is bigger things that fill your mind and this little bit of tissue, who cares? I would have imagined they would have kept the slide, whatever tissue existed on that slide and everything else thrown away, so that slide is sitting somewhere for future reference, like evidence in a murder case or something is just kept there. I would have thought that, but if they had have asked me, Can we keep this for twenty years, I probably would have said, Why? It is bad! No throw it out, do not want it! I was very happy for it to be out of me. page 4
	Tumour material was seen as something that had an alien or intruder form (Dixon-Woods *et al.*)[26] (U)	'Do you want to give them to a big research?' I just thought, 'Well I am not gonna be able to use it so why shouldn't they?' It just did not seem like an issue to me and I have not lost or gained anything by doing it really, apart from maybe if it does do good then I have gained some sort of satisfaction out of helping. (Child 5, female aged 14) page 6

Trust in research and researchers	A need to be informed of the basic information that their tissue would be used in research (Hamilton *et al.*)[30] (U)	To be honest I could have asked for more information but they literally just said it was to go for research but to be honest I was not interested. As long as they could do something with it I was not really bothered about what they did with it. page 232
	A strong sense of trust that the material will not be abused (Skolbekken *et al.*)[40] (U)	As we are living in a well-organized society with laws and regulations, I am pretty confident that [the samples] won't be abused in the society we have at present. And will continue to have in my day, anyhow. (Man, 60) page 340
	Confidence in research process (Dixon-Woods *et al.*)[27] (U)	It is like a trust sort of thing, you do not tend to look into it too much because you know they are looked into anyway the way they sort of conduct themselves and the things that they do. You know they are overseen so it does not hugely bother me what I know it sounds daft but I do read the letters and I do take it all on board but you can skim over it and you know you are safe. [y] like I say if [NHS] was not on the top of the letters then I be a little bit worried about taking part and that is when I start asking around, going on the internet to find out exactly who the people were that were doing it. (Participant 2) page 2218
	Donation as an act of reciprocity for years of research (Morrell *et al.*)[36] (U)	I have a view of what comes around goes around, so I benefited from years of research and technology and medically and psychologically, so I am very much into pushing that back out again and making sure that I was given the benefit, I want someone else then to have that benefit as well. page 3
	Family members trusted the professionals who asked them for consent to use the tissue samples for research (Dixon-Woods *et al.*)[26] (U)	We feel like he is a friend rather than your consultant, you can talk to him and you know that whatever he says he is sincere and he is genuine with the children and you feel comfortable with him, you do. And also because he knows so much about your child and the condition and everything, I think it makes you feel a bit more comfortable, because he only do what he thought was best for your child. (Mother 1) page 7
	Lack of trust and the problem of enforcement (Levitt & Weldon)[34] (U)	We may have many rules and regulations but how many enforcers do we have? How often are these places inspected? How frequently are prosecutions brought? And how effective are they? I suspect it is like the Health and Safety Executive. Nothing happens until you have a disaster and then they go out and investigate it. It is not proactive. (MG1) page 316
	Longer term repercussions of stem cell science on society (Pfeffer)[38] (U)	That is what would bother me that the potential lack of control that you could end up with a situation that you had helped to create. page 2551
	No unprompted concerns about having donated blood or tissue samples for breast cancer research (Kaphingst *et al.*)[33] (U)	I have a lot of confidence in the Institute. . . . I made that decision way back when, when I had the choice whether or not I wanted to come here and . . . I have total confidence here. (Participant 5) page 395
	Participants wanted to advance breast cancer research (Kaphingst *et al.*)[33] (U)	I think it is just maybe a small way to contribute for me . . . to contribute to the whole research aspect of what causes breast cancer . . . maybe trying to cure it or find out better treatments. (Participant 3) page 395
	Personalities of medical researchers (Asai *et al.*)[25] (U)	Who looks at our medical record does matter to me. (35-year old male) page 6
	Positive orientation towards medical research (Dixon-Woods *et al.*)[27] (U)	we were just quite happy to provide the information that was requested in the hope that it would, you know, help you know, future generations and maybe you know stop another family going through the tragedy we had all those years ago you know, that was a sad thing for us, so. (Participant 15) Page 2217
	Science and research is synonymous with societal progress and that it is a duty to participate in this progression (Lind *et al.*)[35] (U)	I believe that it is very important to participate in studies of this kind. It advances research and the development, so I think it is a positive thing [. . .] It is a way in which an enlightened society can progress. page 4
	Trust in medical researchers (Asai *et al.*)[25] (U)	There is no way for us to know whether or not our personal information is dealt with anonymously. We are so naive about what medical research is and how it proceeds. Such powerlessness and ignorance make me uncomfortable. (44-year-old female) page 6
	Trust in the meaningfulness of the study (Lind *et al.*)[35] (U)	You do not want to sit and read..you know, all that ethical stuff..you know what it says already, and you do not bother reading it through [. . .] And I think that it has something to do with that I trust that they are treating the placenta properly. page 4
	Try to find 'safe hands' (Levitt & Weldon)[34] (U)	All I want to know is that my DNA is in safe hands with a group of people in Europe, with a group of people in America, with a group of people in the Far East and so on. And they are all answerable to a body that is part of the UN. . . . (MG5) page 319

Whether it was a desire to do good[27] or seeing donation as an act of reciprocity for the years of research,[36] some patients were willing to donate their tissues for research because of 'the good' that the research could bring to others.[36]

Some people believed that donating their tissues was one way to contribute to medical science[25] and medical education,[28] and, thus, they considered this tissue donation as 'a gift' to humanity. This evidence indicated an unconditional gratitude, with some people not even having a specific reason[26,33,36] for donating their tissues.

A certain group of patients had based their decision on whether or not to donate their residual tissues based on the types of research[34,36,38,39] to be conducted using their tissues. For example, some patients objected to cloning,[36] or non-therapeutic research[38] or research using stem cells[38] and viewed them as 'weird' research[36] in which they would not provide consent for leftover tissue use.

Many patients felt that as there was 'no risk and harm'[25–27] to the donor and as the residual tissues to be donated would otherwise be discarded or destroyed (as it was considered a 'waste'[36] product of the surgery), they would consent to further use. The latter group of patients donated because they believed that they had a 'dependent relationship'[25,32] with the doctors requesting the tissues and consequently felt obliged to donate.

Synthesised finding 2: Healthcare institutions and regulatory authorities must provide clear and transparent safeguards and controls and communicate these to the patient prior to the consenting process

A total of 27 findings were grouped into four categories to support this synthesised finding (Table 3).

Patients believed that research institutions should have strict controls and ethical safeguards[29,34,38] on the collection and storage of their leftover tissues and their related genetic and medical information. Protection of privacy and confidentiality[25,33,34,39] were the main concerns of the patients in terms of safeguards and control. Patients were worried that their private and confidential medical records and genetic information from the tissue identification would be revealed to insurance agents and employers.[33] This could result in economic and financial loss to patients in the future. Furthermore, they were concerned about social and financial discrimination once their medical confidentiality was breached and thus believed that there must be safeguards and controls on the medical or genetic information retained by researchers and their organisations.[34]

Mistrust in research organisations and their governance was one of the main reasons for the refusal to donate their leftover tissues for research.[32,34] Others were also concerned about the manner and timing in which patients were approached for donation.[30,36] It was important that they did not feel coerced to donate, or were placed in a vulnerable position where they felt forced to donate.[38]

Synthesised finding 3: Views on ownership and rights to the future use of the leftover tissue varies between individual patients and influences their willingness to consent to further use

Eighteen of the 29 findings were related to the issue of informed consent (Table 4). Most patients (14 out of 18 findings) agreed that leftover tissues should not be collected, stored, distributed and used for research without the consent of the patients.[23,25,34,35,37,39–41] Other issues mentioned by patients were the question of who should give consent (especially in the case of minors),[42] the use of the stored residual tissues for future research,[36] the length of time of storage[37,40] and the type of research performed on the tissues.[26] The types of consent models, whether broad or specific informed consent, were briefly discussed[38] in two papers,[28,37,42] but the authors did not conclude which type of consent models the interviewed patients preferred. Some patients considered that they owned their tissue samples[25] as they were once part of their own body[12] and they believed that they had the right to know the fate of their tissues.[28,39] These patients were not willing to give up this right of ownership of their tissues[25,30,36,42] when donating the tissues to research institutions.[25,28,33] In contrast, some patients mentioned that informed consent was not required or necessary,[40] and informed consent was not an issue for them. Some patients preferred that they had an option to opt out of the donation or possibility to withdraw their donated samples[34] from the tissue repositories, even though they had a sense of trust that the materials were not misused.[29]

Synthesised finding 4: Patients have opposing views on the use of their leftover tissue for commercial purposes

Patients had divided views on the use of their leftover tissues by commercial companies to generate profit (Table 5). While they may be willing to donate for altruistic reason to a government-funded institution for research of public benefit,[36] they cautioned that such donation should not be used for commercial purpose because they distrusted 'for-profit' organisations.[12] They had a general suspicion[2] of the profiteering motive of private companies compared to the motive of a governmental- or public institution-funded tissue bank. Others viewed commercial company involvement and third party access and usage of the tissues as necessary[36] and as a part of the development of drugs – a 'necessary evil',[1] since commercial companies may be able to advance technology for research. Such patients also cautioned that the use of the tissue must be closely monitored or regulated.[42]

Discussion

Most scientists believe that leftover tissues from diagnostics and procedures are important resources for research.[2,36] These stored tissues are currently used for research to understand disease aetiology, future prognosis, treatment or drug responsiveness, genomics research and genetic testing.[2,36] Collecting such tissues and their associated medical data

Table 3 Synthesised finding 2: Healthcare institutions and regulatory authorities must provide clear and transparent safeguards and controls and communicate these to the patient prior to the consenting process

Category	Finding	Illustration from study
Control and safeguards	Concerns could be blamed on 'media hype' or dismissed as science fiction (Levitt & Weldon)[34] (U)	I do not want people meddling with part of me without telling me. I could have another of me wandering around 'who are you?' That is the downside of giving a sample of DNA. (FG2) page 315
	Consent as a two-way process, rather than simply a process of giving up rights and control (Levitt & Weldon)[34] (U)	. . . to a certain extent . . . there should be a liability from the other side . . . there should be . . . certain points say that are bulleted, what it is going to be used for, why, and you sign it. And with that then you can't sue or anything but if they breach that then you can . . . you should be kept informed what it is used for. (MG2) page 316
	Genetic information and the potential for harm (Levitt & Weldon)[34] (U)	It is impossible to secure it because there is always somebody out there to make a buck out of it. (MG4) page 316
	Information once given will spread inexorably (Levitt & Weldon)[34] (U)	once you give it to one then there is no stopping them (MG3).
	Participants became more concerned on genetic information (Levitt & Weldon)[34] (U)	I would be extremely concerned if anybody were to break into my medical records or look at my DNA . . . I consider that absolutely sacrosanct, that is ME, really the inner me they are looking at. (MG1) page 315
	The duty of care (Pfeffer)[38] (U)	Because it's yours and you are gonna feel like you have done, you are doing it wrong anyway, probably, and then what is gonna happen once it goes? (FG5F7). page 2550
	The issue of control appeared key to resolving ambivalence about access (Haddow *et al.*)[29] (U)	I can see how once you have given up the blood it would be difficult to keep control of what happens to it and so on. But I would hope that there would be ethical safeguards built into you dealing with it and companies would have to meet a certain standard and so on (R1). page 277
	Wondered if stem cell research requires the fetus somehow to be alive (Pfeffer)[38] (U)	And are they taking that fetus, are they taking those cells alive? And is that why because when they take the, the way I did it, would it have been alive or, or is that the reason so that they can take it alive? I know obviously mine it was not alive but. FG3F5: page 2550
	Would be stigmatized especially if they have been found to have a gene for mental illness or personality disorders. (Wong *et al.*)[42] (U)	If you are checking whether I have the gene for cancer or heart disease, it is OK. However, my privacy is very important especially if you are checking for a gene for a personality disorder. I do not want people poking their noses into my family (Indian female manager) page 49
Distrust in research and ethics governance	An air of general disillusionment (Levitt & Weldon)[34] (U)	There is all this corruption going on and God knows what else and you cannot trust them. They never tell you the truth, they cannot answer a straight question and now you want to give them your genetic codes . . . ! (FG2)4 page 315
	Conspiracy theories (Jenkins *et al.*)[32] (U)	Well, not really me, but just dealing with my husband trying to get some tissue from him. He has conspiracy theories, so I had to really talk to him. Biologics Participant (Non-Hispanic Black Case Mother) page 2382
	Fear of government (Jenkins *et al.*)[32] (U)	I am afraid the governments going to have us, our DNA stored in one little chip and they are going to know everything about us . . . they are going to take my DNA and turn it into something bad or decide that . . . I have certain genes that they want and they are going to clone me, I fear that. I feel like the governments taking over our lives. (Biologics Nonparticipant, Low Birth weight Case Mother) Page 2382
	Letter of guarantee from the government or research body (Wong *et al.*)[42] (U)	We like to have a legal cause of action that we can take if we feel that genetic information about us have been let out. There must be a contract between the individual giving blood for genetic research and the institution taking it which will hold in a court of law. (Indian female manager)
	Unethical use (Jenkins *et al.*)[32] (U)	I would think they would do something negative with my DNA . . . Anything that you didn't permit them to do like they could use something, your cells to create another person like you. They might clone you, you don't know. (Biologics Participant, Non-Hispanic Black Control Mother) Page 2381

Table 3 *Continued*

Category	Finding	Illustration from study
Privacy and confidentiality	Concerns over confidentiality (Wong *et al.*)[42] (U)	Our society here in Singapore is very sophisticated. As everything is computerized, there are many opportunities for other people to view our confidential data. For example, look at the credit cards: the information that we have given to credit card companies have been shared. It is very important for the government or research body to put in a lot of effort to keep the results of the genetic research confidential. (Malay male lecturer) page 49
	Fears of potential discrimination from research on residual samples (Rothwell *et al.*)[39] (U)	You are not going to get this job because you are predisposed to or you are predisposed to whatever. page 8
	Health information being used by employers and insurance companies to discriminate against individuals (Levitt & Weldon)[34] (U)	I make no bones of saying this, my wife was an alcoholic many years ago and, thank goodness, she recovered. Now many, many years later on she applied for insurance when we were getting the mortgage . . . and they said 'we have got to write to your doctor'. And they said 'she is an alcoholic'. But that was twenty years ago. Why does that count now? . . . and they would not insure us. (MG1) page 316
	Maintaining confidentiality (Asai *et al.*)[25] (U)	It would be fine if the research served the interests of all and confidentiality was maintained. (55-year-old male) page 5
	No concerns about privacy (Kaphingst *et al.*)[33] (U)	And if it would help to put a sign . . . a neon sign on the top of Dana-Farber with my name on it and my particular medical record, if it would help somebody and me I would do it! (Participant 11) page 396
	Privacy protections might slow research (Kaphingst *et al.*)[33] (U)	I have concerns actually, to some degree, in the opposite direction that all this emphasis on privacy will inhibit the research that goes on. . . . Hate to see it all bogged down. (Participant 6) page 395
	The issue of privacy, participants expressed concerns related to insurance coverage or employment (Kaphingst *et al.*)[33] (U)	People in the medical field, if they know my name and they have the sample, it does not bother me, but it would bother me if an insurance representative of some sort were looking at this information. (Participant 9) page 396
Process of asking for donation	Circumstances surrounding the request to donate (Morrell *et al.*)[36] (U)	No, because when you are going through it you are thinking, Well, that bit of research could be stopping somebody else down the track from having a problem. page 3
	Opposition to the suggestion that an invitation to donate the aborted fetus should be offered on the same day as the abortion is carried out (Pfeffer)[38] (U)	I also think women put in that situation on the day they might actually, if they just about to go down as this lady [another participant] was here, they might be thinking, oh my god, because I have said no, what, I do not really want this doctor now, it is like sending a plate of food back, you know, you do not know how it's all gonna happen. Yeah it is terrible [to ask] on the day. I really think that is awful. (FG5F7) page 2551
	Preferred blood to be taken in the polyclinics, community centres or mobile ambulances (Wong *et al.*)[42] (U)	Where will you be taking our blood specimens? I prefer that your staff do not come to our home to take our blood. Who knows? He may be a conman and inject some drugs in my body as well to make me drowsy. I may be robbed! Also, it is more hygienic to have blood taken at the polyclinic or hospital. At least, I know there are backup services if I should faint or develop complications! (Chinese female assistant nurse) page 48
	Research team should explain how and why they were selected for population based research to avoid suspicion (Wong *et al.*)[42] (U)	The researchers must explain to us why we are selected. Even if you said it is a random process, it is not clear. Where did you get our names? What database did you use? Please explain to us in layman terms what you mean by random selection. This explanation is important to minimize the suspicions of future participants as they might think that there is something wrong with them and that is why they have been selected for the research. page 48
	The timings of the consent being sought (Hamilton *et al.*)[30] (U)	It would have been better if I had been given it a lot further in advance. I was actually given it in the hospital the night before the operation and obviously with the nature of the operation I was not in the right mind to consider it. page 232
	Worried that they would be inconvenienced (Wong *et al.*)[42] (U)	How often will blood specimens be taken? If you come very often, it will cause us a lot of inconvenience. We are all very busy. (Indian female factory worker) page 48

Table 4 Synthesised finding 3: Views on ownernship and rights to the further use of the leftover tissue will vary between individual patients and will influence their willingness to consent to further use

Category	Finding	Illustration from study
Informed consent is not required	Giving consent for tissue use and retention was not an issue (Hamilton *et al.*)[30] (U)	As I say it is a very traumatic time and well that is all I can tell you because I signed it because I just thought, I mean I do not mind them using it or care about them using it. As I say it does not make any difference they have got it. page 231
	Informed consent was unnecessary (Asai *et al.*)[25] (U)	It does not matter at all to me. (45-year old male) page 4
	No need to be asked for permission to use their tissue (Morrell *et al.*)[36] (U)	It would not have bothered me if they had not asked. Personally it would not have bothered me, but I could imagine that some people would prefer to be asked. page 4
	Not concerned as to what is done to their blood samples (Wong *et al.*)[42] (U)	Take the blood and do not bother the donor with its use. Chinese male manager PAGE 49
Informed consent is required	All informants stressed the importance of giving consent in some form (Lind *et al.*)[35] (U)	I think that it is fundamentally right that you give people the opportunity to say no, because it is in a sense intimate to some people [. . .] I think just being asked is important because one is already squeezed into a very efficient system such as the health care system. You feel like a piece being moved around, so it is nice that you sometimes feel that you have some rights and can say yes and no. page 4
	An opportunity to ask questions and making suggestions (Lind *et al.*)[35] (U)	If you are not sure, and there are some things that you want to get clear, then it is important that you have the opportunity to ask some questions before you decide. I think that should always be the case. Page 5
	Autonomy and the Need to Be Informed (Hens *et al.*)[31] (U)	Yes, so, you take your baby to the doctor and you say, I want from my child blood to be taken so that it can be used for scientific research. OK no, I would think that wrong, that is really completely wrong, look that child cannot choose for himself, they would have to have a reason for that, at least done some proper thin king. (FGI0P8, male, 16). page 5
	Children would have to be allowed to decide for themselves once they reach the age of understanding (Hens *et al.*)[31] (U)	No, from the moment that I can decide myself I want to decide myself, but I would not mind too much either. Let's say my parents consented, and I know that now, yes for such a research I would not really mind. (FG1P2, female, 16), page 5
	Contract as a binding agreement between participants and researchers (Murphy *et al.*)[37] (U)	Researchers would have to sign it [the contract] too. page 2131
	Giving people the right to choose (Levitt & Weldon)[34] (U)	Well I think people have choice and you are not going to be forced into giving that information . . . if there is something in your medical history that you are not happy about you are not going to be dragooned into doing it . . . you have control, same as a donor card. . . . I just think the big word is choice. (FG1) page 316
	Information about organ retention (Sque *et al.*)[41] (U)	You need to be able to ask questions and have somebody to answer them I think more than anything else, and to know that someone is there to answer your questions, I think more than anything else. (TLMS003446326) 46550 page 74
	Informed consent for storage of samples (Rothwell *et al.*)[39] (C)	I probably not let them keep it just because of the privacy thing. page 8
	Make participants feel respected and involved in the study (Murphy *et al.*)[37] (U)	It would be nice knowing every time that someone was going to get my permission. page 2131
	Participants be given a choice of broad or study-specific consent at the beginning (Murphy *et al.*)[37] (U)	Why not offer both? Because I know it would annoy me, but maybe someone else would want to know that. page 2131
	Preferring the initial consent to be active, the need for explicit, active consent for each new research project was perceived as unnecessary (Skolbekken *et al.*)[40] (U)	I thought this would be a contribution from me to future generations. I must say that I have actually donated much more than I have realized, then, and I have done it from great trust in the system. That it will be used in an ethically good manner . . . . What I have consented to, if we go into detail . . . I am really not sure what I have given my consent to. (Man, 43) page 340
	Researchers should obtain individual informed consent from subjects (Asai *et al.*)[25] (U)	Different people have different attitudes towards what kind of personal information should be made known to others. Even if a study is well-intended and conducted on behalf of the good of society personal permission should be obtained. (44-year-old female) page 5

Table 4 *Continued*

Category	Finding	Illustration from study
	Should be contacted again and new consent obtained (Wong *et al.*)[42] (U)	I would like to be informed as to what is going on especially if my blood specimen is going to be stored for some time. It is the respect that is shown to the participants in your study. After all it is they that gave you the means to do your research. If you betray the trust it is bad. Give respect to the participants in your study and do not betray the trust. (Indian businessman and community council leader). PAGE 50
	The need for informed consent for biomedical research on anonymous or identifiable residual samples (Rothwell *et al.*)[39] (U)	But I think the whole storing and using without permission is a really slippery slope. (M)2 page 8
Ownership of tissues and records	Donation of an aborted fetus is different to donation of other body parts. (Pfeffer)[38] (U)	Yeah, it is been made by somebody else as well and it is also another person, it is kind of, well not another person, but it is not you, it is not your organ, it is not an organ of your body, it does not belong to you, it is growing inside of you, but you know (FG6F7) page 2550
	Issue of ownership of medical records (Asai *et al.*)[25] (C)	Medical professionals and researchers do not have the right to use what belongs to me whenever they want. (47-year-old female) page 5
	Ownership of the samples (Haddow *et al.*)[29] (U)	The very worst case scenario is you get things like the Minority Report where it is scanning eye, they know everything about you and your most desires, and that's what they are starting to do with technology. Like this new passport they want you to have, different things on. So there is obviously certain things that you do not want it going too far, and you want control over your own things (emphasis added, FG1 R2). page 278
	Parental Responsibility and Trust in Parental Decisions (Hens *et al.*)[31] (U)	'You can then object to the fact that parents know it first, and some people will push this very far, but the real problem is really not with the parents if you have cancer.' (FG5P8, male, 19). page 5
	Parents decision-making process with regard to disposal of the retained organs, bodies or blocks and slides (Sque *et al.*)[41] (U)	And of course it dawns on you that the possibilities open to you will involve pain and re-opening of wounds, of you know your wounds. I felt reluctant to change the status quo (leaving the organs and tissue blocks at the hospital) because I knew that anything I did do, that we did, would bring back all the memories of her death. TLMSAA0312479, 13071 page 74
	Public control of the medical system increased by giving voice to individual patients. (Felt *et al.*)[28] (U)	Not everyone accepts that one [researchers] can simply do research with all [excess] materials but that they [medical staff] are taking care of what areas this goes on in, yes. That means [having] precise controls .. and seeing the patient as a patient and not as a number. (P5) page 98
	Some aspects of personhood persisted in the tissues after removal from the child body, that they were still 'part of' the child in some way (Dixon-Woods *et al.*)[26] (U)	Because it is out of my own body is not it, so should be able to say how I want them to use it and that. (Child 4, male aged 16) page 6
	The aborted fetus somehow persists beyond the abortion (Pfeffer)[38] (c)	When I made the decision to have like a termination, once I had had it done, my way of dealing with it was just to forget completely, forget about it, move on, I have got my life to deal with. My only concern would be if I had, if I agreed to have this fetus in medical research, I would be thinking, what are they doing with it, you know, what was it for? You have to have I would really want to know, then would it bring more emotional side effects because I was quite, I dealt with it individual, as an individual, I think I dealt with it quite well, yeah. I dealt with it on my own, without my other half, and that was it. But I wonder if I would think more about it if I had donated the fetus. (FG6F3) page 2549
Withdrawal from research	Could change my mind (Felt *et al.*)[28] (U)	I could change my mind tomorrow and say: Sorry, but I want to take it [my skin] home (P10). page 98
	Opportunity to opt out (Asai *et al.*)[25] (U)	Ordinary hospitals as well as university-affiliated ones should make public that patient's medical charts and blood samples previously taken during the course of medical diagnosis or treatment are being used for research purposes. Those who do not want their medical charts or blood used in this way should be given a chance to say no. (48-year-old female) page 5
	Possibility of withdrawing their samples from the tissue bank (Kaphingst *et al.*)[33] (U)	That is fine if someone had an issue with it. It is a safety. No, it is not a concern for me, but it is a good thing to have in there if someone did have a concern. (Participant 7) page 395

Table 5 Synthesised finding 4: Patients have opposing views on the use of their leftover tissues for commercial purposes

Category	Finding	Illustration from study
Against financial gains from my tissues	Critical of a company controlling access for profit (Levitt & Weldon)[34] (U)	I think it is a moral question as well. We are not talking about a Dyson Hoover here, we are talking about people's health and well-being here and I do not like to see it patented. (MG1) page 315
	Distrust was expressed of for-profit organizations (Skolbekken *et al.*)[40] (U)	If you can imagine that international corporations enter the scene, and we know what that means . . . with cloning and gene modification and all that. I am personally against it. That would be abuse, in my view. (Woman, 60) page 340
	General suspicion of the profit motive with a marked perception of a public/private divide (Levitt & Weldon)[34] (U)	You cannot have a government institution with the taxpayers paying for it and a private institution making profits out of that information which is being supplied voluntarily by the public. The two are not compatible. One is trying to make a profit out of it, the other may be using it for specific government purposes. (MG1) page 315
	Most patients clearly rejected the idea of receiving financial compensation for a tissue donation (Felt *et al.*)[28] (U)	Because we all benefit from it [the donated tissue] if, for example, a drug against skin cancer will be found; everybody profits! And why . . . just because I have consented [to donate tissue] . . . should I cash in now? (P12). page 97
Pro-financial gain from my tissues	Accept pharmaceutical involvement as a 'necessary evil' and suggested greater personal motivation to participate (Haddow *et al.*)[29] (c)	People have obviously got, when you have got somebody that has got a condition in the family then they are more inclined to help. If you are talking to somebody sitting at the table who did not have anybody in their family with anything wrong, 'why should I bother', 'I am not going to gain anything out of this', this sort of thing. We have obviously got more something to gain somewhere down the line possibly, but somebody else might not have (FG1 R3). page 273
	Private company involvement and third-party access (Morrell *et al.*)[36] (U)	I can see there will be slip-ups; there will be people who do the wrong thing for profit. I think it is a risk you have got to run. page 4

creates numerous ethical, legal, social, methodological and technical problems[2] at the different stages of tissue handling.

The findings of this review indicate that most patients want researchers to understand the various factors that will impact upon their willingness to consent as well as the type of consent they are willing to give with regard to the future use of their leftover tissue. Researchers, research institutions and statutory bodies have a responsibility to the patients for the storage, distribution and use of leftover tissues. This duty of care is particularly important as the tissue donation has usually been given to progress science either for the individual or common good. The refusal of patients to donate their tissues could result in these tissues being discarded as thrown away 'waste'[40] and their valuable research potential would be lost.[34]

From the review, the most common reasons provided by the patients when they donated the tissues included benefits to themselves or others.[27] Some patients hoped to have some direct benefits for themselves and their disease conditions and if not, they hoped that future research using their tissues could benefit other patients, just like they had benefited from the earlier research done.[25] Many patients also mentioned the 'trust' they have, for the researchers and the research institutions that their tissues will not be exploited and will be used for a good cause.[40] Trust is an important reason for patients to freely donate their leftover tissues for research,[34] and the betrayal of such trust can lead to lower donation rates for such tissues.[34,42] This 'trust' is important in ensuring continual donations and once this trust is 'betrayed', the willingness to donate will decrease. This 'betrayal of trust'[32,34] was described in some of the studies when the case of UK Alder Hey Hospital's[41] unauthorised organs retention and other similar cases were mentioned.[36,41] Commercial company access and uses of the leftover tissues were discussed in some studies.[21,28,34,40] And the issue of 'mistrust' was also highlighted in the commodification of human tissues.[21]

The findings of this review also indicate that patients are willing to donate their leftover tissues for research as long as there are proper safeguards on their confidentiality and privacy.[37,40] Concerns over the use of the biological materials for genetic research appear to be related to confidentiality and privacy issues,[39] risk to self and family, religious belief,[42] potential discrimination[32] and loss of employment or insurance coverage.[34]

One of the secondary objectives of this review was to examine the patient's experience and preference on the different consent models when donating their leftover tissues. After reviewing the selected papers, no firm conclusions could be reached as few research papers[2,13,24] mentioned the various consent models. Murphy *et al.*[37] noted

that the patient 'could be given a choice of broad or study specific consent at the beginning of a research'[1,11,43] whereas Skolbekken *et al.*[40] noted that patients preferred 'initial consent to be active, the need for explicit, active consent for each new research project was perceived as unnecessary'.[20] Depending on whether the tissues are identifiable, coded or anonymous (with no identifiable patient's information), the preference of consent model may differ.[34] Some authors had recommended that coded and anonymous tissues may not require the same stringent specific consent as identifiable tissues.[3,5,6] Unfortunately, due to the limitation of qualitative studies available on the models of informed consent, no determination can be made on the basis of this review as to exactly which consent model is most preferred by patients. This suggests the need for such research in the future.[2]

Conclusion

The four meta-syntheses of the results emphasised that patients had different concerns at different stages of the handling of their leftover tissue by researchers and the research institutions. The three stages of tissue handling are collection, storage (includes processing) and future use of the tissues. These stages were illustrated in the four synthesised findings namely: during collection or donation of the tissues (synthesised finding 1), the patients had expressed that they have different reasons for donating their leftover tissues; during the processing and storage of the tissues in biobanks or research institutions (synthesised finding 2) where patients had concerns on the safeguards and controls on the collection and storage of their leftover tissues; and the subsequent distribution or access the tissues and the subsequent usage of the tissues for future research (synthesised findings 3 and 4) where patients have different views on their ownership and rights on the ethical uses of their tissues, and whether they would allow the commercial access and use of their tissues.

From the analysis, we can conclude that institutions requesting such a donation need to first establish good governance systems for the collection and storage of the tissues, as well as a system for protecting the rights and confidentiality of the patients. Most patients wanted an ethical and effective system for deciding on the future use of their tissues, especially when a full informed consent was not obtained from the donor at the point of donation. Institutions and research organisations need to play an important custodian role for these stored tissues to ensure that the medical research is ethically conducted and will generate public good. The results of this review may also be useful in increasing the number of tissue donations, which is an important and valuable source of samples for biomedical research on any specific disease of future patients. Increasing the patients' acceptance and positive donation rate are important because these leftover or residual tissues have no direct cost to the patients and the research institutions, most of which consider the tissues as surgical waste that are to be discarded rather than used for research. Thus, understanding patient experiences and attitudes could improve future donation rates of these important medical resources.

Implications for practice

Several implications for practice may be derived from this review. Each of these recommendations is assigned a level of evidence according to JBI criteria (Appendix II).

1 Healthcare professionals should be aware that patient's consent to the use of their leftover tissues is a complex interaction between many factors and not solely driven by perceptions of benefits to self or others. (Level 1 Evidence)
2 Healthcare institutions and regulatory authorities must provide clear and transparent safeguards and controls and communicate these to the patient prior to the consent process on the storage, subsequent distribution and future use of the tissue. In particular, consent should ensure the patients privacy and confidentiality are protected. (Level 1 evidence)
3 Healthcare professionals should be aware that the views on ownership and rights to the future use of leftover tissues will vary between individual patients and will influence their willingness to consent to further use. (Level 1 Evidence)
4 Healthcare professionals, institutions and regulatory authorities should be aware that patients have opposing views on the use of their leftover tissue for commercial purposes. (Level 1 Evidence)

Implications for research

This systematic review has highlighted the paucity of good quality research into the meaningfulness of being a donor of leftover tissue. Further research studies should be undertaken to ascertain:

- The patient's preference on the different models of informed consent, as these different models may increase patient's willingness to donate the leftover tissues. The study should ascertain if there is a need for re-consent when a new researcher requires the tissues
- Whether culture, age, ethnicity or religion affect patients' willingness to donate their leftover tissues
- Whether informed consent models for donating tissues should be based on the types of identifiable information attached to the tissues
- The patients' reasons to donate their leftover tissues and how to gain patients' trust in order to increase their willingness to donate

References

1. Vermeulen E, Schmidt MK, Aaronson NK *et al.* Opt-out plus, the patients' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. *J Clin Pathol* 2009; **62**: 275–8.
2. Oosterhuis JW, Coebergh JW, van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer* 2003; **3**: 73–7.

3. Goodson ML, Vernon BG. A study of public opinion on the use of tissue samples from living subjects for clinical research. *J Clin Pathol* 2004; **57**: 135–8.
4. Wendler D. One-time general consent for research on biological samples: is it compatible with the Health Insurance Portability and Accountability Act. *Arch Intern Med* 2006; **166**: 1449–52.
5. Robertson JA. Ethical and legal issues in human embryo donation. *Fertil Steril* 1995; **64**: 885–94.
6. van Veen EB, Riegman PH, Dinjens WN *et al*. TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer* 2006; **42**: 2914–23.
7. Deplanque D, Birraux G, Bertoye PH, Postaire E. Collections of human biological samples for scientific purposes. Why do current regulation need to be clarified and how? *Therapie* 2009; **64**: 259–67.
8. Hofmann B. Broadening consent – and diluting ethics? *J Med Ethics* 2009; **35**: 125–9.
9. Singapore BAC. Human tissue research: a report by Bioethics Advisory Committee Singapore. 2002; November 2002.
10. Mello MM, Wolf LE. The Havasupai Indian tribe case – lessons for research involving stored biologic samples. *N Engl J Med* 2010; **363**: 204–7.
11. Vermeulen E, Schmidt MK, Aaronson NK *et al*. A trial of consent procedures for future research with clinically derived biological samples. *Br J Cancer* 2009; **101**: 1505–12.
12. Bryant RJ, Harrison RF, Start RD *et al*. Ownership and uses of human tissue: what are the opinions of surgical in-patients? *J Clin Pathol* 2008; **61**: 322–6.
13. Hoeyer K, Olofsson BO, Mjorndal T, Lynoe N. Informed consent and biobanks: a population-based study of attitudes towards tissue donation for genetic research. *Scand J Public Health* 2004; **32**: 224–9.
14. Caulfield T, Upshur RE, Daar A. DNA databanks and consent: a suggested policy option involving an authorization model. *BMC Med Ethics* 2003; **4**: E1.
15. Conrad S, Renninger M, Hennenlotter J *et al*. Generation of pluripotent stem cells from adult human testis. *Nature* 2008; **456**: 344–9.
16. Helft PR, Champion VL, Eckles R, Johnson CS, Meslin EM. Cancer patients' attitudes toward future research uses of stored human biological materials. *J Empir Res Hum Res Ethics* 2007; **2**: 15–22.
17. Wheeler J, Agarwal M, Sugden J, Bladon M, Quirke P. Experiences from the front-line routine consenting of surplus surgically removed tissue: without investment by the National Health Service fully informed consent for all is not available. *J Clin Pathol* 2007; **60**: 351–4.
18. Common consent. *Nature* 2009; **460**: 933.
19. Hunter D. One-time general consent for research on biological samples: autonomy and majority rules have been misunderstood. *BMJ* 2006; **332**: 665–6.
20. Abou-Zeid A, Silverman H, Shehata M *et al*. Collection, storage and use of blood samples for future research: views of Egyptian patients expressed in a cross-sectional survey. *J Med Ethics* 2010; **36**: 539–47.
21. Haddow G. 'Because you're worth it?' The taking and selling of transplantable organs. *J Med Ethics* 2006; **32**: 324–8.
22. Treweek S, Doney A, Leiman D. Public attitudes to the storage of blood left over from routine general practice tests and its use in research. *J Health Serv Res Policy* 2009; **14**: 13–19.
23. Hens K, Dierickx K. Human tissue samples for research. A focus group study in adults and teenagers in Flanders. *Genet Couns* 2010; **21**: 157–68.
24. Secko DM, Preto N, Niemeyer S, Burgess MM. Informed consent in biobank research: a deliberative approach to the debate. *Soc Sci Med* 2009; **68**: 781–9.
25. Asai A, Ohnishi M, Nishigaki E, Sekimoto M, Fukuhara S, Fukui T. Attitudes of the Japanese public and doctors towards use of archived information and samples without informed consent: preliminary findings based on focus group interviews. *BMC Med Ethics* 2002; **3**: E1.
26. Dixon-Woods M, Cavers D, Jackson CJ *et al*. Tissue samples as 'gifts' for research: a qualitative study of families and professionals. *Med Law Int* 2008; **9**: 131–50.
27. Dixon-Woods M, Ashcroft RE, Jackson CJ *et al*. Beyond 'misunderstanding': written information and decisions about taking part in a genetic epidemiology study. *Soc Sci Med* 2007; **65**: 2212–22.
28. Felt U, Bister MD, Strassnig M, Wagner U. Refusing the information paradigm: informed consent, medical research, and patient participation. *Health (London)* 2009; **13**: 87–106.
29. Haddow G, Laurie G, Cunningham-Burley S, Hunter KG. Tackling community concerns about commercialisation and genetic research: a modest interdisciplinary proposal. *Soc Sci Med* 2007; **64**: 272–82.
30. Hamilton S, Hepper J, Hanby A, Hewison J. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics* 2007; **33**: 229–33.
31. Hens K, Nys H, Cassiman JJ, Dierickx K. The storage and use of biological tissue samples from minors for research: a focus group study. *Public Health Genomics* 2011; **14**: 68–76.
32. Jenkins MM, Reed-Gross E, Rasmussen SA *et al*. Maternal attitudes toward DNA collection for gene-environment studies: a qualitative research study. *Am J Med Genet A* 2009; **149A**: 2378–86.
33. Kaphingst KA, Janoff JM, Harris LN, Emmons KM. Views of female breast cancer patients who donated biologic samples regarding storage and use of samples for genetic research. *Clin Genet* 2006; **69**: 393–8.
34. Levitt M, Weldon S. A well placed trust?: Public perceptions of the governance of DNA databases. *Crit Public Health* 2005; **15**: 311–21.
35. Lind U, Mose T, Knudsen LE. Participation in environmental health research by placenta donation – a perception study. *Environ Health* 2007; **6**: 36.
36. Morrell B, Lipworth W, Axler R, Kerridge I, Little M. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res* 2011; **21**: 75–84.
37. Murphy J, Scott J, Kaufman D, Geller G, LeRoy L, Hudson K. Public perspectives on informed consent for biobanking. *Am J Public Health* 2009; **99**: 2128–34.
38. Pfeffer N. What British women say matters to them about donating an aborted fetus to stem cell research: a focus group study. *Soc Sci Med* 2008; **66**: 2544–54.
39. Rothwell E, Anderson R, Botkin J. Policy issues and stakeholder concerns regarding the storage and use of residual newborn dried blood samples for research. *Policy Polit Nurs Pract* 2010; **11**: 5–12.
40. Skolbekken J-A, Ursin LØ, Solberg B, Christensen E, Ytterhus B. Not worth the paper it's written on? Informed consent and biobank research in a Norwegian context. *Crit Public Health* 2005; **15**: 335–47.
41. Sque M, Long T, Payne S, Roche WR, Speck P. The UK post-mortem organ retention crisis: a qualitative study of its impact on parents. *J R Soc Med* 2008; **101**: 71–7.
42. Wong ML, Chia KS, Wee S *et al*. Concerns over participation in genetic research among Malay-Muslims, Chinese and Indians in Singapore: a focus group study. *Community Genet* 2004; **7**: 44–54.
43. Wendler D. One-time general consent for research on biological samples. *BMJ* 2006; **332**: 544–7.
44. Kvale S. *InterViews: An Introduction to Qualitative Research Interviewing*. Thousand Oaks, CA: Sage Publications, Inc., 1996.

Appendix I

Level of evidence (JBI)

Joanna Briggs Institute level of evidence for qualitative studies

Degrees of credibility	
Unequivocal (U)	Unequivocal relates to evidence beyond reasonable doubt which may include findings that are matter of fact, directly reported/observed and not open to challenge.
Credible (C)	Credible relates to those findings that are, albeit interpretations, plausible in the light of the data and theoretical framework. They can be logically inferred from the data. Because the findings are interpretive they can be challenged.
Unsupported (S)	Unsupported is when the findings are not supported by the data.

Appendix II

JBI level of evidence for meaningfulness M (1–4)

Level of evidence	Meaningfulness
1	Metasynthesis of research with unequivocal synthesised findings
2	Metasynthesis of research with credible synthesised findings.
3	(a) Methasynthesis of test/opinion with credible synthesised findings
	(b) One or more single research studies of high quality
4	Expert Opinion

APPENDIX 5

Office of Deputy President (Research and Technology)
Institutional Review Board

NUS National University of Singapore

NUS-IRB REFERENCE CODE: 10-252E

09 June 2010

Mr Chan Tuck Wai
Centre for Biomedical Ethics
Yong Loo Lin School of Medicine
National University of Singapore

Dear Mr Chan,

EXEMPTION FROM FULL IRB REVIEW

Protocol Title: Consent for Donating Leftover Tissues in Singapore

Principal Investigator: Mr Chan Tuck Wai
Co-Investigator(s): Prof Leonardo D.De Castro

Source of Funding: Nil

We are pleased to inform you that your application for exemption from NUS-IRB review for the above-mentioned research has been approved based on your declaration that your research only involves human subjects as stated in the following category:

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Please note that:
1. The Principal Investigator should promptly inform the NUS-IRB if any significant deviations from the information submitted in this application arise.
2. The Principal Investigator should apply for IRB approval if he decides to include any other human subjects in his research at a later point in time.

Thank you.

Yours sincerely,

Professor Lee Hin Peng
Chairman, Institutional Review Board
National University of Singapore

Cc: Deputy Director, Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, NUS

Block MD 11, #03-02, 10 Medical Drive, Singapore 117597
Tel: (65) 6516 4311 Fax: (65) 6778 3430
Website: www.nus.edu.sg/irb

NUS-IRB REFERENCE CODE: 10-252E

09 June 2010

Mr Chan Tuck Wai
Centre for Biomedical Ethics
Yong Loo Lin School of Medicine
National University of Singapore

Dear Mr Chan,

EXEMPTION FROM FULL IRB REVIEW

Protocol Title: Consent for Donating Leftover Tissues in Singapore

Principal Investigator: Mr Chan Tuck Wai
Co-Investigator(s): Prof Leonardo D.De Castro

Source of Funding: Nil

We are pleased to inform you that your application for exemption from NUS-IRB review for the above-mentioned research has been approved based on your declaration that your research only involves human subjects as stated in the following category:

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Please note that:
1. The Principal Investigator should promptly inform the NUS-IRB if any significant deviations from the information submitted in this application arise.
2. The Principal Investigator should apply for IRB approval if he decides to include any other human subjects in his research at a later point in time.

Thank you.

Yours sincerely,

Professor Lee Hin Peng
Chairman, Institutional Review Board
National University of Singapore

Cc: Deputy Director, Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, NUS

Consent for Donating Leftover Tissues in Singapore

Chan Tuck Wai

Abstract

Singapore inherited a health system and a legal system based on the British model, but has in recent years been increasingly influenced by US-style medical/patient attitudes on their rights over their tissues.

In April 2002, in view of the Alder Hey and the UK retained organs scandal, a detail informed consent system was implemented for all leftover tissues in Singapore's National University Hospital.

In the consent form, the patient was asked if he/she would agree to allow the remainder of any tissue not required for diagnosis or residual diseased and normal leftover tissues obtained after clinically indicated surgery and diagnosis to be used for medical research, education and study purposes. The patient was also informed that only excess tissue that remained after all necessary medical tests were completed would be used, and no extra tissue would be removed. An explanation, in the form of a Patient Information Sheet, was given to the patient that in the course of many procedures, tissues might be removed as part of the surgical procedure, and these tissues would otherwise be discarded if not required for diagnostic purposes.

With the introduction of a new consent form, we discovered that it was necessary to have a tracking system to link the consent or non-consent with the individual tissue specimen in order to follow the patients' wishes. This was achieved by the addition of an electronic `tag' to the patient's identification number at the hospital, which was linked to all the patient's investigations results. With this in place, we launched the use of the informed consent system in April 2002 and monitored the results of such consent till this date (April 2010).

A review of the data collected showed the level of increased positive consent over a period of 8 years. There were some initial resistance and these were discovered to be at the level of the doctors and nurses, who had not been adequately briefed and were not enthused with having to request another consent form to be filled by the patient. After a few meetings, the hospital staff (junior and senior) could see the importance of this new development for the purposes of medical research and education. The 8 years data also showed that different departments/specialties in this tertiary hospital have different level of positive consent from their patients.

Based on these positive results, other hospitals in Singapore were encouraged to implement this consent system to seek consent from patients for use of their residual leftover tissues.

Research Protocol

My thesis will be on Consent for Donating residual tissues in Singapore and research ethics in the use of such tissues for research.

NUHS have collected some unidentified data on patient informed consent in donating residual/leftover tissues for medical research and education, we would like to request for IRB approval to use this unidentified data for research.

The data was originally collected for Quality Assurance purpose and do not have any patient identifiable information and not linked to medical records. Department of Pathology has been the custodian in collecting this information with the help of NHG ICARE and IHIS - Clinical Ancillary Services.

We have been collecting detailed statistics on the consent for donating residual tissue in National University Hospital, for quality assurance purposes to analyse the success of the implement of this consent process.

From these results and discussions, I plan to investigate a workable model of obtaining consent for such tissue and develop and evaluate appropriate safeguards to prevent the misuse of these tissues.

Approval

Approval has been obtained from Prof Teh Ming, Head of Department of Pathology for the use of the data for this research.

Please refer to attached email dated 24 May 2010.

Contact information

Tuck Wai CHAN:: Associate Director / Human Protection Administrator, Institutional Review Board :: National University of Singapore :: Clinical Research Centre, Block MD 11, #03-02, 10 Medical Drive, Singapore 117597 :: 65-6516 1234 (DID) :: 65-6778 3430 (Fax) :: dprctw@nus.edu.sg (E)

NUS-IRB REFERENCE CODE: 11-234

8 August 2011

Dr Eng Chon Boon
Dept of Pathology
Yong Loo Lin School of Medicine
National University of Singapore

Dear Dr Eng,

APPROVAL TO CONDUCT RESEARCH AT NUS

Protocol Title: Patients' Experiences Towards the Donation of their Leftover Tissues and the Impact of these Experiences on the Type of Consent Given for Secondary Use.

Principal Investigator: Dr Eng Chon Boon

Corresponding PI: Mr Chan Tuck Wai (PhD Student)

Source of Funding: Nil

We refer to your application for ethics review.

We are pleased to inform you that the NUS Institutional Review Board has approved the above-mentioned research to be carried out in the Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore.

The following documents have been reviewed and approved by the NUS-IRB:

Documents		**Document Date**
1.	NUS-IRB Application Form	Version 2, 27 Jul 2011
2.	Participant Information Sheet	Version 2, 27 Jul 2011
3.	Interview Guide	Version 1, 22 Jul 2011
4.	Investigators' Curricula Vitae	--

We have enclosed the Approval Certificate NUS 1370 for this research.

Please let the Board have reports on the annual progress of the research. The first continuing review report will be due on 30 June 2012.

Thank you.

Yours sincerely

Professor Lee Hin Peng
Chairman, Institutional Review Board
National University of Singapore

Cc: Head, Dept of Pathology, Yong Loo Lin School of Medicine, NUS) - without certificate
Vice Dean (Research), Yong Loo Lin School of Medicine, NUS) - without certificate

NUS-IRB REFERENCE CODE: 11-234

8 August 2011

Dr Eng Chon Boon
Dept of Pathology
Yong Loo Lin School of Medicine
National University of Singapore

Dear Dr Eng,

APPROVAL TO CONDUCT RESEARCH AT NUS

Protocol Title: Patients' Experiences Towards the Donation of their Leftover Tissues and the Impact of these Experiences on the Type of Consent Given for Secondary Use.

Principal Investigator: Dr Eng Chon Boon

Corresponding PI: Mr Chan Tuck Wai (PhD Student)

Source of Funding: Nil

We refer to your application for ethics review.

We are pleased to inform you that the NUS Institutional Review Board has approved the above-mentioned research to be carried out in the Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore.

The following documents have been reviewed and approved by the NUS-IRB:

Documents		Document Date
1.	NUS-IRB Application Form	Version 2, 27 Jul 2011
2.	Participant Information Sheet	Version 2, 27 Jul 2011
3.	Interview Guide	Version 1, 22 Jul 2011
4.	Investigators' Curricula Vitae	--

We have enclosed the Approval Certificate NUS 1370 for this research.

Please let the Board have reports on the annual progress of the research. The first continuing review report will be due on 30 June 2012.

Thank you.

Yours sincerely

Professor Lee Hin Peng
Chairman, Institutional Review Board
National University of Singapore

Cc: Head, Dept of Pathology, Yong Loo Lin School of Medicine, NUS) - without certificate
Vice Dean (Research), Yong Loo Lin School of Medicine, NUS) - without certificate

NUS Institutional Review Board (IRB)

APPLICATION FORM FOR SOCIAL, BEHAVIOURAL & EDUCATIONAL RESEARCH

NUS National University of Singapore

I. BASIC INFORMATION

Protocol (Research) Title:
Patients' experiences towards the donation of their leftover tissues and the impact of these experiences on the type of consent given for secondary use.

Simplified Title (where applicable): NA
(simplified title for Participant Information Sheet & Consent Form)

Applicant:

Title	Name	Role	Position	Dept./Institution
Dr	Eng Chon Boon	☒ PI / Supervisor	Head	*NUH/NUS Tissue Repository*
Mr	Chan Tuck Wai	☒ Corresponding PI	Assoc Dir	*NUS-IRB*

(please complete section III for all co-investigators)

Source of Funding:

☐ BMRC ☐ NMRC ☐ NUS ARF ☐ Others ☒ None

If Commercial Company/ Other organisation, please specify: _____

Total amount of grant/fund: $ _____

Status of grant: ☐ Approved ☐ Pending ☒ Not applicable

Nature of Research:

☐ Archived/ Existing Database ☐ Experiments

☒ Questionnaire/ Survey ☐ Others, please specify: _____

Research May Involve:

Human Subjects: (Target Number: 100)

☒ Healthy Volunteers ☐ Children (under 21 yrs old) ☐ Pregnant Women

☐ Outpatients ☐ Inpatients ☐ Prisoners

☐ Cognitively Impaired Persons, please specify: _____

Research Subjects Will Be:

☐ Reimbursed $_____ ☒ Not reimbursed ☐ Others – please specify: _____

Has this research been rejected by any IRB / REC / DERCs?

☒ No ☐ Yes If yes, please provide details.

Site details:

Site(s) of research (Dept. & Institution): NUH and NUS

☒ Single-centre study

☐ Multi-centre study - No. of local sites:_____ No. of overseas sites: _____

This research is also submitted to or has been approved by: Not applicable

SingHealth: ☐ SGH ☐ NHC ☐ NCC ☐ CGH ☐ SERI ☐ KKH ☐ NDC ☐ NNI ☐ SHP

NHG: ☐ DSRB A ☐ DSRB B ☐ DSRB C ☐ DSRB D ☐ DSRB E ☒ **Not Applicable**

II. DECLARATION OF THE PRINCIPAL INVESTIGATOR

The information provided in this form is correct.

a. I will not initiate this research until I receive written notification of NUS-IRB approval and regulatory authority approval (if applicable).

b. I will not initiate any change in protocol without prior written approval from NUS-IRB except when it is necessary to reduce or eliminate risk to the subject.

c. I will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that may occur in the course of this research.

d. I will maintain all relevant documents and recognize that the NUS-IRB staff and regulatory authorities may inspect these records.

e. I understand that failure to comply with all applicable regulations, institutional and NUS-IRB policies and requirements may result in the suspension or termination of this research.

f. I declare that there is no existing or potential conflict of interest for any of the investigators participating in this research.

Remarks (if any):

Eng Chon Boon

Principal Investigator's signature _____ Date _____

Phone: 6772 2379 Fax 6772 2346

Mailing Address: NUH/NUS Tissue Repository , National University Hospital, Department of Pathology, 5 Lower Kent Ridge Road, Singapore 119074

Email: medecb@nus.edu.sg;

III. CO-INVESTIGATORS

All co-investigators who have a responsibility for the consent process or direct data collection for this research should be listed below. Multiple copies of this form may be submitted as necessary. All co-investigators need not sign on the same form.

Name: Chan Tuck Wai
Position: PhD Student
Department: Centre for Biomedical Ethics
Institution: NUS

Email: dprctw@nus.edu.sg
Phone: 65161234
Fax: 67783430

Signature of Co-investigator

Date

Name: Dr Rajeev Singh
Position: Deputy Head
Department: NUH/NUS Tissue Repository
Institution: NUS

Email: rajeev_singh@nuhs.edu.sg
Phone: 67722310
Fax: 6772 2346

Signature of Co-investigator

Date

Name: Margaret Low Cheng Lian
Position: Principal Consent Nurse
Department: NUH/NUS Tissue Repository
Institution: NUS

Email: margaret_low@nuhs.edu.sg
Phone: 67722310
Fax: 6772 2346

Signature of Co-investigator

Date

Name: Lim Lay Pheng
Position: Consent Nurse
Department: NUH/NUS Tissue Repository
Institution: NUS

Email: lay_pheng_lim@nuhs.edu.sg
Phone: 67722310
Fax: 6772 2346

Signature of Co-investigator

Date

Name: Tee Suan Geok Felicia
Position: Consent Nurse
Department: NUH/NUS Tissue Repository
Institution: NUS

Email: suan_geok_tee@nuhs.edu.sg
Phone: 67722310
Fax: 6772 2346

Signature of Co-investigator

Date

IV. COMMENTS OF HEAD OF DEPARTMENT *	*(Please circle accordingly)*	
1. Significance: *Does the research address an important problem? Will the research affect concepts and methods that drive the field?*	**YES**	**NO**
2. Approach: *Is the conceptual framework adequately developed? Are the design, methods and analyses adequately developed and appropriate?*	**YES**	**NO**
3. Innovation: *Does the research challenge existing paradigms? Does it employ novel concepts, approaches and methods?*	**YES**	**NO**
4. Principal Investigator: *Is the Principal Investigator appropriately trained to conduct this research? Does the Principal Investigator have evidence of commitment (e.g. previous track record)?*	**YES**	**NO**
5. Environment: *Is the Principal Investigator's environment suited to perform the research? Is there an adequate patient/subject pool and are there adequate resources?*	**YES**	**NO**
6. Peer/ Scholarly/Scientific Review: *Has this project undergone a peer/ scholarly/ scientific review?*	**YES**	**NO**
7. Budget (*to be completed ONLY for funded projects*): *If this research is funded, are the projected costs appropriate (i.e. accurate)?*	**YES**	**NO**

Comments

_____

_____

_____

_____

_____

_____

I acknowledge that this research is in keeping with standards set by the Principal Investigator's department.

_____ _____

Signature of Head / Chief / Vice-Dean(Research)* Date

Name: Teh Ming

Title: Assoc Prof

Position: Head of Department of Pathology

*The Department Representative can be the Head / Chief / Research Head of the PI's Department.
If the PI or co-investigators is the Head or Chief of PI's Department, this section should be completed by the Vice-Dean (Research) or Dean of the Faculty.

**** IMPORTANT - Please complete Section V and VI, only if your existing research protocol submitted do not contain the relevant sections.**

V. ABSTRACT OF RESEARCH PROPOSAL

In no more than 300 words, describe concisely the specific aims, hypotheses, methodology and approach of the application, indicating where appropriate the application's importance to science, existing knowledge and applications. The abstract must be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. Please use lay terms. If this is not possible, the technical terms should be explained in simple language.

Background: Residual or leftover clinical tissues are valuable resources for biomedical research. There is on-going discussion about the methodological, legal, and ethical issues on the collection, storage and use of these tissues for future research. This research will conduct qualitative interviews with human subjects who had previously agreed or not agreed to donate of their leftover tissues to NUH/NUS Tissue Repository.

Objectives: The aim of this research is to understand potential or current donors' preferences, experiences and willingness to donate their leftover tissues.

Data collection & analysis: The qualitative interviews will be conducted by the research team after the subjects have made their decisions as to whether they wished to donate their leftover tissues for research. The qualitative interview results will be analysed thematically.

Implications for Practice: The results from this research can assist researchers and policy makers understand the experiences of donors and their attitudes and preferences on the collection, storage, distribution and use of their leftover tissue for research.

VI. PROTOCOL CHECKLIST

Organise details of the research protocol under the following headings (in no more than 7 pages).

1. Specific Aims:

1.1 State concisely and realistically what the research described in this application is intended to accomplish and/or what hypothesis is to be tested.

The aim of this research is to understand potential or current donors' preferences, experiences and willingness to donate their leftover tissues.

2. Introduction:

2.1 Briefly describe the background to the current proposal.

Residual or leftover clinical tissues are valuable resources for biomedical research. There is on-going discussion about the methodological, legal, and ethical issues on the collection, storage and use of these tissues for future research. This research will conduct qualitative interviews with subjects who have previously agreed or not agreed in the donation of their leftover tissues to NUH/NUS Tissue Repository.

2.2 State concisely the importance of the research described in this application.

Residual or leftover clinical tissues are valuable resources for biomedical research. The results from this research can assist researchers and policy makers understand the experiences of donors and their attitudes and preferences on the collection, storage, distribution and use of their leftover tissue for research.

2.3 Relevant references

1. Vermeulen E, Schmidt MK, Aaronson NK, Kuenen M, van der Valk P, Sietses C, et al. Opt-out plus, the donors' choice: preferences of cancer patients concerning information and consent regimen for future research with biological samples archived in the context of treatment. J Clin Pathol. 2009 Mar;62(3):275-8.
2. Oosterhuis JW, Coebergh JW, van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. Nat Rev Cancer. 2003 Jan;3(1):73-7.
3. Goodson ML, Vernon BG. A study of public opinion on the use of tissue samples from living subjects for clinical research. J Clin Pathol. 2004 Feb;57(2):135-8.
4. Wendler D. One-time general consent for research on biological samples: is it compatible with the Health Insurance Portability and Accountability Act. Archives of Internal Medicine. 2006;166(14):1449-52.

3. Preliminary Studies:

3.1 Provide an account of the Principal Investigator's preliminary/pilot studies (if any) pertinent to the application.

nil

4. Methodology:

4.1 Discuss in detail the design and procedures to be used to accomplish the specific aims of the research.

The qualitative interviews will be conducted by the research team after the potential donors (research subjects) had already decided whether or not they wanted to donate their leftover

tissues for research. The qualitative interview results will be analysed thematically.

Subjects' verbal informed consent will be sought before the interviews begin. Each subject participates in one 30-minute interview at a time convenient for them. The interviewers are the NUH/NUS tissue Consent Nurses working in NUH, which is where the interviews will take place. The interviews will be conducted only in the English Language and audio-recorded if the subjects consent to it.

4.2 Include details on sample size calculation and the means by which data will be analysed and interpreted.

Qualitative interview of 100 donors.

4.3 List all subject-related procedures. Please also describe the subject research visits (frequency and procedures involved).For studies with multiple visits, please attach visits schedule.

Subjects will participate in one qualitative interview each that lasts about 30 minutes. Subjects will not be re-contacted after the interviews.

4.4 What are the anticipated benefits and risks to human subjects participating in this research?

There are no direct benefits to subjects.

4.5 Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. Please provide information on how these limitations/ difficulties faced may be minimized or overcome.

Subjects may be reluctant to participate in the interviews. They do not need to answer any question that they feel uncomfortable with and can withdraw their participation at any time during the interview.

4.6 Will any part of the procedures be placed on audiotape, film/video, or other electronic media?
☒ *Yes* ☐ *No*

If Yes, what is the media? Explain how the recorded information will be used? How long will the tapes, etc, be retained and how will they be disposed of?

The interview will be recorded with the subjects' consent for the purpose of transcribing into field notes for analysis. The informed consent process will be recorded. No personal identifiable information will be recorded in the questionnaire and the recording. If subjects feel uncomfortable with the audio-recording, field notes will be taken instead.

5. Additional Information on Methodology:

5.1 If research involves creating new databases or making use of archived/ existing databases, please complete the sections below. In addition, if your research involves making use of archived/ existing databases, please furnish the necessary documentation, e.g., permissions to use those databases.

5.1.1 Where will the data be stored?

The database will be stored in a Password protected PC at the NUH/NUS tissues repository for seven years.

5.1.2 Who will have access to the data?

The research team will have access.

5.1.3 What will happen to the data after research completion?

The data collected, including transcripts and audio-recordings, will be stored in a Password protected PC at the NUH/NUS tissues repository for a maximum period of seven years after the last publication, afterwhich it will be destroyed.

5.1.4 Any other remarks?

6. Characteristics of Target subjects / Target Subject Data:

6.1 *What is the number of subjects to be enrolled? Give a breakdown by institution for multi-center studies (if applicable).*

Institution/Site of Recruitment	Total	Men	Women	Children
NUH	100	50	50	

6.2 *Lower Age Limit*: 21 *Upper Age Limit (if any):* 80

6.3 *Total number of subjects targeted for enrolment worldwide (for international studies):* nil

6.4 *Are there any subject recruitment restrictions based on race of the subject?* No.

6.5 *Inclusion criteria:* Any donor who have been asked to donate their leftover tissues. English speaking only.

6.6 *Exclusion criteria:* Any donors who are unable to speak English or understand the research.

6.7 *Are the subjects vulnerable or in a dependent relationship with the researchers?*

☐ *Yes* ☒ *No*

If Yes, please provide details.

7. Participant Information Sheet and Written Informed Consent Form:

7.1 *The PI is responsible for ensuring that all research subjects give informed consent before enrolling into the research. Please submit a copy of the Participant Information Sheet and Consent Form. (A sample of Participant Information Sheet and Consent Form is available on the IRB website at http://www.nus.edu.sg/irb/Guide.htm)*

7.2 *Summarise the consent procedure. Please specify how will informed consent be obtained and who will obtain consent.*

The NUH/NUS tissue consent nurse will routinely ask research subjects whether they wish to donate their leftover tissues before their scheduled surgery. After the nurses have noted their decisions on the donation, the subjects will then be invited to participate in this research. They will be visited by the research team after their surgery for the interview.

7.3 ***If waiver of consent is required**, please justify how your research meets the following criteria:*

*(The NUS-IRB may waive the requirement to obtain informed consent if the NUS-IRB finds that the research meets the following 4 criteria. Please note that all studies involving **deception** must apply for waiver of informed consent. Subjects in these studies **must** be debriefed.)*

YES A WAIVER OF DOCUMENTATION OF INFORMED CONSENT IS REQUESTED.

7.3.1 The research involves no more than minimal risk to the subjects.

This is a qualitative interview. Only demographic information, e.g., age, sex, etc, will be transferred from the initial Tissue Repository Consent Form to the researchers' records. Subjects' identities will be coded on the questionnaire and the Tissue Repository Consent Form.

7.3.2 The waiver or alteration will not adversely affect the rights and welfare of the subjects.

Yes, subjects can withdraw anytime they wish.

7.3.3 Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Yes.

7.3.4 The research could not practicably be carried out without the waiver or alteration.

Not applicable.

8. Recruitment Process:

8.1 *Explain the process of recruitment in detail. For example state how the list of potential research subjects will be obtained. Please submit a copy of any advertisements/posters that will be used.*

The NUH/NUS tissue consent nurse routinely asks research subjects whether they wish to donate their leftover tissues to the NUH/NUH Tissue Repository before any surgical procedures. After subjects have made their decision on the donation, they will be given a short explanation of this research study and invited to participate. If the subject agrees to participate in the interview, they will be visited by the research team after their surgery. The researcher will first call on the research subjects 2 to 3 days post surgery to check with the donor that s/he feels well enough to be interviewed. In any case, the NUH/NUS tissue Consent Nurse are usually make their rounds routinely in the wards and will visit the subjects in any case. No advertisements will be used.

If subject prefer to be interviewed during their clinical follow-up appointments or other visits, the research team will arrange with the subject for a suitable date for this interview, to the convenience of the research subjects.

9. Timelines:

9.1 What are the estimated start and end dates of the research?

Start Date: Aug 2011 *End Date:* Aug 2012

9.2 Indicate the duration of subject involvement in the research. Please also state the recruitment period.

About 30 minutes.

10. Financial Aspects/Conflicts of Interest:

10.1 Who will be responsible for research related costs? For sponsored research, list the costs that will be borne by the sponsor.

NIL

10.2 For industry sponsored research, please complete the following.

11.2.1 Name of the sponsor company?

NIL

11.2.2 Address of the sponsor?

NIL

11.2.3 Sponsor contact person?

NIL

11.2.4 Have any of the investigators received any financial support, sponsorship from the company supporting this research? ☐ *Yes* ☒ *No*

11.2.5 Do any of the investigators hold any ownership interest, e.g. stock options in this company? ☐ *Yes* ☒ *No*

11.2.6 Is the sponsor offering any incentive connected with subject recruitment or completion of research (e.g. finders' fee, recruitment bonuses etc) that will be paid to the research staff? ☐ *Yes* ☒ *No*

11.2.7 If you have answered 'yes' to Q 10.2.5, please elaborate.

NA

11.2.8 Any other remarks?

NIL

10.3 Will subjects receive financial payment/ incentive for participation? If yes, please elaborate.

No, subjects are not reimbursed for participating in the research.

VII. ATTACHMENT CHECKLIST:

Document	Attached?	Not Applicable?
Research Protocol (latest version)*+	☐	☒
Grant Application Form	☐	☒
Participant Information Sheet and Consent Form+	☒	☐
Investigator(s)' CV	☒	☐
Survey Form(s)/Questionnaire(s) / Interview Guide +	☒	☐
Data Collection Form+	☐	☒
Advertisement for Recruitment of Subjects+	☐	☒
Letter of Invitation to Subjects+	☐	☒
Relevant Publications	☐	☒
Subject Payment Details*	☐	☒
Financial Agreement	☐	☒

+Version number and date is required.
*If information is not included in sections V and VI of the application form.

1. **Project title :**
Patients' experiences towards the donation of their leftover tissues and the impact of these experiences on the type of consent given for secondary use.

2. **Principal Investigator and co-investigator(s), if any, with the contact number and organization.**

Dr Eng Chon Boon
Dept of Pathology, National University of Singapore
Phone: 6772 2379 Email: medecb@nus.edu.sg;
Address: NUH/NUS Tissue Repository, 5 Lower Kent Ridge Road, Singapore 119074

3. **What is the purpose of this research?**

The aim of this research is to understand potential or current donors' preferences, experiences and willingness to donate their leftover tissues.

You are invited to participate in a research. This information sheet provides you with information about the research. The Principal Investigator or his/her representative will also describe this research to you and answer all of your questions. Read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

4. **Who can participate in the research? What is the expected duration of my participation? What is the duration of this research?**

Any English speaking potential or current donor who has been asked to donate their leftover tissue can participate in this interview research.

The NUH/NUS tissue consent nurse will routinely ask research subjects whether they wish to donate their leftover tissues before their scheduled surgery. After the nurses have noted their decisions on the donation, the subjects will then be invited to participate in this research. They will be visited by the research team after their surgery for the interview.

Subjects' verbal informed consent will be sought before the interviews begin. Each subject participates in one 30-minute interview at a time convenient for them. The interviewers are the NUH/NUS tissue Consent Nurses working in NUH, which is where the interviews will take place. The interviews will be conducted only in the English Language and audio-recorded if the subjects consent to it.

5. **What is the approximate number of participants involved?**

Approximately 100 research subjects will be involved in this research.

6. What will be done if I take part in this research?

The qualitative interviews will be conducted by the research team after the potential or current donors (research subjects) had already decided whether or not they wanted to donate their leftover tissues for research. The qualitative interview results will be analysed thematically.

7. How will my privacy and the confidentiality of my research records be protected?

This is a 30 minutes qualitative interview. We will not collect any personal information from you. Only demographic information, e.g., age, sex, etc, will be transferred from the initial Tissue Repository Consent Form to the researchers' records. Subjects' identities will be coded on the questionnaire and the Tissue Repository Consent Form.

The data collected, including transcripts and audio-recordings, will be stored in a Password protected PC at the NUH/NUS tissues repository for a maximum period of seven years after the last publication, afterwhich it will be destroyed.

8. What are the possible discomforts and risks for participants?

No risks or discomforts are expected for participants participating in this research.

9. What is the compensation for any injury?

This is an interview. No injury is expected from participating in this research. Hence, there will be no compensation awarded.

10. Will there be reimbursement for participation?

Participants are not reimbursed for participating in this research.

11. What are the possible benefits to me and to others?

There is no direct benefit to you by participating in this research. The results from this research can assist researchers and policy makers understand the experiences of potential or current donors and their attitudes and preferences on the collection, storage, distribution and use of their leftover tissue for research.

12. Can I refuse to participate in this research?

Yes, you can. Your decision to participate in this research is voluntary and completely up to you. You can also withdraw from the research at any time without giving any reasons, by informing the principal investigator and all your data collected will be discarded.

13. Whom should I call if I have any questions or problems?

Please contact the Principal Investigator, Dr Eng Chon Boon at **telephone 65-** 6772 2379 **and email** medecb@nus.edu.sg for all research-related matters and in the event of research-related injuries.

For an independent opinion regarding the research and the rights of research participants, you may contact a staff member of the National University of Singapore

Institutional Review Board (Attn: Ms Tan Hui Cheng, at telephone 65- 6516 7359 or email at irb@nus.edu.sg).

Tissue Consent - Interview Guide

Code Number:

Highest Educational Level:

1. University/Post Graduate
2. Diploma
3. A Level
4. O Level
5. Others _____

Reason for donation

1. Can you tell me why you have or have not consented or given permission to the donation of your tissues?
   Do you know of any benefits and risk in this donation and the uses of your tissues? *(Prompt: Example of risk and Benefits)*
   What would influence your decision?
   Do you think you would have given consent if it was a different organ? For example, the brain versus the skin? Why?

Types of consent models

2. Do you remember that you have earlier agreed to donate your leftover tissues in the surgical consent form?
   (Prompt: show surgical consent)
   Do you think that is sufficient information or do you think you need more detailed information on such donation? Why?
   (Prompt: show NUHS TR detailed consent)

Pre or Post surgery Consent

3. When is the best time for someone to approach you to get your consent or permission to donate the leftover tissue?
   Prompts:
   I. Before admission at the clinic when told (ask why or why not)
   II. On admission (ask why or why not)
   III. After the surgery procedure (ask why or why not)
   IV. After the tissue has been fully analyzed (ask why or why not)

   Who would be the most appropriate person to ask for this consent or permission? Why?
   (Prompts: The doctors, the nurse or the researchers?)

Withdrawal and Rights

4. If you change your mind to this donation, what do you think would be the best way to do this? Under what circumstances would you want to change your decision whether to donate your tissues or not?

Medical records and privacy

5. Do you object, if the researchers, who are carrying out research on your donated specimen, know about your name and IC number etc., and medical records for their purpose of the research if you knew they would keep such information confidential?
   (Prompts: If they object, why. Or If they don't object, why)

Governance, safeguard and controls

6. Can you tell me who you think should monitor the use of your leftover tissues and the consent? Are you aware of any safeguards and controls available for your tissues, and what governance would you expect?
   (Prompts: IRB, Government, Institution, Doctors, Researcher. And explore why/why not?)

Access and uses of tissues

7. Do you have any objection if the following groups of researchers have access your tissues for their research? (e.g. How do you feel about the commercial use or _____ of donated left over tissue?)

   - Hospital researchers, University scientists, and students (and why)
   - Government funded agency (and why)
   - Commercial laboratories and Drugs companies (and why)
   - Foreign researchers and foreign institutions (and why)

Tissue Consent - Interview Guide

Code Number:

Highest Educational Level:

1. University/Post Graduate
2. Diploma
3. A Level
4. O Level
5. Others _____

Reason for donation

1. Can you tell me why you have or have not consented or given permission to the donation of your tissues?

Do you know of any benefits and risk in this donation and the uses of your tissues? *(Prompt: Example of risk and Benefits)*

What would influence your decision?

Do you think you would have given consent if it was a different organ? For example, the brain versus the skin? Why?

Types of consent models

2. Do you remember that you have earlier agreed to donate your leftover tissues in the surgical consent form? *(Prompt: show surgical consent)*

Do you think that is sufficient information or do you think you need more detailed information on such donation? Why? *(Prompt: show NUHS TR detailed consent)*

Pre or Post surgery Consent

3. When is the best time for someone to approach you to get your consent or permission to donate the leftover tissue?

I. Before admission at the clinic when told (ask why or why not)
II. On admission (ask why or why not)
III. After the surgery procedure (ask why or why not)
IV. After the tissue has been fully analyzed (ask why or why not)

Who would be the most appropriate person to ask for this consent or permission? Why?*(Prompts: The doctors, the nurse or the researchers?)*

Withdrawal and Rights

4. If you change your mind to this donation, what do you think would be the best way to do this? Under what circumstances would you want to change your decision whether to donate your tissues or not?

Medical records and privacy

5. Do you object, if the researchers, who are carrying out research on your donated specimen, know about your name and IC number etc., and medical records for their purpose of the research if you knew they would keep such information confidential? *(Prompts: If they object, why. Or If they don't object, why)*

Governance, safeguard and controls

6. Can you tell me who you think should monitor the use of your leftover tissues and the consent? Are you aware of any safeguards and controls available for your tissues, and what governance would you expect? *(Prompts: IRB, Government, Institution, Doctors, Researcher. And explore why/why not?)*

Access and uses of tissues

7. Do you have any objection if the following groups of researchers have access your tissues for their research? (e.g. How do you feel about the commercial use or _____ of donated left over tissue?)

- Hospital researchers, University scientists, and students (and why)
- Government funded agency (and why)
- Commercial laboratories and Drugs companies (and why)
- Foreign researchers and foreign institutions (and why)

Appendix 6: Statistical Analysis

Research Ethics and Consent on the Collection and Use of Human Biological Materials: A Singapore Perspective

gender * response Crosstabulation

			response		
			No	Yes	Total
gender	Female	Count	28389	67020	95409
		% within gender	29.8%	70.2%	100.0%
	Male	Count	15819	56097	71916
		% within gender	22.0%	78.0%	100.0%
Total		Count	44208	123117	167325
		% within gender	26.4%	73.6%	100.0%

The odds of males in willing to donate the human biological materials is significantly higher compared with females (OR = 1.50, 95% CI = 1.47 to 1.54, $p < 0.001$).

race * response Crosstabulation

			response		
			No	Yes	Total
race	Chinese	Count	29070	86207	115277
		% within race	25.2%	74.8%	100.0%
	Malay	Count	5633	12831	18464
		% within race	30.5%	69.5%	100.0%
	Indian	Count	4362	9570	13932
		% within race	31.3%	68.7%	100.0%
	Eurasian	Count	113	309	422
		% within race	26.8%	73.2%	100.0%
	Sikh	Count	1287	3770	5057
		% within race	25.4%	74.6%	100.0%
	Other Races	Count	3744	10433	14177
		% within race	26.4%	73.6%	100.0%
Total		Count	44209	123120	167329
		% within race	26.4%	73.6%	100.0%

$p < 0.001$

a) Chinese compared with Malay: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with Malay (OR = 1.30, 95% CI 1.25 to 1.36, $p < 0.001$).

b) Chinese compared with Indian: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with Indian (OR = 1.35, 95% CI 1.29 to 1.42, $p < 0.001$).

c) Chinese compared with Eurasian: OR = 1.08, 95% CI 0.82 to 1.44, $p = 1$

d) Chinese compared with Sikh: OR = 1.01, 95% CI 0.93 to 1.10, $p = 1$

e) Chinese compared with Other Races: The odds of Chinese in willing to donate the human biological materials is significantly higher compared with other races (OR = 1.06, 95% CI 1.01 to 1.12, $p = 0.011$).

religion * response Crosstabulation

			response		
			No	Yes	Total
religion	Buddhism	Count	9907	28827	38734
		% within religion	25.6%	74.4%	100.0%
	Christianity	Count	3508	9937	13445
		% within religion	26.1%	73.9%	100.0%
	Hinduism	Count	2023	4497	6520
		% within religion	31.0%	69.0%	100.0%
	Islam	Count	5551	12782	18333
		% within religion	30.3%	69.7%	100.0%
	Roman Catholicism	Count	68	189	257
		% within religion	26.5%	73.5%	100.0%
	Sikhism	Count	191	446	637
		% within religion	30.0%	70.0%	100.0%
	Non-Denomination	Count	2860	8790	11650
		% within religion	24.5%	75.5%	100.0%
	Other Religion	Count	20101	57652	77753
		% within religion	25.9%	74.1%	100.0%
Total		Count	44209	123120	167329
		% within religion	26.4%	73.6%	100.0%

$p < 0.001$

a) Buddhism compared with Christianity: OR = 1.03, 95% CI 0.97 to 1.09, p = 1

b) Buddhism compared with Hinduism: The odds of Buddhism in willing to donate the human biological materials is significantly higher compared with Hinduism (OR = 1.31, 95% CI 1.21 to 1.42, $p < 0.001$).

c) Buddhism compared with Islam: The odds of Buddhism in willing to donate the human biological materials is significantly higher compared with Islam (OR = 1.26, 95% CI 1.20 to 1.33, $p < 0.001$).

d) Buddhism compared with Roman Catholicism: OR = 1.05, 95% CI 0.71 to 1.53, p = 1

e) Buddhism compared with Sikhism: OR = 1.25, 95% CI 0.98 to 1.58, p = 0.082

f) Buddhism compared with Non-Denomination: OR = 0.95, 95% CI 0.89 to 1.01, p = 0.178

g) Buddhism compared with Other Religion: OR = 1.01, 95% CI 0.98 to 1.05, p = 1

age group * response Crosstabulation

			response		
			No	Yes	Total
age group	0 to 49	Count	19986	48050	68036
		% within age group	29.4%	70.6%	100.0%
	50 and above 50	Count	24223	75070	99293
		% within age group	24.4%	75.6%	100.0%
Total		Count	44209	123120	167329
		% within age group	26.4%	73.6%	100.0%

The odds of patients who were 50 and above 50 years old in willingness to donate the human biological materials were significantly higher compared with those who were below 50 years old (OR = 1.29, 95% CI = 1.26 to 1.32, $p < 0.001$).

fee * response Crosstabulation

			response		
			No	Yes	Total
fee	Private	Count	14033	44378	58411
		% within fee	24.0%	76.0%	100.0%
	Subsidised	Count	30150	78685	108835
		% within fee	27.7%	72.3%	100.0%
	Other Fee Schedule	Count	26	57	83
		% within fee	31.3%	68.7%	100.0%
Total		Count	44209	123120	167329
		% within fee	26.4%	73.6%	100.0%

$p < 0.001$

a) Private compared with Subsidised: The odds of those who had private fee schedule in willingness to donate the human biological materials were significantly higher compared with those who had subsidised fee schedule (OR = 1.21, 95% CI 1.18 to 1.24, $p < 0.001$).

b) Private compared with Other Fee Schedule: OR = 1.44, 95% CI 0.84 to 2.45, $p = 0.244$

Results

Rate of increase per year

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	-3450.700	1232.985		-2.799	.027	-6366.246	-535.154
	year	1.757	.615	.734	2.858	.024	.303	3.210

a. Dependent Variable: percent

rate of increase per year = 1.76% (95% CI 0.30% to 3.21%), p = 0.024

Slide 31. Comparison by gender

gender * response Crosstabulation

			response		
			yes	no	Total
gender	female	Count	60409	25038	85447
		% within gender	70.7%	29.3%	100.0%
	male	Count	49020	13757	62777
		% within gender	78.1%	21.9%	100.0%
Total		Count	109429	38795	148224
		% within gender	73.8%	26.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1022.343[b]	1	.000		
Continuity Correction[a]	1021.960	1	.000		
Likelihood Ratio	1034.799	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	1022.336	1	.000		
N of Valid Cases	148224				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 16430.77.

	total	yes	%	lower 95% CI	upper 95% CI
female	85447	60409	70.70	70.39	71.00
male	62777	49020	78.09	77.76	78.41

Comparison by race

Combining Eurasian, Japanese & others

race * response Crosstabulation

			response		
			yes	no	Total
race	chinese	Count	77005	25673	102678
		% within race	75.0%	25.0%	100.0%
	malay	Count	11535	4983	16518
		% within race	69.8%	30.2%	100.0%
Total		Count	88540	30656	119196
		% within race	74.3%	25.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	198.591[b]	1	.000		
Continuity Correction[a]	198.321	1	.000		
Likelihood Ratio	192.915	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	198.590	1	.000		
N of Valid Cases	119196				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 4248.26.

race * response Crosstabulation

			response		
			yes	no	Total
race	chinese	Count	77005	25673	102678
		% within race	75.0%	25.0%	100.0%
	indian	Count	8530	3807	12337
		% within race	69.1%	30.9%	100.0%
Total		Count	85535	29480	115015
		% within race	74.4%	25.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	198.071[b]	1	.000		
Continuity Correction[a]	197.764	1	.000		
Likelihood Ratio	191.162	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	198.070	1	.000		
N of Valid Cases	115015				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3162.15.

race * response Crosstabulation

			response		
			yes	no	Total
race	chinese	Count	77005	25673	102678
		% within race	75.0%	25.0%	100.0%
	sikh	Count	3734	1271	5005
		% within race	74.6%	25.4%	100.0%
Total		Count	80739	26944	107683
		% within race	75.0%	25.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.389[b]	1	.533		
Continuity Correction[a]	.369	1	.544		
Likelihood Ratio	.388	1	.533		
Fisher's Exact Test				.537	.272
Linear-by-Linear Association	.389	1	.533		
N of Valid Cases	107683				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1252.33.

race * response Crosstabulation

			response		
			yes	no	Total
race	chinese	Count	77005	25673	102678
		% within race	75.0%	25.0%	100.0%
	others	Count	8628	3062	11690
		% within race	73.8%	26.2%	100.0%
Total		Count	85633	28735	114368
		% within race	74.9%	25.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.899[b]	1	.005		
Continuity Correction[a]	7.836	1	.005		
Likelihood Ratio	7.835	1	.005		
Fisher's Exact Test				.005	.003
Linear-by-Linear Association	7.899	1	.005		
N of Valid Cases	114368				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 2937.12.

race * response Crosstabulation

			response		
			yes	no	Total
race	malay	Count	11535	4983	16518
		% within race	69.8%	30.2%	100.0%
	indian	Count	8530	3807	12337
		% within race	69.1%	30.9%	100.0%
Total		Count	20065	8790	28855
		% within race	69.5%	30.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.593[b]	1	.207		
Continuity Correction[a]	1.561	1	.212		
Likelihood Ratio	1.592	1	.207		
Fisher's Exact Test				.210	.106
Linear-by-Linear Association	1.593	1	.207		
N of Valid Cases	28855				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3758.18.

race * response Crosstabulation

			response		
			yes	no	Total
race	malay	Count	11535	4983	16518
		% within race	69.8%	30.2%	100.0%
	sikh	Count	3734	1271	5005
		% within race	74.6%	25.4%	100.0%
Total		Count	15269	6254	21523
		% within race	70.9%	29.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	42.441[b]	1	.000		
Continuity Correction[a]	42.210	1	.000		
Likelihood Ratio	43.247	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	42.439	1	.000		
N of Valid Cases	21523				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1454.32.

race * response Crosstabulation

			response		
			yes	no	Total
race	malay	Count	11535	4983	16518
		% within race	69.8%	30.2%	100.0%
	others	Count	8628	3062	11690
		% within race	73.8%	26.2%	100.0%
Total		Count	20163	8045	28208
		% within race	71.5%	28.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	53.023[b]	1	.000		
Continuity Correction[a]	52.829	1	.000		
Likelihood Ratio	53.313	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	53.021	1	.000		
N of Valid Cases	28208				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3334.02.

race * response Crosstabulation

			response		
			yes	no	Total
race	indian	Count	8530	3807	12337
		% within race	69.1%	30.9%	100.0%
	sikh	Count	3734	1271	5005
		% within race	74.6%	25.4%	100.0%
Total		Count	12264	5078	17342
		% within race	70.7%	29.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	51.331[b]	1	.000		
Continuity Correction[a]	51.067	1	.000		
Likelihood Ratio	52.214	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	51.328	1	.000		
N of Valid Cases	17342				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1465.54.

race * response Crosstabulation

			response		
			yes	no	Total
race	indian	Count	8530	3807	12337
		% within race	69.1%	30.9%	100.0%
	others	Count	8628	3062	11690
		% within race	73.8%	26.2%	100.0%
Total		Count	17158	6869	24027
		% within race	71.4%	28.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	63.985[b]	1	.000		
Continuity Correction[a]	63.757	1	.000		
Likelihood Ratio	64.096	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	63.982	1	.000		
N of Valid Cases	24027				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3342.02.

race * response Crosstabulation

			response		
			yes	no	Total
race	sikh	Count	3734	1271	5005
		% within race	74.6%	25.4%	100.0%
	others	Count	8628	3062	11690
		% within race	73.8%	26.2%	100.0%
Total		Count	12362	4333	16695
		% within race	74.0%	26.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.163[b]	1	.281		
Continuity Correction[a]	1.122	1	.289		
Likelihood Ratio	1.167	1	.280		
Fisher's Exact Test				.289	.145
Linear-by-Linear Association	1.163	1	.281		
N of Valid Cases	16695				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1298.99.

	total	yes	%	lower 95% CI	upper 95% CI
chinese	102678	77005	75.00	74.73	75.26
malay	16518	11535	69.83	69.13	70.53
indian	12337	8530	69.14	68.33	69.96
sikh	5005	3734	74.61	73.40	75.81
others	11690	8628	73.81	73.01	74.60

Comparison by religion

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	47719	100.0%	0	.0%	47719	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
Total		Count	35545	12174	47719
		% within religion	74.5%	25.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.618[b]	1	.203		
Continuity Correction[a]	1.588	1	.208		
Likelihood Ratio	1.614	1	.204		
Fisher's Exact Test				.206	.104
Linear-by-Linear Association	1.618	1	.203		
N of Valid Cases	47719				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3101.22.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	41472	100.0%	0	.0%	41472	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
Total		Count	30633	10839	41472
		% within religion	73.9%	26.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	77.109[b]	1	.000		
Continuity Correction[a]	76.828	1	.000		
Likelihood Ratio	74.892	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	77.107	1	.000		
N of Valid Cases	41472				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1544.36.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	52135	100.0%	0	.0%	52135	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
Total		Count	38170	13965	52135
		% within religion	73.2%	26.8%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	115.486[b]	1	.000		
Continuity Correction[a]	115.258	1	.000		
Likelihood Ratio	114.137	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	115.484	1	.000		
N of Valid Cases	52135				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 4439.01.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	35820	100.0%	0	.0%	35820	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
Total		Count	26732	9088	35820
		% within religion	74.6%	25.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.162[b]	1	.688		
Continuity Correction[a]	.109	1	.741		
Likelihood Ratio	.160	1	.689		
Fisher's Exact Test				.671	.371
Linear-by-Linear Association	.162	1	.688		
N of Valid Cases	35820				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 65.20.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	36142	100.0%	0	.0%	36142	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
Total		Count	26950	9192	36142
		% within religion	74.6%	25.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.666[b]	1	.017		
Continuity Correction[a]	5.439	1	.020		
Likelihood Ratio	5.479	1	.019		
Fisher's Exact Test				.018	.010
Linear-by-Linear Association	5.666	1	.017		
N of Valid Cases	36142				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 147.26.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	46186	100.0%	0	.0%	46186	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	34577	11609	46186
		% within religion	74.9%	25.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.270[b]	1	.039		
Continuity Correction[a]	4.223	1	.040		
Likelihood Ratio	4.296	1	.038		
Fisher's Exact Test				.039	.020
Linear-by-Linear Association	4.276	1	.039		
N of Valid Cases	46186				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 2670.13.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	102132	100.0%	0	.0%	102132	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	buddhism	Count	26543	9020	35563
		% within religion	74.6%	25.4%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	76083	26049	102132
		% within religion	74.5%	25.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.577[b]	1	.447		
Continuity Correction[a]	.566	1	.452		
Likelihood Ratio	.578	1	.447		
Fisher's Exact Test				.451	.226
Linear-by-Linear Association	.577	1	.447		
N of Valid Cases	102132				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 9070.42.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	18065	100.0%	0	.0%	18065	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
Total		Count	13092	4973	18065
		% within religion	72.5%	27.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	46.640[b]	1	.000		
Continuity Correction[a]	46.398	1	.000		
Likelihood Ratio	46.114	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	46.638	1	.000		
N of Valid Cases	18065				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1626.65.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	28728	100.0%	0	.0%	28728	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
Total		Count	20629	8099	28728
		% within religion	71.8%	28.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	52.509[b]	1	.000		
Continuity Correction[a]	52.317	1	.000		
Likelihood Ratio	52.769	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	52.507	1	.000		
N of Valid Cases	28728				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3427.02.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	12413	100.0%	0	.0%	12413	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
Total		Count	9191	3222	12413
		% within religion	74.0%	26.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.034[b]	1	.853		
Continuity Correction[a]	.013	1	.909		
Likelihood Ratio	.034	1	.853		
Fisher's Exact Test				.834	.455
Linear-by-Linear Association	.034	1	.853		
N of Valid Cases	12413				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 66.71.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	12735	100.0%	0	.0%	12735	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
Total		Count	9409	3326	12735
		% within religion	73.9%	26.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.050[b]	1	.044		
Continuity Correction[a]	3.858	1	.050		
Likelihood Ratio	3.945	1	.047		
Fisher's Exact Test				.046	.025
Linear-by-Linear Association	4.050	1	.044		
N of Valid Cases	12735				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 151.22.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	22779	100.0%	0	.0%	22779	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	17036	5743	22779
		% within religion	74.8%	25.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.452[b]	1	.006		
Continuity Correction[a]	7.369	1	.007		
Likelihood Ratio	7.460	1	.006		
Fisher's Exact Test				.006	.003
Linear-by-Linear Association	7.452	1	.006		
N of Valid Cases	22779				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 2678.25.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	78725	100.0%	0	.0%	78725	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	christianity	Count	9002	3154	12156
		% within religion	74.1%	25.9%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	58542	20183	78725
		% within religion	74.4%	25.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.719[b]	1	.397		
Continuity Correction[a]	.700	1	.403		
Likelihood Ratio	.717	1	.397		
Fisher's Exact Test				.397	.201
Linear-by-Linear Association	.719	1	.397		
N of Valid Cases	78725				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 3116.48.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	22481	100.0%	0	.0%	22481	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
Total		Count	15717	6764	22481
		% within religion	69.9%	30.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.846[b]	1	.174		
Continuity Correction[a]	1.801	1	.180		
Likelihood Ratio	1.840	1	.175		
Fisher's Exact Test				.175	.090
Linear-by-Linear Association	1.845	1	.174		
N of Valid Cases	22481				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1777.88.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	6166	100.0%	0	.0%	6166	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
Total		Count	4279	1887	6166
		% within religion	69.4%	30.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.169[b]	1	.141		
Continuity Correction[a]	1.970	1	.160		
Likelihood Ratio	2.226	1	.136		
Fisher's Exact Test				.147	.079
Linear-by-Linear Association	2.168	1	.141		
N of Valid Cases	6166				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 78.65.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	6488	100.0%	0	.0%	6488	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
Total		Count	4497	1991	6488
		% within religion	69.3%	30.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.288[b]	1	.592		
Continuity Correction[a]	.239	1	.625		
Likelihood Ratio	.289	1	.591		
Fisher's Exact Test				.604	.314
Linear-by-Linear Association	.288	1	.592		
N of Valid Cases	6488				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 177.68.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	16532	100.0%	0	.0%	16532	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	12124	4408	16532
		% within religion	73.3%	26.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	79.831[b]	1	.000		
Continuity Correction[a]	79.504	1	.000		
Likelihood Ratio	78.843	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	79.826	1	.000		
N of Valid Cases	16532				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1575.54.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	72478	100.0%	0	.0%	72478	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	hinduism	Count	4090	1819	5909
		% within religion	69.2%	30.8%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	53630	18848	72478
		% within religion	74.0%	26.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	76.341[b]	1	.000		
Continuity Correction[a]	76.071	1	.000		
Likelihood Ratio	73.854	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	76.340	1	.000		
N of Valid Cases	72478				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1536.64.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	16829	100.0%	0	.0%	16829	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
Total		Count	11816	5013	16829
		% within religion	70.2%	29.8%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.383[b]	1	.240		
Continuity Correction[a]	1.226	1	.268		
Likelihood Ratio	1.414	1	.234		
Fisher's Exact Test				.272	.134
Linear-by-Linear Association	1.383	1	.240		
N of Valid Cases	16829				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 76.55.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	17151	100.0%	0	.0%	17151	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
Total		Count	12034	5117	17151
		% within religion	70.2%	29.8%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.005[b]	1	.945		
Continuity Correction[a]	.001	1	.982		
Likelihood Ratio	.005	1	.945		
Fisher's Exact Test				.961	.491
Linear-by-Linear Association	.005	1	.945		
N of Valid Cases	17151				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 172.74.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	27195	100.0%	0	.0%	27195	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	19661	7534	27195
		% within religion	72.3%	27.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	96.630[b]	1	.000		
Continuity Correction[a]	96.357	1	.000		
Likelihood Ratio	97.631	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	96.626	1	.000		
N of Valid Cases	27195				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 2942.96.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	83141	100.0%	0	.0%	83141	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	islam	Count	11627	4945	16572
		% within religion	70.2%	29.8%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	61167	21974	83141
		% within religion	73.6%	26.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	123.752[b]	1	.000		
Continuity Correction[a]	123.533	1	.000		
Likelihood Ratio	121.392	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	123.750	1	.000		
N of Valid Cases	83141				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 4379.95.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	836	100.0%	0	.0%	836	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
Total		Count	596	240	836
		% within religion	71.3%	28.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.917[b]	1	.338		
Continuity Correction[a]	.765	1	.382		
Likelihood Ratio	.926	1	.336		
Fisher's Exact Test				.363	.191
Linear-by-Linear Association	.916	1	.339		
N of Valid Cases	836				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 73.78.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	10880	100.0%	0	.0%	10880	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	8223	2657	10880
		% within religion	75.6%	24.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.592[b]	1	.441		
Continuity Correction[a]	.485	1	.486		
Likelihood Ratio	.582	1	.446		
Fisher's Exact Test				.464	.243
Linear-by-Linear Association	.592	1	.442		
N of Valid Cases	10880				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 62.76.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	66826	100.0%	0	.0%	66826	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	roman catholicism	Count	189	68	257
		% within religion	73.5%	26.5%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	49729	17097	66826
		% within religion	74.4%	25.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.104[b]	1	.747		
Continuity Correction[a]	.063	1	.802		
Likelihood Ratio	.103	1	.748		
Fisher's Exact Test				.779	.401
Linear-by-Linear Association	.104	1	.747		
N of Valid Cases	66826				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 65.75.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	11202	100.0%	0	.0%	11202	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
Total		Count	8441	2761	11202
		% within religion	75.4%	24.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.414[b]	1	.004		
Continuity Correction[a]	8.129	1	.004		
Likelihood Ratio	8.087	1	.004		
Fisher's Exact Test				.004	.002
Linear-by-Linear Association	8.413	1	.004		
N of Valid Cases	11202				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 142.71.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	67148	100.0%	0	.0%	67148	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	sikhism	Count	407	172	579
		% within religion	70.3%	29.7%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	49947	17201	67148
		% within religion	74.4%	25.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.127[b]	1	.024		
Continuity Correction[a]	4.913	1	.027		
Likelihood Ratio	4.965	1	.026		
Fisher's Exact Test				.024	.013
Linear-by-Linear Association	5.127	1	.024		
N of Valid Cases	67148				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 148.32.

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
religion * response	77192	100.0%	0	.0%	77192	100.0%

religion * response Crosstabulation

			response		
			yes	no	Total
religion	non denominational	Count	8034	2589	10623
		% within religion	75.6%	24.4%	100.0%
	others	Count	49540	17029	66569
		% within religion	74.4%	25.6%	100.0%
Total		Count	57574	19618	77192
		% within religion	74.6%	25.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.068[b]	1	.008		
Continuity Correction[a]	7.004	1	.008		
Likelihood Ratio	7.123	1	.008		
Fisher's Exact Test				.008	.004
Linear-by-Linear Association	7.068	1	.008		
N of Valid Cases	77192				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 2699.79.

	total	yes	%	lower 95% CI	upper 95% CI
BUDDHISM	35563	26543	74.64	74.18	75.09
CHRISTIANITY	12156	9002	74.05	73.27	74.83
HINDUISM	5909	4090	69.22	68.04	70.39
ISLAM	16572	11627	70.16	69.46	70.86
ROMAN CATHOLICISM	257	189	73.54	68.15	78.93
SIKHISM	579	407	70.29	66.57	74.02
NON-DENOMINATION	10623	8034	75.63	74.81	76.44
OTHERS	66569	49540	74.42	74.09	74.75

Slide 34. age trend (ignoring the > 100 age group)

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	70.576	1.468		48.078	.000	67.191	73.961
	age_group	.503	.237	.601	2.127	.066	-.042	1.049

a. Dependent Variable: percent

trend = 0.5% (95% -0.4% to 1.05%),p = 0.066

slide 35. comparison by fee

fee * response Crosstabulation

			response		
			yes	no	Total
fee	private	Count	39086	12339	51425
		% within fee	76.0%	24.0%	100.0%
	subsidised	Count	70289	26431	96720
		% within fee	72.7%	27.3%	100.0%
	others	Count	57	26	83
		% within fee	68.7%	31.3%	100.0%
Total		Count	109432	38796	148228
		% within fee	73.8%	26.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	194.181[a]	2	.000
Likelihood Ratio	195.903	2	.000
Linear-by-Linear Association	194.161	1	.000
N of Valid Cases	148228		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 21.72.

fee * response Crosstabulation

			response		
			yes	no	Total
fee	private	Count	39086	12339	51425
		% within fee	76.0%	24.0%	100.0%
	subsidised	Count	70289	26431	96720
		% within fee	72.7%	27.3%	100.0%
Total		Count	109375	38770	148145
		% within fee	73.8%	26.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	193.054[b]	1	.000		
Continuity Correction[a]	192.882	1	.000		
Likelihood Ratio	194.806	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	193.053	1	.000		
N of Valid Cases	148145				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 13458.08.

fee * response Crosstabulation

			response		
			yes	no	Total
fee	private	Count	39086	12339	51425
		% within fee	76.0%	24.0%	100.0%
	others	Count	57	26	83
		% within fee	68.7%	31.3%	100.0%
Total		Count	39143	12365	51508
		% within fee	76.0%	24.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.441[b]	1	.118		
Continuity Correction[a]	2.056	1	.152		
Likelihood Ratio	2.297	1	.130		
Fisher's Exact Test				.120	.076
Linear-by-Linear Association	2.441	1	.118		
N of Valid Cases	51508				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 19.92.

fee * response Crosstabulation

			response		
			yes	no	Total
fee	subsidised	Count	70289	26431	96720
		% within fee	72.7%	27.3%	100.0%
	others	Count	57	26	83
		% within fee	68.7%	31.3%	100.0%
Total		Count	70346	26457	96803
		% within fee	72.7%	27.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.667[b]	1	.414		
Continuity Correction[a]	.481	1	.488		
Likelihood Ratio	.649	1	.421		
Fisher's Exact Test				.462	.244
Linear-by-Linear Association	.667	1	.414		
N of Valid Cases	96803				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 22.68.

	total	yes	%	lower 95% CI	upper 95% CI
Private	51425	39086	76.01	75.64	76.37
Subsidised	96720	70289	72.67	72.39	72.95
Others	83	57	68.67	58.70	78.65