Full Title of the Study:

UK Brain Archive Information Network

Short Study Title / Acronym:

BRAIN UK

Protocol Version Number and Date

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Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator

Signature: 

Name: (please print): Prof. J.A.R. Nicoll
Date: 01/04/2019

This protocol has regard for the HRA guidance and order of content

Key Study Contacts

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Key Study Contributors	Dr. David Hilton, BRAIN UK Deputy Director, Contact details as above. Tabitha Bloom BRAIN UK Data and Governance Officer Contact details as per Study Co-ordinator

Study Summary

Brain tissue can be difficult for researchers to access; yet UK National Health Service (NHS) diagnostic neuropathology archives contain a wealth of tissue. BRAIN UK was set up to facilitate access to tissue already existing in order to reduce time and administrative burden to researchers. This low cost solution has been especially successful for studies that require large numbers of rare cases; with some studies needing to utilize tissue collected over 30 year time spans.

Study Title	UK Brain Archive Information Network
Internal ref. no. (or short title)	BRAIN UK
Study Design	Virtual Research Tissue Bank
Study Participants	Participants with central nervous system (CNS) tissue stored in a UK Neuropathology Archive participating in the BRAIN UK study. These archives typically extend back 30 years or more.
Planned Size of Sample (if applicable)	Currently 26(/27) NHS Neuropathology Centres take part in the BRAIN UK study. There are currently around 500,000 neuropathology specimens in these archives, with approximately 18,500 accrued per year.
Planned Study Period	Ongoing
Research Question/Aim(s)	To facilitate the provision of neuropathologically characterized, human, central nervous system tissue from neuropathology archives for high quality research projects in the UK and internationally.

Funding And Support In Kind

Funders	**Financial And Non-Financial Support Given**
Medical Research Council *Contact details as per the Key Study Contacts*	Financial Support
Brain Tumour Research *Contact details as per the Key Study Contacts*	Financial Support
British Neuropathological Society Contact*:* BNS President Colin Smith Department of Pathology Alexander Donald Building Western General Hospital Crewe Road Edinburgh EH4 2XU	Non-Financial Support

Role of Study Sponsor and Funder

Study Sponsor

As an employer of researchers and educational institution for student research, the University can act as Sponsor for staff and student research subject to a successful application through the Research Governance Office. When agreeing to act as Sponsor the University takes ultimate responsibility for the research, but this is conditional on the researchers fulfilling their obligations. All researchers are expected to adhere to University Ethics Policy[1].

By acting as a sponsor, the University of Southampton has agreed to take ultimate responsibility for this project but does not control any of the following: study design, conduct, data analysis and interpretation, manuscript writing, or dissemination of results.

Study Funders

Medical Research Council (MRC)
MRC supported scientists must adhere to various terms and conditions of funding including the conduct and reporting of research[2]. The core terms and conditions[3] are those that Research Councils have agreed for all grants funded by UK research councils, including the MRC. The MRC has some additional supplementary terms and conditions[4]. These terms and conditions set out detailed operational, legislative and ethical requirements relating to medical research and are considered to be normal practice for human tissue research.
The MRC does not have control of any of the following: study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.
It does support and fund the MRC Brain Banks Network, an initiative to establish a coordinated national network of UK brain tissue resources (banks) for researchers to use. BRAIN UK is a member of this network, along with other MRC funded and non-MRC funded brain banks. The main aim is for banks to work together to agree common standards of operation and to harmonise protocols for consent, tissue handling and storage, quality indicators and the application process for access to tissue samples. The MRC Brain Banks Network does not have control of any of the following: conduct, data analysis and interpretation, manuscript writing, or dissemination of results. It may influence the study design due to intelligence sharing and anticipation of future direction and needs of research.

Brain Tumour Research
Brain Tumour Research has not provided any terms and conditions that have control of any of the following: study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.
It does support and fund a network of Centres of Excellence, an initiative to establish a collaboration with each of the centres, and other institutes both within the UK and internationally, in order to accelerate progress in brain tumour research. BRAIN UK is a member of this network. The network does not have control of any of the following: conduct, data analysis and interpretation, manuscript writing, or dissemination of results. It may influence the study design due to intelligence sharing and anticipation of future direction and needs of research.

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[1] University of Southampton Ethics Policy https://www.southampton.ac.uk/about/governance/policies/ethics.page
[2] Information for award holders. Terms and Conditions. http://www.mrc.ac.uk/funding/guidance-for-mrc-award-holders/information-for-award-holders/
[3] Terms And Conditions Of Research Council fEC Grants, April 2018. https://www.ukri.org/funding/information-for-award-holders/grant-terms-and-conditions/
[4] MRC Additional Terms and Conditions, June 2018. https://mrc.ukri.org/documents/pdf/mrc-additional-terms-and-conditions/

British Neuropathological Society
The British Neuropathological Society (BNS) is frequently described in BRAIN UK communications as having provided 'support' to BRAIN UK. BNS does not provide any financial assistance to BRAIN UK. BNS involvement with BRAIN UK is that the main contact in all of the neuroscience centres participating with BRAIN UK are members of the BNS, due to their role as Neuropathologists, supporting the access to well characterized, high quality post-diagnosis tissue. BRAIN UK has the Chair of the BNS Academic Committee as a member of the BRAIN UK Committee. BRAIN UK is provided an opportunity to provide an annual report to the society at its annual meeting, as a result, the society may influence the study design due to intelligence sharing and anticipation of future direction and needs of research. The BNS has not provided any terms and conditions that have control of any of the following: study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

Roles and Responsibilities of Study Management Committee

The BRAIN UK Committee performs two main functions, one is to review applications from researchers and the other is to take an overview of BRAIN UK. The BRAIN UK Committee reviews applications in order to provide different viewpoints on the acceptability and scientific credibility of a study. The committee is also invited to attend the annual committee meeting, which usually takes place via teleconference, to review and discuss the operation and progress of BRAIN UK over the previous year which typically includes a review of the BRAIN UK metrics (such as number of applications and tissues released for study), grant applications and future plans. They are independent of the Sponsors.

The BRAIN UK Committee includes the following roles:
BRAIN UK Director
BRAIN UK Deputy Director
BRAIN UK co-ordinator
Chair of the BNS Academic Committee (or their nominated representative)
Participating Centre representation
A clinician with expertise in neurological research
A basic scientist with expertise in neurological research
A lay individual

For completeness, below is a list of the current BRAIN UK Committee. The BRAIN UK website will provide updates or changes.
Prof. James A R Nicoll (BRAIN UK Director)
Dr. David Hilton (BRAIN UK Deputy Director)
Dr. Kathreena Kurian (Brain Tumour Bank Network Lead)
Prof. Sebastian Brandner (Neuropathologist)
Prof. Silvia Marino (Chair of the BNS Academic Committee)
Mr Michael Jenkinson (Clinician with expertise in neurological research)
Prof. Stephen Gentleman (Neuroscientist)
Dr. William Stewart (Participating Centre representative)
Mr Ricky Williams (Participating Centre laboratory representative)
Dr. Helen Bulbeck (Lay member)
Ms Dagmar Turner (Lay member)
Mr Paul Saunders (Lay member)
Dr. Clare Mitchell (BRAIN UK Manager)
Mrs Tabitha Bloom (BRAIN UK Data and Governance Officer)

1 Study Flow Charts

The three main activities that BRAIN UK conducts are described here. The first is the collection of data, from participating NHS Neuropathology Centres, to BRAIN UK to form the 'BRAIN UK Database'. The second describes the application lifecycle, from enquiry, the ethical review process, obtaining of the tissues to closure of the study. The third is the maintenance of the studies approved by BRAIN UK.

1.1 Collection of Data for the BRAIN UK Database

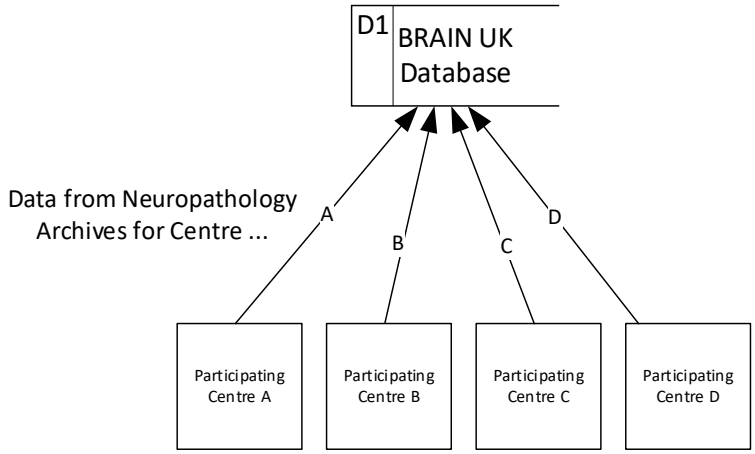

Figure 1 Pseudonymised tissue data is supplied to BRAIN UK from Participating Centres which is collated on to a central database, D1.

1.2 Researcher Application Process

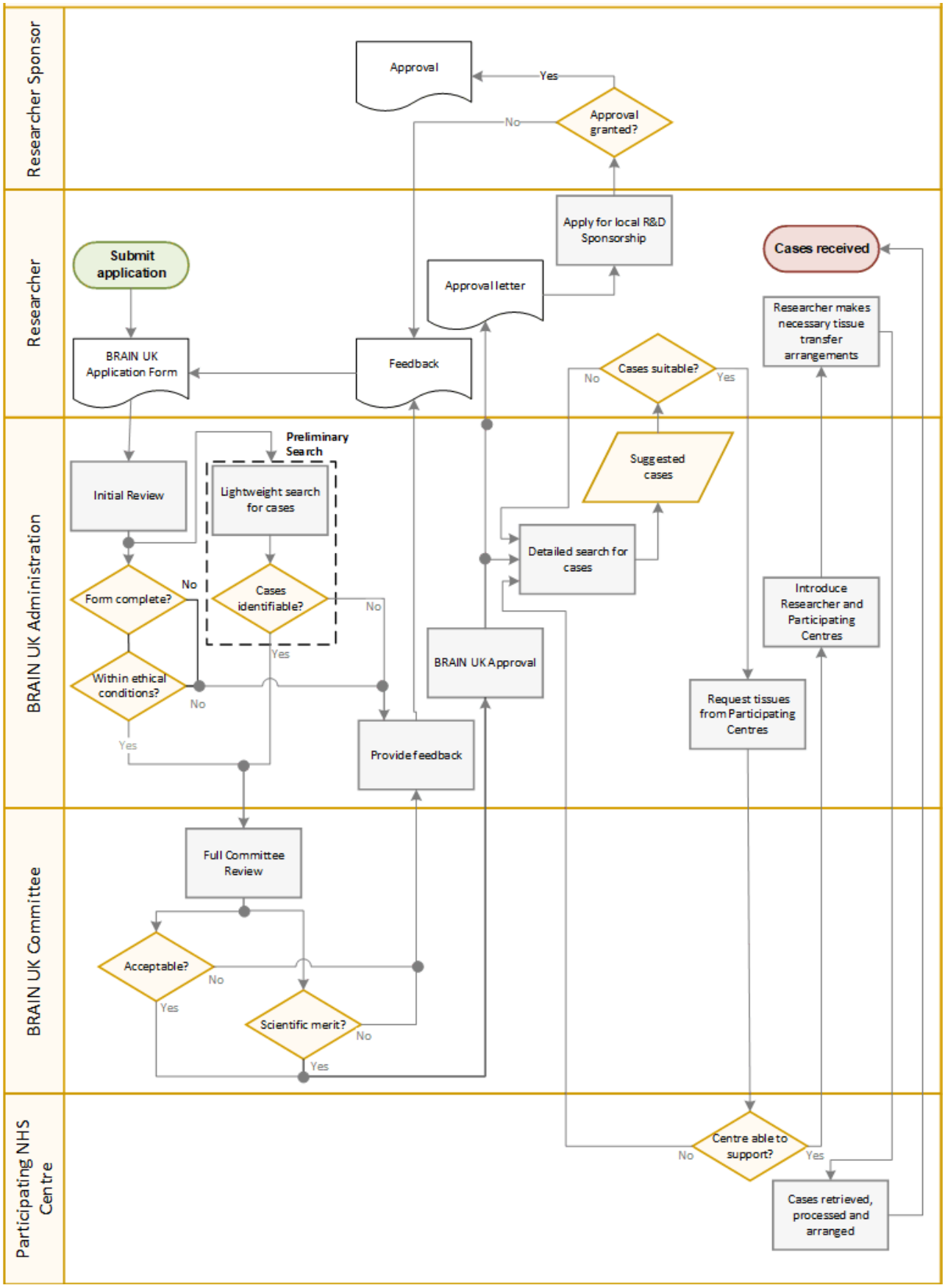

Figure 2. Cross-functional flow chart describing the steps, decisions and owners for the BRAIN UK application process to obtain cases (of tissue and/or data) and ethics.

1.3 Researcher Study Maintenance Process

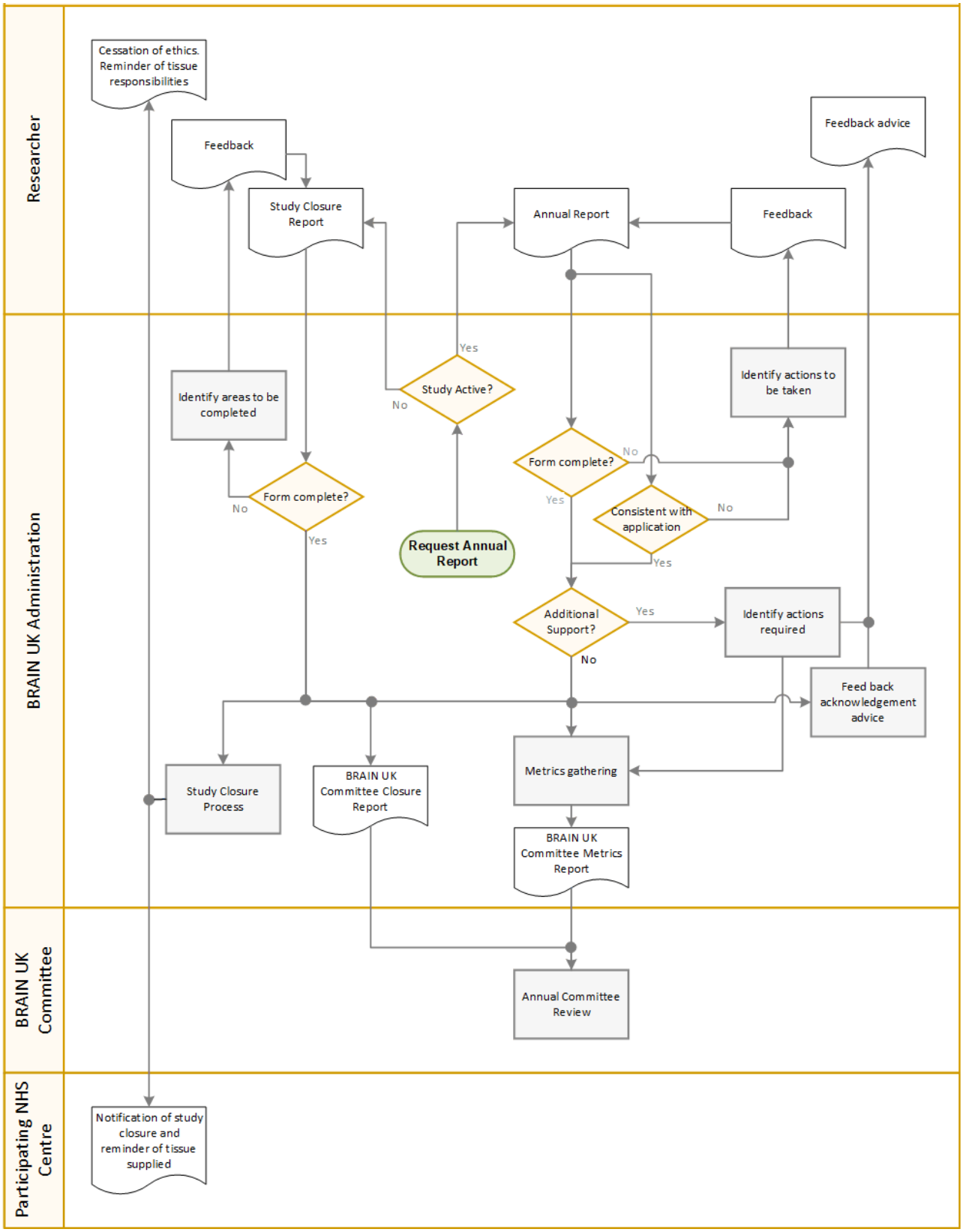

Figure 3. Cross-functional flow chart describing the steps, decisions and owners for the BRAIN UK monitoring process of an approved study, once an annual report has been requested.

2 Glossary of Terms

Biopsy: A biopsy is a medical test involving extraction of sample cells or tissues for examination to determine the presence, nature and/or extent of a disease.
BRAIN UK 1: Encompasses tissues removed and archived by a NHS Neuropathology service prior to 1st September 2006 as part of a post mortem examination in the UK which are defined as part of an 'Existing Holding' under the Human Tissue Act.
BRAIN UK 2: Encompasses tissues removed and archived by a NHS Neuropathology service on or after 1st September 2006 as part of a post mortem examination in the UK and has informed consent for the retention and use of the tissue for research purposes.
BRAIN UK 3: Encompasses tissues or other samples (e.g. cerebrospinal fluid) removed either during the course of surgery or a diagnostic procedure in the UK and whose samples have been archived by a Neuropathology service. These tissues were removed from patients during life.
BRAIN UK Database: Term used to describe the central research tissue bank database populated with data that has been derived from the medical records of the Deceased and Living. This is the primary resource that BRAIN UK uses to support researchers. The data was not primarily collected for the purpose of research and is considered to be sensitive by the GDPR[5]
Case: Typically refers to both the tissue and associated data from an individual in a Neuropathology Archive.
CNS or Central Nervous System: All Participating Centres are NHS Neuropathology departments and consequently BRAIN UK includes all tissues/materials derived from diagnostic Neuropathology practice, which are loosely described as Central Nervous System tissue. This is mainly from the following anatomical regions: brain, spinal cord, meninges, skull, spine, associated soft tissues, peripheral nerve and muscle. Less frequently sampled structures include the eye and related structures, skin and other organs/tissues in relation to neurological disease.
Human Tissue Act: Refers to both the Human Tissue Act 2004[6], and the equivalent Human Tissue (Scotland) Act 2006[7].
iSolutions: The name of the University of Southampton Information Technology Department.
Living Patients: Patients who have had tissue samples taken during surgery (biopsy).
Participating Centre: An NHS Neuropathology Centre participating in the BRAIN UK study.
R&D: Research and Development typical term for a department provide research governance support.
'Section 251': Section 251 of the National Health Service Act 2006[8] and its current regulations, the Health Service (Control of Patient Information) Regulations 2002[9]

[5] General Data Protection Regulation (EU) 2016/679 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN
[6] Human Tissue Act 2004 http://www.legislation.gov.uk/ukpga/2004/30/contents
[7] Human Tissue (Scotland) Act 2006 http://www.legislation.gov.uk/asp/2006/4/contents
[8] National Health Service Act 2006 https://www.legislation.gov.uk/ukpga/2006/41
[9] The Health Service (Control of Patient Information) Regulations 2002 http://www.legislation.gov.uk/uksi/2002/1438/contents/made

3 Background

3.1 Rationale

Impact of Disease

Neurological and psychiatric diseases represent an increasing social and economic burden for developed nations such as the United Kingdom[10]. Estimates of the global burden of disease indicate that neuropsychiatric disease affects up to one billion people worldwide and causes 12% of deaths (6.8 million/year in Europe alone) and 14% of years of healthy life lost as a result of disability and 1/3 of the burden of all diseases[11]. Recent analysis estimated that 13% of global disease is due to disorders of the brain, surpassing both cardiovascular diseases and cancer[12]. In Europe, disorders of the brain are the largest contributor to the morbidity burden[13]. The economic cost is vast, estimated at 798 billion Euros each year in Europe alone, average cost per inhabitant 5,550 Euros[11]. A WHO report[14] describes disorders of the brain are expected to become an even more serious and unmanageable threat to public health unless acted upon immediately.

Brain tumours represent a particular challenge. Unlike the majority of cancers, survival for brain tumour patients has increased only slightly over time[15]. Five-year relative survival rates for brain tumours increased by around 8% in England and Wales from 1971-1975 to 2005-2009[16,17,18,19]. Over the same time period, ten-year relative survival rates have only increased by around 3%[20,21,19]. Brain "cancer" is one of the most lethal human diseases. Age-standardised relative survival rates for brain cancer in England during 2005-2009 show that only 41.5% of patients are expected to survive their disease for at least one year[18,21]. The five-year relative survival rates for brain cancer are the fourth lowest of the 21 most common cancers in England[20], with five-year rates falling to 14.5% for men and 16.1% for women. Broadly similar rates have been reported for Wales and Northern Ireland[22,23,24]. Brain cancer survival continues to fall beyond five years after diagnosis with ten-year survival rates falling to 9.3% for men and 9.6% for women[18].

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[10] Wittchen HU and Jacobi F (2005) Size and burden of mental disorders in Europe – a critical review and appraisal of 27 studies. *European Neuro-Psychopharmacology* 15: 357 – 376

[11] J. Olesen, A. Gustavsson, M. Svensson, H.-U. Wittchen and B. Jonsson (2012) The economic cost of brain disorders in Europe. *European Journal of Neurology* 19: 155–162

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[16] For data for 1971-1990: Coleman MP, Babb P, Damiecki P, et al. Cancer Survival Trends in England and Wales, 1971-1995: Deprivation and NHS Region. Series SMPS No 61. London: ONS; 1999.

[17] For data for 1991-1995: Office for National Statistics (ONS). Cancer Survival: England and Wales, 1991-2001, twenty major cancers by age group. London: ONS; 2005.

[18] For data for 2005-2009: Office for National Statistics (ONS). Cancer survival in England: Patients diagnosed 2005-2009 and followed up to 2010. London: ONS; 2011.

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[22] Welsh Cancer Intelligence and Surveillance Unit (WCISU). Cancer Survival Trends in Wales 1985-2004. Cardiff: WCISU; 2010.

[23] Information Services Division Scotland (ISD Scotland). Cancer Statistics. Cancer of the Brain. Accessed September 2011.

[24] Northern Ireland Cancer Registry (NICR). Cancer Survival Online Statistics. Brain. Accessed September 2011.

Brain cancer is the most common cause of death in children and accounts for nearly a fifth of all deaths in boys and girls aged 1-14 (18% and 19%, respectively) (UK, 2009-2011)[25,26,27]. Central nervous system (CNS) tumours form the second most common group of cancers in children, accounting for a more than a quarter (27%) of all childhood cancers overall[28]. Between 1966 and 2005 there was an average increase in incidence of 1.3% per year[29]. In 2007 Stiller[30] described Brain, other CNS and intracranial tumours as ranking second in childhood cancer incidence, and were the most common cause of deaths from cancer in childhood, accounting for around a third of all cancer deaths in boys and girls (31% and 33%, respectively). A report by Murray, Mokdad, Naghavi et al[31] published in 2018, reconfirmed this, however, highlighted the poor progress in improving outcomes in brain and nervous system cancer as compared to leukaemia.

The Need to Study Human Brain Tissue

Animal models of human neurological diseases have an important role to play, particularly in understanding specific dynamics of biological processes and cause-and-effect relationships but they have limitations. There are increasing concerns that some animal models may not fully reflect or replicate the human disease[32,33,34, 35], and increasingly, their limitations are being recognised. Animal models can only simulate certain aspects of a disease process, which have to be selected in advance by the researchers, and these may not be the most important aspects. Animal models are particularly valuable for studying rare genetic variants of disease, or rare diseases caused by single gene mutations. Some of the problems may relate to the development of models based on rare genetically caused variants of diseases which are much more commonly sporadic (i.e. non-genetic) in nature. However, most human neurological diseases are sporadic and have a multifactorial pathogenesis which is still poorly understood and cannot therefore be reflected in animal models. In particular, age-associated neurodegenerative diseases have a multifactorial pathogenesis and are associated with coexistence of multiple cerebral pathologies. Human brain tissue is therefore essential for investigation of the pathophysiology of these complex and poorly understood conditions.

The progress towards effective therapy has been met with increasing frustration at the lack of translational success from animal and cell line models of neurological disease to the human disease itself[36], highlighting a need to study human brain tissue, derived from biopsies or from post mortem examinations, affected by the relevant disease processes. A limited number of specific neurological disorders, particularly chronic disorders such as Alzheimer's disease, Parkinson's disease and Multiple Sclerosis are well-catered for by high quality prospective brain banking facilities. However, many common and increasingly medically and economically important disorders in terms of mortality and morbidity, such as stroke, tumour and most rare neurological disorders are not provided for in this way. However, NHS Neuropathology archives contain a vast collection of tissue that is suitable in supporting research.

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[25] Office for National Statistics. Mortality Statistics: Deaths registered in England and Wales (Series DR).

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BRAIN UK Initiative

There are currently 27 NHS Neuropathology services in the UK, each with a catchment population of approx. 1 to 3 million people. After the analysis of human tissue derived from a post mortem examination or surgical biopsy has been completed it is archived according to guidelines published by the Royal College of Pathologists[37]. This archive of pathologically verified residual tissue represents a valuable resource for research purposes especially as it can be readily linked to relevant clinical data. A review of NHS neuropathology post mortem archives revealed around 90,000 stored samples [Appendix B] and biopsy archives revealed around 400,000 stored samples, accruing a further 18,500 annually [Appendix C].

Despite NHS neuropathology archives containing a wealth of brain tissue researchers find it difficult to access; and simply trying to identify suitable tissue to help shape a study can pose challenges. In addition, the legal and ethical considerations required for approval to use human tissue can be difficult to researchers and can prove time consuming. [Appendix A].

BRAIN UK has addressed this research opportunity by benefitting from the extensive archival collections of human brain tissue held by NHS neuropathology services around the UK and employing such holdings for high quality research. Since its inception it has sought to facilitate the provision of neuropathologically characterized, human, central nervous system tissue from neuropathology archives for high quality research projects in the UK and internationally. In 2009, BRAIN UK began a systematic attempt to organise and utilise this national resource for research purposes. It started by facilitating access to post mortem archives held prior to the enactment of the Human Tissue Act, defined as 'Existing Holdings'. BRAIN UK was extended in 2011 to include post mortem tissue removed on or after the enactment of the Human Tissue Act. BRAIN UK was further extended in 2014 to include residual diagnostic tissue from living patients.

A large amount of archived tissue is now available to the research community and has supported 125 applications to date. This has helped to further a better understanding of the aetiology and progression of a range of neurological diseases and disorders and could potentially allow therapeutic intervention strategies to be identified and developed. This research could, in the future, conceivably increase an individual's chances of survival, provide a better quality of care, contribute towards determining the evolving health needs of an ageing population and the improvement of public health in the UK and beyond through improved therapeutic and medical practice.

A major benefit of these archival collections is that they comprehensively cover the spectrum of neurological disorders as they do not discriminate what they collect (unlike disease specific tissue banks) and reflect the disease burden on society. They contain large numbers of common disorders, and provide useful numbers of rare disorders and non-diseased tissues suitable for control studies. The continuing addition of new cases usefully supplement the archival collections maintaining numbers of rare conditions and allowing the correlation of pathology to be made with current investigations[38,39] (*e.g.* anti-voltage gated potassium channel encephalitis, aquaporin-associated demyelination) and for the effects of current treatment modalities to be studied. The ongoing collection will also have the advantage of having been diagnosed using the latest classification and investigatory techniques[40] (*e.g.* FUS and TDP-43 related diseases).

The creation of a comprehensive national database of neuropathology tissue archives throughout the UK has the support of the British Neuropathological Society, the professional society of Neuropathologists who have responsibility for the diagnosis and custodianship of these tissues, the Medical Research Council and the brain cancer charity Brain Tumour Research. The importance of such an initiative has been reiterated by

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[37] The Royal College of Pathologists/Institute of Biomedical Sciences (2005) The retention and storage of pathological records and archives (3rd Edition)

[38] Graus F, Saiz A, Lai M, Bruna J, López F, Sabater L, Blanco Y, Rey MJ, Ribalta T and Dalmau J (2008) Neuronal surface antigen antibodies in limbic encephalitis. *Neurology* 71(12): 930 – 936

[39] Jarius S, Paul F, Franciotta D, Waters P, Zipp F, Hohlfeld R, Vincent A and Wildemann B (2008) Mechanisms of Disease: aquaporin-4 antibodies in neuromyelitis optica. *Nature Clinical Practice Neurology* 4(4): 202 – 214

[40] Munoz DG, Neumann M, Kusaka H, Yokota O, Ishihara K, Terada S, Kuroda S and Mackenzie IR (2009) FUS pathology in basophilic body inclusion disease. *Acta Neuropathologica* 118: 617 – 627

bodies such as the Medical Research Council (through the creation of the UK Brain Banks Network of which BRAIN UK is a member[41]) and the UK Clinical Research Collaboration which have identified a continuing need for the study of human brain tissue to further understand the basis and progression of neurological disease[42].

Benefits of Research to Society

Medical and biomedical research is of great importance to human health and society in general. Through high quality research, factors influencing or causing human diseases or disorders can be identified which, ultimately, may lead to reliable and efficacious therapies being developed through the use of animal and *in vivo* models and refined through clinical trial protocols. This will ultimately, through an altruistic interpretation, benefit both individuals and society at large by reducing the social and economic burden of morbidity and mortality by improving an individual's health and quality of life.

To date (26/02/2019) 116 research projects have been supported. Of particular note, many of the studies performed have been on neurological conditions using tissue that is not available through other brain banks or are not in sufficient quantity to be able to perform the study. 31% of applicants report that the study would still have taken place without BRAIN UK, but it may have had a significant effect on time, costs or outputs; and they would have needed to redesign the study to proceed alone. 56% report that the study would not have taken place without BRAIN UK. This is clearly a benefit, ultimately, to other patients who suffer from these conditions. Looking specifically at BRAIN UK 3, having had five years of running, it is now possible to see how many of these 48 living patient studies would have been affected. Most (46/48) of the living patient studies have related to brain tumours and have involved:

- Large numbers of uncommon tumours that needed to be sourced from multiple centres and dated back many years. For example a study of chordoma involved the use of tissues from 17 centres and dated over 20 years; and a multicentre study of high risk paediatric brain tumour involved the use of tissues from 14 centres and dated over 30 years.
- Complex case needs, for example, when looking for recurrent glioblastoma from the same patients, dating back over 10 years.
- Extremely rare cases.
- Several of the studies have involved glioblastomas, which although one of the most common primary brain tumours, many of the patients had died within a few months of diagnosis which would make ascertaining their consent to research impossible.

Many of these 46 studies would not have taken place as they would have been unable to either identify or source the cases in sufficient quantities to produce a statistically meaningful study.

Applicants are encouraged to disseminate the findings of their research to ensure that the research is of benefit to all. This is achieved by requesting plans for publication of the work at application stage and at annual review requests are made for details of any published outputs. On study closure, researchers are asked for a summary of the research performed, which is shared with the BRAIN UK Committee. 92 BRAIN UK studies have been surveyed with annual reports. 54 of these studies have generated 302 outputs: 46 Publications; 34 Grant Applications (generating £2.7m); 36 Published Abstracts, 2 Unpublished Abstracts; 124 Presentations; 59 Posters; and 1 Prize. Over 73% of the published outputs are in journals with a Research Impact Factor (RIF) of over 5, with almost 37% being in a journal with a RIF of over 10, indicating a high quality of research.

[41] The UK Brain Banks Network: http://www.mrc.ac.uk/Ourresearch/Resourceservices/UKBrainBanksnetwork/index.htm
[42] UKCRC Brain Banking Strategy Advisory Committee (2008) Towards a national framework for brain banking in the UK: Report to UKCRC http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC006116

3.2 Ethical and Legal Considerations

Given high profile publicity relating to the removal and storage of organs and tissues from the deceased in particular it is imperative that BRAIN UK acts upon the ethical and legal outcomes of various public inquiries and reports to Parliament (in particular the Isaacs Report[43], the Kennedy Report[44], the Campbell Report[45] and the Redfern Report[46]). Subsequent reports from the Chief Medical Officer for England and the Retained Organs Commission laid the foundation for the enactment of the Human Tissue Act and the establishment of the Human Tissue Authority in England, Wales and Northern Ireland to oversee and regulate the use of human tissue for a variety of purposes of which research is one component.

Additionally, the data of interest to the BRAIN UK study is derived from the medical records (primarily the computerised laboratory records) of both living and deceased individuals. The health sector handles some of the most sensitive personal data, and patients have the right to expect that information will be looked after. The Information Commissioner's Office reports that 1214 Health sector data breaches reported to them in the last financial year (April 2017 – March 2018), with more than 35% due to use of paper records[47]. Other causes such as data being: emailed to an incorrect recipient; left in insecure location; failure to redact data; lost or theft of unencrypted device; and high profile breaches are reported on. Many of the BRAIN UK approaches aim to mitigate or eliminate the risks of these types of incidence occurring.

The formal adoption of a legal framework has removed ambiguity and concerns occasioned by past events and now permits research using human tissue to be undertaken in an environment that balances the rights of donors and participants against the benefits of any research outcome. The following sections describe how the various legislation fits together with the BRAIN UK study.

3.3 Use of Human Tissue for Research

Consent forms the basis of any relationship between a participant and a researcher in medical and biomedical research. However, BRAIN UK 'virtual' brain bank is not a traditional model for tissue banking. BRAIN UK itself does not collect or store tissue or samples. Instead, BRAIN UK catalogues and facilitates access for research, archival tissue and other biological samples, which are stored in Participating Centres NHS Neuropathology Archive. This archival tissue was originally obtained for diagnostic purposes and the residual material subsequently archived. Participating Centres maintain custodianship of the tissue samples. Consequently, BRAIN UK does not seek to obtain informed consent to use samples and data in research, but does encourage its collection.

Human Tissue Act and Consent

The Human Tissue Act, enacted on the 1st September 2006, places the fundamental principle of 'Informed Consent' ('Authorisation' in Scotland) as a mandatory requirement for the removal, storage and use of human tissues from the deceased for a 'Scheduled Purpose' for which 'research in connection with

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[43] The Investigation of Events that followed the death of Cyril Mark Isaacs (The 'Isaacs Report'): http://www.archive2.official-documents.co.uk/reps/isaacs00/isaacs02.htm

[44] Learning from Bristol: the Department of Health's response to the Report of the Public Inquiry into children's heart surgery at the Bristol Royal Infirmary 1984-1995 (The 'Kennedy Report'). http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4002859

[45] Organ retention at Central Manchester and Manchester Children's University Hospitals Trust: report of an independent investigation (The 'Campbell Report'). http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077605

[46] The Royal Liverpool Children's Enquiry: Summary and Recommendations (30 January 2001): http://www.official-documents.gov.uk/document/hc0001/hc00/0012/0012_i.pdf

[47] ICO, What action we've taken in Q4, what you've reported to us and what you can do to stay secure. https://ico.org.uk/media/2014675/data-security-trends-pdf.pdf

disorders, or the functioning, of the human body' is one[48]. Therefore, in order for post mortem human tissues removed on or after 1st September 2006 to be utilised for research purposes evidence must be available that such 'Informed Consent' (or 'Authorisation') has been obtained and is valid. The legal position for consent to use in research differs for each of the three components of BRAIN UK and each is summarised below. We have shared our operating model with the Head of Regulation at the Human Tissue Authority who is happy with our approach, and we provide the HTA with annual updates on our activity.

3.3.1 Consent Status in BRAIN UK

The status of consent to research within BRAIN UK is influenced by its three component parts and is described below. However, in line with the spirit of the relevant legislation and guidance, if it is known, or becomes known that there is a request for tissue and/or data not to be used for research or that pre-existing consent is withdrawn then such wishes will be respectively adhered to, with such cases not being made available for research purposes.[48]

BRAIN UK 1 (encompassing post mortem "existing holdings")
In some cases consent may have been given for use of samples/data in research, although this is not a requirement of the Human Tissue Act. Consequently, in compliance with the Human Tissue Act, BRAIN UK 1 samples are available for research provided suitable ethical approval is in place and anonymity is maintained, regardless of consent status. BRAIN UK 1, by its nature of being "existing holdings", is a historic archive, the most recent cases dating from 2006 and stretching back 40-50 years. Checking for consent would likely be difficult and it would be unlikely to meet current standards and expectations.

BRAIN UK 2 (encompassing post mortem tissue removed on or after 1st September 2006)
According to the Human Tissue Act, consent must have been received, specifically for research use, from the donor in life, or of their nominated individual, or an individual in a qualifying relationship after death to be able to such samples for research purposes. Each Participating Centre has standard operating procedures in place to obtain informed consent as mandated by the Human Tissue Act and associated Human Tissue Authority Codes of Practice. Participating Centres, as custodians of the archive, identify cases that have consent for research purposes and consequently can be utilised by BRAIN UK and its approved researchers.

BRAIN UK 3 (encompassing tissue from the living)
In some cases consent has been given for use of samples/data in research. For BRAIN UK 3 consent is not required for anonymised tissue and/or data to be used in research where it has Research Ethics Committee approval. From a study we performed in 2015, Appendix E: Consent to Research in Participating Centres, consenting procedures and rates are very variable across the UK. In some centres consent for research rates are high, 95-100%, but much less in others. We estimate that the overall current consent rate to be about 30%. Where consent is obtained, from exemplars sent to BRAIN UK, it is "broad" consent for storage and use in future research; an example is included in Appendix F: Consent to Research for Surgical Patients.

3.3.2 Use of Consented Tissue in BRAIN UK 2

This section discusses an issue specifically related to BRAIN UK 2 only. Informed consent is a mandatory requirement for tissue to be used for a 'Scheduled Purpose' of which research is one. All BRAIN UK Participating Centres have a Human Tissue Authority Licence, which has been considered satisfactory by the Human Tissue Authority Head of Regulation. Part of the audit process undertaken by the Human Tissue Authority determines that each centre has procedures in place to obtain informed consent from potential donors. Therefore, Participating Centres with valid Human Tissue Authority Licences have demonstrated evidence of having the necessary informed consent procedures in place. The consent obtained from recent donors is typically "broad" consent for storage and use in future research; an example is included in

[48] Human Tissue Authority (April 2017) Code of Practice A: Guiding principles and the fundamental principle of consent https://www.hta.gov.uk/sites/default/files/HTA%20Code%20A_1.pdf

Appendix G: Consent to Research for Post Mortems. Informed consent can be obtained from an individual during life or an individual in a qualifying relationship after death. These routes to informed consent for BRAIN UK 2 are described below.

Consent for Hospital Post Mortem Examinations[49]
Informed Consent must be obtained for a hospital post mortem examination (e.g. to gain further understanding of a patient's illness or the efficacy of a drug regimen or any other treatment administered) and this consent is separate from the Informed Consent required for the removal, storage and use of human tissue for a Scheduled Purpose. Informed Consent for the latter activities should be obtained separately.

Coroner's (or Procurator's Fiscal) Post Mortem Examinations[49]
Informed Consent is not required for post mortem examinations that have been ordered as part of a Coroner's (or Procurator's Fiscal) examination into an individual's cause of death. However, informed consent is a mandatory requirement for the continued storage and use of human tissues derived from such investigations removed on or after 1st September 2006 (i.e. that form part of BRAIN UK *2*) after a Coroner (or Procurator Fiscal) has discharged their responsibility.

3.3.3 Obtaining of Consent

BRAIN UK does not seek to obtain informed consent to use samples and data in research, but does encourage its collection by Participating Centres. For post mortem donors, Participating Centres have protocols and procedures in place to obtain and record informed consent as part of their compliance with the Human Tissue Act, Human Tissue Authority Codes of Practice and Human Tissue Authority Licensing obligations. For tissue taken from the living, the residual diagnostic material encompassed by BRAIN UK 3, Participating Centres have standard operating procedures in place to obtain relevant and necessary consent for the operation and associated diagnostic process, which led to the archiving of the tissue. Additionally, there will be standard operating procedures in place to obtain informed consent, when collected.

The inclusion of 26/27 NHS Neuropathology Archives, results in all main groups of donors being included. Each centre will have processes and procedures in place in order to provide information to the patient and their families and agents, in the necessary and appropriate formats, and to collect and record informed consent for research purposes. The consent considerations from these different groups are briefly described here:

Adults[48]
'Informed Consent' (or 'Authorisation') may be obtained from adults in life, however, where an adult has refused to give consent this cannot be revoked after their death.

Adults who had not indicated their consent prior to death[48]
If an adult did not provide informed consent prior to their death, their nominated representative (or an appointed representative in Wales) or someone who was in a 'qualifying relationship' with the adult can be appointed to take those decisions. Under the Human Tissue Act, children cannot appoint nominated representatives and therefore provisions related to seeking consent from nominated representatives do not apply.

Consent from Children[48]
The archives maintained by Participating Centres will invariably contain residual tissue derived from children, infants, neonates and foetuses. Under the Human Tissue Act a child is defined as an individual under the age of 18 years (or under 16 years in the parallel Scottish legislation). A child is deemed competent to give valid consent for themselves if they are able to demonstrate sufficient intelligence and an understanding of the situation (so-called 'Gillick competency') although this concept does not apply to Scottish law. Where children are unable to give valid consent for themselves (either due to not being competent or willing to do

[49] Human Tissue Authority (April 2017) Code B: Post-mortem examination
https://www.hta.gov.uk/sites/default/files/Code%20B.pdf

so) then this obligation passes to those with parental responsibilities (as covered by the Children Act 1989[50]).

Adults with Lack of Capacity to Consent[48]

The archives maintained by Participating Centres will invariably contain residual tissue derived from adults lacking the capacity to consent as defined by the Mental Capacity Act 2005[51] and the equivalent Adults with Incapacity (Scotland) Act 2000[52]. The Mental Capacity Act does not apply in Northern Ireland. The Mental Capacity Act requires that care be taken to ensure that patients are given every opportunity, and support where needed to make their own decisions.

Human Tissue Authority Licensing

For BRAIN UK's post mortem cases (BRAIN UK 1&2), it is a requirement for all Pathology Departments undertaking autopsy work to have procedures in place to ensure that appropriate informed consent is obtained for the storage and use of tissue removed at a post mortem examination, in order to comply with the Human Tissue Act. All Participating Centres in BRAIN UK are licensed by the Human Tissue Authority, which has robust mechanisms in place to ensure that the procedures for obtaining consent comply with the Human Tissue Act and the Human Tissue Authority Codes of Practice. Model consent forms and communication pathways are available on the Human Tissue Authority website: https://www.hta.gov.uk/policies/post-mortem-model-consent-forms.

For BRAIN UK's living patient cases (BRAIN UK 3), these diagnostic archives do not need to be stored under a Human Tissue Authority Licence. However, where the diagnostic tissue functions as a resource for researchers, as it does for BRAIN UK, it is functioning as a Research Tissue Bank and it must therefore be encompassed within the HTA's licensing framework[53]. BRAIN UK has agreed a position with the Human Tissue Authority who are supportive of the BRAIN UK virtual network model, whereby:

a) centres may hold either a post mortem or research licence, and
b) the processing by the supplying centres helps to allow the local Designated Individuals maintain oversight and governance.

All Participating Centres in BRAIN UK are licensed by the Human Tissue Authority.

3.3.4 Lawful Basis for use of Unconsented Tissue in BRAIN UK 1 & 3

BRAIN UK relies on effective anonymisation of donors as the lawful basis to use unconsented tissue in research for BRAIN UK 1 and 3. Additionally, to maintain confidentiality, BRAIN UK uses effectively anonymised data for all donors, regardless of the consent status.

For BRAIN UK 1 and BRAIN UK 3 there is no mandatory requirement for informed consent to be in place for tissue to be used for research purposes so long as:

a. 'The material is used for a specific research project with ethical approval'. BRAIN UK must be subject to approval by a UK Research Ethics Committee.
b. The 'researcher is not in possession, and not likely to come into possession of information that identifies the person from whom it has come'. BRAIN UK supplies tissue and/or data to researchers in an effectively anonymised format.

The BRAIN UK Information Governance[54] document more fully discusses anonymisation, in relation to issues of confidentiality, but to summarise, BRAIN UK uses a minimal dataset that excludes directly

[50] Children Act 1989 https://www.legislation.gov.uk/ukpga/1989/41/contents
[51] Mental Capacity Act 2005 https://www.legislation.gov.uk/ukpga/2005/9/contents
[52] Adults with Incapacity (Scotland) Act 2000 https://www.legislation.gov.uk/asp/2000/4/contents
[53] Human Tissue Authority, Information for research tissue banks https://www.hta.gov.uk/policies/information-research-tissue-banks
[54] BRAIN UK Information Governance

identifiable fields. BRAIN UK uses pseudonymisation, using the laboratory number (or equivalent) to provide a link back to the Participating Centre, so that the researcher cannot reasonably use it to identify an individual. However, the original provider of the information can identify individuals in order to locate tissue or further approved data.

3.4 Use of Data and/or Tissue in BRAIN UK

A health record is any record which consists of information relating to the physical or mental health or condition of an individual made by a health professional in connection with the care of that individual. It can be recorded in a computerised form, in a manual form or a mixture of both. Information covers expression of opinion about individuals as well as fact. Health records may include notes made during consultations, correspondence between health professionals such as referral and discharge letters, results of tests and their interpretation, X-ray films, videotapes, audiotapes, photographs, and tissue samples taken for diagnostic purposes.[55]

Various regulations cover the consented and unconsented use of health records. Those that relate specifically to tissue have been discussed in the previous section, 3.3 Use of Human Tissue for Research. This subsection focuses on the regulations of significance to BRAIN UK's use of data and/or tissue.

3.4.1 The Common Law Duty of Confidentiality

Common law is not recorded in one document like an Act of Parliament. It is a form of law based on previous court cases decided by judges. As a result of this its impact and applications are not always transparent and there is an obvious scope for it to change over time. For the Common Law Duty of Confidentiality the general position is that, if information is given in circumstances where it is expected that a duty of confidence applies, that information cannot normally be disclosed without the data subject's consent.

Whilst it may be possible for varying interpretations of the Common Law, there is a bound obligation to a duty of confidentiality in relation to the disclosure of information about a living individual and this is enshrined in employment contracts of the NHS and other organisations as well as being established in professional codes of conduct. There is no such readily defined legal obligation relating to the disclosure of information from the medical records of the deceased, but, it is widely accepted that an ethical obligation to a duty of confidentiality and privacy should extend to individuals after death.

In practice, this means that all patient information, must not normally be disclosed without the consent of the patient. However, the Data Protection Act 2018 makes provision for use of patient information gathered to provide healthcare to be used for research if the information is anonymised.[56]

3.4.2 Data Protection Act 2018

The Data Protection Act 2018[57] sets out the framework for data protection law in the UK. It sits alongside the General Data Protection Regulation[5] (GDPR), and tailors how the GDPR applies in the UK - for example by providing exemptions. This Act describes the regulations for processing of information relating to individuals, including the obtaining, holding, use or disclosure of information and applies to the living. With regards to the medical records of the deceased, these are in part catered for by the Access to Medical Records Act 1990 but this legislation primarily relates to access to the medical records of the deceased by those who may

[55] BMA Ethics. Access to health records. Guidance for health professionals in the United Kingdom. August 2014
[56] Department of Health (September 2007) NHS Information Governance: Guidance on Legal and Professional Obligations https://www.gov.uk/government/publications/nhs-information-governance-legal-and-professional-obligations
[57] Data Protection Act 2018 http://www.legislation.gov.uk/ukpga/2018/12/contents/enacted

have a claim arising from the patient's death and only applies to records created since 1st November 1991[58]. Despite the Act not applying to the deceased, BRAIN UK commits as far as possible to adhere to the principles for the deceased participants of BRAIN UK.

The Data Protection Act 2018[57] is broadly similar to Data Protection Act 1999[59] and sets out six data protection principles as follows:

a. processing be lawful and fair;
b. processing be specified, explicit and legitimate;
c. personal data be adequate, relevant and not excessive;
d. personal data be accurate and kept up to date;
e. personal data be kept for no longer than is necessary;
f. personal data be processed in a secure manner.

Article 5(2) of the GDPR adds a seventh principle that the data controller shall be responsible for, and be able to demonstrate compliance with, the above principles.

How BRAIN UK provides for these is summarised below.

Confidential Acquisition and Processing of Personal Data (Principles a, b, c and f)

Personal data is acquired by the health care professionals involved with the subject, then suitably anonymised before it is securely transferred to BRAIN UK. As a secondary measure, personal data may be acquired by BRAIN UK staff or permitted researchers. In the case of BRAIN UK staff they would be required to anonymise data at the earliest possible opportunity and any conversions to be performed as soon as practicable with data deleted after conversion. Researchers would be required to anonymise data prior to leaving the site of collection. The data accrued by BRAIN UK is kept to a minimum to enable researchers to identify tissues of interest to their research needs. Accompanying demographic information is included to allow inference about patient gender and age at procedure to be made, which are important research variables. This is more fully described in the BRAIN UK Information Governance[54] document.

Participating Centres are informed of the research to take place on the sample and, despite approval from BRAIN UK for the research, as the custodians of the sample, they maintain the option to decline the distribution of the tissue. Individuals may have provided consent for the use of their data and/or tissue samples to be used in research, however, data is linked anonymised but they can find out about BRAIN UK via the website which now includes lay summaries of the studies supported.

Holding, Safeguarding and Disposal of Personal Data (Principles d, e and f)

Every effort is made to ensure that all data accrued, held and processed is accurate. Minimal data sets are requested from Participating Centres to reduce the chance or error when merging data sets. Original data sets are held to facilitate recovery of any corrupted information. Prior to release of tissue or data to the researcher the data held on the case is checked with the Participating Centre.

The BRAIN UK initiative is intended to be enduring, therefore, all data maintained in relation to those individuals meeting the inclusion criteria will be kept for a minimum period of ten years, see BRAIN UK Information Governance[54] for further details. Application will be made to the relevant Research Ethics Committee on a five−yearly basis to renew all approvals. This is more fully described in the BRAIN UK Information Governance[54] document.

A number of measures are implemented to increase data security and to mitigate against loss, theft or disclosure to unauthorised individuals. BRAIN UK has an Information Governance[54] document detailing the mechanisms in place to ensure the confidentiality of personal data.

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[58] Access to Health Records Act 1990 https://www.legislation.gov.uk/ukpga/1990/23/contents
[59] Data Protection Act 1998 https://www.legislation.gov.uk/ukpga/1998/29

3.4.3 Challenges Around Obtaining Consent

The development of stratified treatments for brain cancer and other neurological conditions will depend on the availability of this range and quantity and also large, population based, high-resolution datasets of clinical information on individual patients[60]. Rooney *et al*[61] discusses the differences between population based registers, which BRAIN UK is an example of, and prospective based registers, in relation to neurodegenerative disease. As a result of being a population based register, BRAIN UK identifies and characterize all cases of CNS disease, including those that might otherwise be neglected. BRAIN UK recognises that obtaining consent to research is desirable, however, Section 3.4.4 Section 251 National Health Service Act 2006, describes the challenges in obtaining consent in this cohort. Below is a brief literature review around collecting consent.

Furness and Nicholson[62] attempted to obtain informed consent for research on surplus material from 495 renal transplant patients. After one year the opinion of 26% of the patients had still not been ascertained (via postal correspondence and in-clinic reminders), although of those that had been ascertained 3% had declined. The authors demonstrated the considerable effort involved in following up consent in the 32% of cases that did not respond to the initial consent request and highlighted the distress caused by mistakenly approaching deceased patients. The authors concluded that demands for explicit consent may have led to the abandonment of many research projects in the UK. Secondly, well documented differences between individuals who consent to participating in biobank research and those who do not[63,64,65,66] can threaten the validity of the results[67].

Stjernschantz Forsberg et al argue[68]: Since the risks imposed by biobank research are minimal (with appropriate safeguards such as adequate data protection and ethical approval) the interest of the individual as a research subject is outweighed by his or her interest in medical advances. Furthermore, because robust research depends on access to samples and data from as many people as possible, a system that facilitates general contribution is in the interest of all.

Barrett et al[69] found that the majority of the British public does not consider the confidential use of personal, identifiable information by the National Cancer Registry for the purposes of public health research and surveillance to be an invasion of privacy. Furthermore, four fifths of the public would support a law making cancer registration statutory. Two studies that examined rates of consent to health registers (the Canadian

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[60] European Commission, DG Research – Brussels (2010) Workshop report: Stratification biomarkers in personalized medicine. Available from http://ec.europa.eu/research/health/pdf/biomarkers-for-patient-stratification_en.pdf

[61] Rooney JPK, Brayne C, Tobin K, Logroscino G, Glymour MM, Hardiman O (2017) Benefits, pitfalls, and future design of population-based registers in neurodegenerative disease. *Neurology*. 88(24):2321-2329. doi: 10.1212/WNL.0000000000004038

[62] Furness PN, Nicholson ML. Obtaining explicit consent for the use of archival tissue samples: practical issues. *J Med Ethics* 2004;30:561-4

[63] Mezuk B, Eaton WW, Zandi P. Participant characteristics that influence consent for genetic research in a population-based survey: the Baltimore epidemiologic catchment area follow-up. *Community Genet* 2008;11:171-8.

[64] Aagaard-Tillery K, Sibai B, Spong CY, Momirova V, Wendel G Jr, Wenstrom K, et al. Sample bias among women with retained DNA samples for future genetic studies. *Obstet Gynecol* 2006;108:1115-20.

[65] Arruda-Olson AM, Weston SA, Fridley BL, Killian JM, Koepsell EE, Roger VL. Participation bias and its impact on the assembly of a genetic specimen repository for a myocardial infarction cohort. *Mayo Clin Proc* 2007;82:1185-91.

[66] Ness KK, Li C, Mitby PA, Radloff GA, Mertens AC, Davies SM, et al. Characteristics of responders to a request for a buccal cell specimen among survivors of childhood cancer and their siblings. *Pediatr Blood Cancer* 2010;55:165-70.

[67] Ransohoff DF, Gourlay ML. Sources of bias in specimens for research about molecular markers for cancer. *J Clin Oncol* 2010;28:698-704.

[68] Stjernschantz Forsberg J, Hansson MG, Eriksson S. Biobank research: who benefits from individual consent? *BMJ* 2011;343:d5647

[69] Barrett G, Cassell JA, Peacock JL, Coleman MP. National survey of British public's views on use of identifiable medical data by the National Cancer Registry. *BMJ* 2006;332:1068 (Published 04 May 2006).

stroke network register[70] and the paediatric intensive care audit network register in the United Kingdom[71]) found that obstacles to consent were primarily due to logistical problems in gaining access to patients to ask for consent; when it was possible to ask patients or their representatives for permission to use identifiable information, consent was almost always given.

Busby et al paper on obtaining informed consent for registration of congenital anomalies highlight the issues with insistence on obtaining consent with a survey of such registries demonstrating falling recruitment when opt in consent was demanded despite evidence that patient opt-out rates would be small (1% or less)[72].

Al-Shahi et al[73] investigated the consent bias on all 187 adults in Scotland in whom brain arteriovenous malformation was first diagnosed in 1999-2002. Within the first year of their notification to the study, the study team was discouraged from approaching 56 (30%) of these patients for consent by their general practitioner or consultant. Twenty adults (11% of the whole cohort, 15% of those approached) did not respond to the postal invitation to consent. None explicitly withheld consent to the team examining his or her medical records. The remaining 111 adults (59%) in the cohort gave their explicit informed consent.

Al-Shahi et al[73] found that adults who consented were significantly different from those who did not in both anticipated and unpredictable ways. Consenters were significantly less likely to have intracranial haemorrhage or to be dead or dependent at presentation, reflecting the difficulty in gaining consent from brain damaged patients (and, of course, from those who had died before the study team knew about them). During follow-up, consenters were significantly more likely to receive interventional treatment, less likely to die, and more likely to have an epileptic seizure. These differences affected the overall result of the study if non-consenters were excluded from the final analysis. The team noted that this kind of consent bias probably invalidates the findings of many observational studies, as it would have their own if non-consenters had been excluded.

3.4.4 Section 251 National Health Service Act 2006

This legislation provides for the use of such confidential patient information for medical research purposes. BRAIN UK applies for the assessment of the use of confidential patient information in this study from the Health Research Agency Confidentiality Advisory Group (HRA CAG), which considers applications for approval to use 'Section 251 support'. As part of our previous applications (Refs: 09/H0504/68, 11/SC/0395 and 14/SC/0098) BRAIN UK has received conditional exemption from Section 251 support. Previous guidance and advice from the Approvals Manager of the HRA CAG (formerly known as the National Information Governance Board's Ethics and Confidentiality Committee) have been utilised to create the necessary processes and procedures to obtain 'Section 251 support' should this become a mandatory requirement.

Although there is agreement upon the ethical basis for the maintenance of the privacy and the common law confidentiality of individuals and their relatives after death, it is felt that the intended nature and scope of this study would make it insupportable in terms of available time and resources to undertake obtaining consent for access to and disclosure from the medical records and that this would greatly restrict the scope, coverage and depth of the proposed research. Therefore, an application has been made to seek permission for disclosure under Section 251 of the National Health Service Act 2006[8].

Section 251 of the NHS Act 2006[8] allows the common law duty of confidentiality with regard to patient information to be set aside in specific circumstances, where anonymised information is not sufficient and where patient consent is not practicable. It applies in England, Scotland, Wales and Northern Ireland, to both

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[70] Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, et al. Impracticability of informed consent in the registry of the Canadian Stroke Network. *N Engl J Med* 2004; 350:1414–21.
[71] McKinney PA, Jones S, Parslow R, Davey N, Darowski M, Chaudhry B, et al. A feasibility study of signed consent for the collection of patient identifiable information for a national paediatric clinical audit database. *BMJ* 2005; 330:877–9.
[72] Busby A, Ritvanen A, Dolk H, Armstrong N, De Walle H, Riano-Galan I, Gatt M, McDonnell R, Nelen V, Stone D. Survey of Informed Consent for Registration of Congenital Anomalies in Europe. *BMJ* 2005;331:140–141.
[73] Al-Shahi R, Vousden C, Warlow C. Bias from requiring explicit consent. *BMJ* 2005;331: 942.

the living and deceased. In practice, this means that the person responsible for the information can disclose the information to the applicant without being in breach of the common law duty of confidentiality. They must still comply with all other relevant legal obligations e.g. the Data Protection Act[57].

BRAIN UK does not store identifiable data; it utilises linked anonymised data with the keys relating to patient identification held by Participating Centres. In practice, assessing the risk that additional relevant information will be used by others to reveal identity is difficult because of lack of reliable information about the variables influencing risk. Although the law makes a clear distinction between identifying and non-identifying data, where that line should be drawn may be far from clear in practice. The answer depends on several factors: on the actual content of the information listed, on the availability of other information now and in the future that could be used to reveal the identity of patients, and on the likelihood that someone will get hold of other information and use it to learn something about one of the patients represented on the study. Some of these factors cannot be measured, only assessed. [74]

As BRAIN UK has access to large quantities of data, there is a potential risk for re-identification, for example, by the inclusion of the following:

- It is possible that potentially patient identifiable data could be supplied for conversion by BRAIN UK, whose staff would anonymise it at the earliest convenience.
- BRAIN UK uses a minimal dataset that excludes directly identifiable fields and uses pseudonymisation, using the laboratory number (or equivalent) to provide a link back to the Participating Centre, so that the holder cannot reasonably use it to identify an individual. However, the original provider of the information can identify individuals in order to locate tissue or further approved data.
- As a consequence of the inclusion of all patients in Neuropathology Archives, some of the conditions are rare and not evenly distributed across the population, and are therefore vulnerable to re-identification.

Summary of the components to BRAIN UK

As previously described, BRAIN UK itself does not collect or store tissue or samples. Instead, BRAIN UK catalogues and facilitates access for research, archival tissue and other biological samples, which are stored in Participating Centres NHS Neuropathology Archives because of a potential future clinical diagnostic need. Participating Centres maintain custodianship of the tissue samples. BRAIN UK's existing collections are composed of BRAIN UK 1 and BRAIN UK 2 encompassing around 90,000 post mortem cases, with the majority from the "existing holdings" (BRAIN UK 1); BRAIN UK 3 encompasses around 500,000 living patient cases in Participating Centres' archives. A summary of the status with the law for each of the components is as follows:

- BRAIN UK 1: Concerning human post-mortem tissue samples stored prior to implementation of the HTA Act on 1st September 2006, consent is not required for use in research, as it is regarded as an "existing holding". Tissue can lawfully be used in research provided that the information is anonymised and the research has gained ethical approval from a UK Research Ethics Committee.
- BRAIN UK 2: Post mortem tissue collected and stored on or after 1st September 2006; these cases must have informed consent for research purposes. Cases that do not have consent for research cannot be used and retrospective consent will not be sought by BRAIN UK.
- BRAIN UK 3: Tissue obtained from a living person that has not been consented for research can lawfully be used in research provided that the information is anonymised and the research has gained ethical approval from a UK Research Ethics Committee.

[74] Anonymisation Standard for Publishing Health and Social Care Data. Supporting Guidance: Drawing the line between identifying and non-identifying data. 2013. NHS and The Information Centre for Health and Social Care. http://webarchive.nationalarchives.gov.uk/+/http://www.isb.nhs.uk/documents/isb-1523/amd-20-2010/1523202010guid.pdf

Impracticality of obtaining consent

The Health Research Authority Confidentiality Advisory Group offer advice on what would be considered for the 'Reasonable impracticability of Consent[75]. Due to the low survival rate amongst brain tumour patients (which are the majority of BRAIN UK 3 cases) and as we are not involved in the clinical care team consent would often be on a retrospective basis. As a result, there is an element of 'impossibility'[75] in some cases, since the majority of adults will not survive beyond the first year of diagnosis.

It is felt that obtaining individual consent for access to and disclosure from the medical records of each individual would be both impracticable and disproportionate. Measures to maintain patient anonymity and the common law duty of confidentiality have been implemented (see BRAIN UK Information Governance[54]) and given that this initiative facilitates the undertaking of high quality research that could result in a direct patient benefit for individuals who develop neurological diseases and disorders in the future, it is felt that exemption from the requirement to obtain consent for the access to and disclosure from medical records under Section 251 of the National Health Service Act 2006 can be reasonably applied for in this instance. This project does not propose to check for consent for each individual case that is included, but still wishes to include them, for the following reasons:

1. For living patients, from our own research, Appendix E: Consent to Research in Participating Centres, and other published studies (Section 3.4.3 Challenges Around Obtaining Consent), most patients in the UK with archived tissue have not had the opportunity to consent to research but where they are given the opportunity are likely to consent to research.

2. BRAIN UK has access to an estimated 500,000 cases. To attempt to obtain new consents from the majority of this cohort would be insupportable in terms of both time and expense.

3. It would not be reasonably practical to obtain consent retrospectively.

   As many of the archived cases date from many years or decades ago it would be inappropriate to return to patients or bereaved relatives so long after death or illness. Approaching relatives following bereavement could cause distress and harm especially if the nature of the bereavement related to a distressing condition or incident. In addition, it would also be inappropriate to return to the bereaved family if a number of years have elapsed since the time of death as this may again have the potential to cause harm and revisit events that may have been emotionally adjusted to. There may be difficulty in tracing patients or relatives or in contacting them after many years due to factors such as migration and death.

   In particular, BRAIN UK 3 brings the opportunity to provide access for research for neurological conditions not well represented in the post mortem archives under BRAIN UK 1&2. Of particular importance in this regard are brain tumours, which represent a large proportion of biopsies taken by neurosurgeons. Unfortunately, many types of brain tumours have a very poor prognosis with around 40% of patients only expected to survive their disease for at least one year; with five-year rates falling to around 18%; and survival continuing to fall with ten-year survival rates at around 13%.

   It is not feasible to obtain consent from a person who is deceased. Medical records are likely to record the Next of Kin, however, the Next of Kin cannot give consent in this situation, unless they are the Legal Personal Representative or the person administering the estate. Additionally, in some cases, finding out an individual's mortality status (whether deceased or not) could lead to the further disclosure of identifiable information, and it has been therefore accepted, by the Confidentiality Advisory Group, that it is not practicable to do so.[76]

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[75] Health Research Authority Confidential Advisory Group. Principles of Advice: Exploring the concepts of 'Public Interest' and 'Reasonably Practicable'. 19th April 2012.

[76] NHS HRA Confidentiality Advisory Group, Precedent Set Categories, Version 2.0 https://www.hra.nhs.uk/documents/1056/confidentiality-advisory-group-precedent-set-criteria.pdf

4. The Confidentiality Advisory Group also considers bias[75]. Excluding cases would introduce intolerable bias, which could preclude the investigation of some disease types, and would take many years to replicate with prospective banking.

   BRAIN UK represents the cohort of diseases that affect the neurological health of the UK population over the past 40-50 years, representing an irreplaceable and likely unrepeatable source of knowledge anywhere else in the world. Post mortems represent a significant cost so many other brain banks can only reflect those diseases that can attract significant funding, resulting in many common conditions, such as stroke and traumatic brain injury, and many rare diseases not represented in them, although they are in BRAIN UK.

   For the living patient cases, tumours represent a large proportion of biopsies taken by neurosurgeons. As a group, Central Nervous System tumours are relatively rare; figures for 2015[77] in the UK show that there were 11,432 brain tumours registered in adults.

   In addition to that, they encompass a very large number of different histological types; the WHO histological classification of brain tumours[78] identifies more than 130 different varieties. Data from the UK shows that gliomas and meningiomas account for the majority of brain tumours with over 60 of the brain tumour types in the WHO classification having fewer than 10 cases diagnosed over the period[79], presenting a problem of 'intolerable bias'[75]. When considering that in children, 405 cases were reported per year between 2006-2007[28] this situation is further exacerbated.

5. BRAIN UK specifies that, where pre−mortem wishes of the deceased or the wishes of surviving relatives (for BRAIN UK 1 & 2) or the wishes of surviving patients (for BRAIN UK 3) are known to preclude the use of their tissues or data for research then such declarations will be respectfully honoured. Since the start of BRAIN UK operating in 2009, no centre has needed to exclude cases based on these wishes.

6. The absolute requirement for consent would limit the size and scope of the research, with the available resources, and diminish its potential benefits to the research community and the UK as a whole. Many studies supported by BRAIN UK would not have taken place, see Benefits of Research to Society for details.

7. Patient identity is protected by the use of linked anonymised data which renders the probability that any individual could be identified by the recipient of such data to be extremely small. For practical purposes, this data is considered as anonymous thus there is no common law requirement for consent.

BRAIN UK has been, and will continue to be involved with national schemes to encourage consent for research from living patients and will assist Participating Centres requesting a need for assistance with prospective consent.

Additionally, from consideration of the advice received from previous applications and reviews from the NHS HRA Confidentiality Advisory Group, some of which are now described in the Precedent Set Categories, BRAIN UK has devised its policies to meet these requirements. For example, the BRAIN UK Information Governance[54] document describes the preferred method for access to patient data is for the direct care team to extract and anonymise the information from the case notes, avoiding any breach of patient confidence. With applications under this category only being made where this method is not practicable and there is justification for the applicant to access patient identifiable data for a short period of time in order to anonymise the data on-site. [76]

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[77] Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours, Accessed Mar 2019.

[78] WHO classification of Tumours of the Central Nervous System. Eds Louis, D.N. 4th Edition IARC Lyon.

[79] National Cancer Intelligence Network Data Briefing (2011) Central Nervous System (CNS) Tumours – developing a national tumour registry

3.5 Discovery and Disclosure of Clinically Significant Information

There currently exists no encompassing consensus concerning the responsibility of researchers to disclose individual results to participants in human research and information and guidance that is available demonstrates that this is a complex, potentially contentious and highly variable issue[80].

Potential to Generate Clinically Significant Results

All types of medical and biomedical research have the inherent capacity to reveal biological data and information that may have clinical or psychosocial implications for participants and their relatives. This is especially true for research investigating the genetic and heritable basis of human disease which could reveal data relating to paternity issues or indicate if an individual is predisposed to a particular condition or at an elevated risk of developing diseases such as cancer or neurodegenerative conditions later in life. Data accrued from genetic research also has implications for those who share a common ancestry with the participant and those who are yet to be born. In addition to the medical implications of such knowledge, there are also other, perhaps less obvious, social, legal and financial implications for example, stigma, exclusion, anxiety, stress to family relationships and the ability to obtain health, life, disability or any other kind of insurance and may have a bearing upon an individual's prospects of employment.

The offer and receipt of research results to participants and their relatives has a number of potential benefits and may have direct implications for their quality of life. Beyond a purely scientific basis, the disclosure of data generated as part of biomedical research may aid in demonstrating at a societal level the benefits of research by engaging the general public in terms of its enthusiasm and support for the principal of medical research. However, although there is an ethical onus to disclose findings of clinical relevance to the families of participants where appropriate, there will be situations when an individual does not wish to receive such information or where disclosure may be of more harm than benefit to an individual.

3.5.1 Nuremburg Code and the Declaration of Helsinki

Central to the use of humans in medical research and clinical trials is the principle that participants should be fully informed of any inherent risks and that, with an appreciation and understanding of this knowledge, their informed consent should be forthcoming. The modern legal and ethical concerns governing research upon human subjects and their tissues was a direct result of the Nuremburg war crimes trials. The Nuremburg Code (1947)[81] was drawn up as a response to this and set out ten principles to be satisfied for human participation in medical research or clinical trials including the need for informed consent, the right of withdrawal, that human experimentation should only be considered when other approaches had been exhausted (e.g. the use of animal models) and that there should be consideration given to the balance between the expected benefits of any research and the risks run by research subjects[82,83].

The principals of The Nuremburg Code (1947) were adopted and developed subsequently by the World Medical Association in the Declaration of Helsinki[84]. This fundamentally recognised the principal that research utilising human participants should not take precedence over the interests of science and society in general. The Declaration also emphasised that all research carries inherent risks and that this should be assessed and managed and that any risk is outweighed by the importance of the research question. As part

[80] Steinsbekk KS, Solberg B. (2012) Should genetic findings from genome research be reported back to the participants? *Tidsskr Nor Laegeforen*.132(19):2190-3. https://tidsskriftet.no/en/2012/10/should-genetic-findings-genome-research-be-reported-back-participants

[81] Nuremberg. The Nuremberg Code (1947). BMJ 1996;313:1448 https://doi.org/10.1136/bmj.313.7070.1448

[82] Reilly PR, Boshar MF and Holtzman SH (1997) Ethical issues in genetic research: disclosure and informed consent. *Nature Genetics* 15: 16-20 https://doi.org/10.1038/ng0197-16

[83] Cho MK (2008) Understanding incidental findings in the context of genetics and genomics. *Journal of Law, Medicine and Ethics* 36(2): 280-285 https://doi.org/10.1111/j.1748-720X.2008.00270.x

[84] World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. *Bulletin of the World Health Organization*, 2001, 79 (4): 373-374 https://www.who.int/bulletin/archives/79(4)373.pdf?ua=1

of this appraisal process there should be evidence of scientific rigour and independent ethical and peer review processes and that informed consent from participants or their legal representatives should ideally be sought.

3.5.2 Disclosure

Cost of Disclosure[85]

Although largely arbitrary, the cost of disclosing data must be weighed against the risk (be that physical, emotional or societal) to the individual or their relatives. The cost of disclosure may be measured in the following ways:

1. Each study will present a variable risk to those individuals participating dependent upon the study question being addressed. As risk increases, disclosure is more likely to happen and be expected and at greater cost, in terms of time and finance, to the study group. This type of risk should be factored into the funding structure of a particular piece of research with high risk research requiring greater funds to disseminate data appropriately and to validate results independently.
2. The size and structure of a study will present logistical difficulties. For instance a large multicentre study with disparate geographical scatter would increase the costs associated with disclosure. Again, the contribution of logistical factors should be incorporated into the funding process for each particular study.

Requirements for Disclosure[86,87]

The disclosure of clinically important information to the relatives of donors should only occur if the following can be reasonably satisfied:

1. All findings are scientifically valid and confirmed through repeat and accredited experimentation. The analytic and clinical validity should be assessed and the predictive value of the results determined.
2. Findings have significant implications for the subject's health concerns and for the health concerns of future individuals *e.g.* the discovery of a genetic predisposition in tissue previously believed to be normal.
3. A course of action to ameliorate or treat these concerns is readily available.
4. Results indicate an enhanced susceptibility to environmental factors *e.g.* increased susceptibility to adverse drug reactions.

Investigators should formulate and integrate plans about appropriate disclosure of individual genetic results when designing their research studies.

3.5.3 Determination of Disclosure Threshold

The decision to offer to disclose data or not will be made on a case-by-case basis by the healthcare team. Typically, it will utilise a result-evaluation approach based upon an ethical framework[87] which incorporates the principals of:

- Beneficence: Are results clinically useful or likely to contribute towards a participant's physical and emotional well-being?
- Reciprocity: Consideration of the nature, depth and duration of the relationship between participant and researcher.
- Justice: Consideration of the balance between a participant's preferences and resource allocation to maximise the benefits of the research to society as a whole.

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[85] Fernandez CV, Skedgel C and Weijer C (2004) Considerations and costs of disclosing study findings to research participants. *Canadian Medical Association Journal* 170(9): 1417-1419

[86] Resnik DB (2004) Disclosing conflicts of interest to research subjects: an ethical and legal analysis. *Accountability in Research* 11: 141-159

[87] Ravitsky V, Wilfond BS. (2006) Disclosing individual genetic results to research participants. *Am J Bioeth*.6(6):8-17. https://doi.org/10.1080/15265160600934772

- Respect: Are the results of interest to participants? What are the participants' preferences, to receive, or not receive, a certain result?

The result-evaluation approach should consider the following facets in determining whether a minimum threshold has been achieved in permitting clinically significant results to be offered to participants and their relatives:

Analytic Validity

Results of a clinically significant nature should be of the highest quality and should be validated by additional testing. This is best achieved using the facilities of a laboratory accredited to undertake such testing.

Clinical Utility

Clinical utility is an empirical measure of whether a result can be used to improve a participant's well-being. It is based upon three assessments:

- Clinical validity is a measure of the strength of association between a result and a particular clinical outcome.
- The likelihood of a clinically effective outcome should determine whether intervention is safe and that such intervention will offer palpable benefits when compared to no intervention at all.
- The value of outcome determines whether any intervention or disclosure will be of clinical, emotional or other benefit to the participant or their relatives or enables them to make better informed life choices (*e.g.* reproductive decisions). It is also important to consider the personal meaning of any disclosure to individuals and whether such information would have any effect upon relationships and personal identity.

Study Context

The context of a study is important in being able to rationally determine whether a disclosure threshold is reached, what the capabilities of an investigator are and whether there is a relationship between a participant and investigator.

3.5.4 Policy Declaration

Based upon all the criteria discussed above, the majority of research studies that would potentially utilise the archival tissue holdings of Participating Centres in the BRAIN UK network would not, by default, be in a position to offer the disclosure of clinically significant information for the following reasons:

1. The tissue held is diagnostically verified therefore, for diseased tissues, there would be reduced scope to discover additional information of clinical pertinence.
2. The tissue archive collections are retrospective and, in some instances, extend back a number of decades. It would likely be considered either inappropriate or unpractical to return to individuals if many years had elapsed.
3. The majority of neurological and psychiatric diseases and disorders remain incurable and there is limited scope in terms of effective curative therapy.

All tissue and clinical data supplied to researchers is in a linked anonymised format which, for practical purposes, is considered as fully anonymised. In the case where the extraction and subsequent analysis of DNA or RNA is intended and there is an above 'minimal' risk that any data obtained is likely to have clinical significance then BRAIN UK will require evidence that the ethical questions surrounding the disclosure of clinically significant information have been addressed by the researcher.

An example would be when tumour tissue has been supplied as being pathologically characterised but, possibly because of the recent changes in World Health Organisation classification of tumours of the central

nervous system[88] or the availability of new techniques, it becomes apparent that the diagnosis may have changed. In such cases, if analysed using the results-evaluation model, a minimum threshold in terms of analytic validity, clinical utility and study context would need to be attained before the offer of such data to the individual, if they were still alive. Although BRAIN UK and the relevant research group may offer advice and guidance on such matters, the decision to offer to disclose clinically significant data will be ultimately made by the relevant NHS Trust as, being in possession of the key to patient identity, they will be the only body capable of approaching individuals.

3.5.5 Decision Making

The ultimate decision as to whether clinically significant data from a particular study should be disclosed to an individual will be made by the relevant Participating Centre NHS Trust. Researchers should inform either BRAIN UK or BRAIN UK and the Participating Centre of a clinically significant result.

BRAIN UK is not in a position to determine alone whether disclosure should occur but can, at the application stage, make an informed decision concerning the risk that a particular research study presents in terms of generating clinically significant results. If a particular study does present an above 'minimal' risk then it may be required for a particular study to obtain approval from a UK Research Ethics Committee for that work.

Means of Disclosure

All clinically significant information should be delivered by the Healthcare Professionals that form part of an individual's medical care team. The Participating Centre from which the tissue sample originated forms a part of the relevant healthcare team and so any communication of findings would be through them.

[88] Louis, D.N., Perry, A., Reifenberger, G. et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 131(6):803-820. https://doi.org/10.1007/s00401-016-1545-1

4 Research Question/Aims

4.1 Objectives

Research Objective
To facilitate the provision of neuropathologically characterized, human, central nervous system tissue from neuropathology archives for high quality research projects in the UK and internationally.

This study aims to continue to make available high quality, well-characterised human brain tissue for biomedical research with BRAIN UK acting as a 'virtual brain bank' with the tissue samples being retained in the departments of origin, remaining under NHS custodianship. This approach has been successfully used by the Confederation of Cancer Biobanks[89] and the Cancer Research UK Bio-Specimen Biorepository[90] and has a number principle that has served it well:

- A national archive, with joint "ownership" by all Participating Centres.
- Tissues from individuals are stored in the department of origin and are therefore readily available for diagnostic review if required.
- Not limited to diseases that can attract sufficient funding for dedicated brain banks.
- No major capital requirements, low maintenance costs as utilising existing facilities.
- Participating Centres maintain custodianship of tissue samples.

4.2 Outcome

The broad outcomes for the study which will reflect the research question aim are:

- Form a collaborative network of NHS Neuropathology Centres, in order to access surplus diagnostic tissue.
- Creation of a linked anonymised database with sufficient information to permit BRAIN UK to either identify tissue for approved studies or enquiries in order to support researchers in forming their research questions or grant applications.
- A process that supports researchers in gaining the ethical and regulatory approvals necessary to study human tissue.

This study has been in progress since 2009 and has built up over time, starting with post mortem tissues and, in 2014, adding living patient tissue with the specific aim to better support tumour studies. As the study increases in maturity it is encouraging the collaboration of researchers either working in similar areas or in complementary fields where a common cohort is being used.

[89] The Confederation of Cancer Biobanks: http://www.ncri.org.uk/ccb/
[90] Cancer Research UK Bio-Specimen Biorepository: https://brd.nci.nih.gov/BRN/brnHome.seam

5 Study Design and Methods of Data Collection and Analysis

This sections sets out to describe the decisions and ethical arrangements used in BRAIN UK. This is augmented by the BRAIN UK Information Governance[54] document which sets out, in detail, the physical methods for data collection and analysis. It describes how the system catalogues the tissue archival holdings of participating NHS Neuropathology Centres around the UK in order to provide a 'virtual' brain tissue bank, and the security in place to maintain confidentiality. And, that the data of interest to BRAIN UK is derived primarily from the medical records from living and deceased individuals. It also describes the collection of data about researchers, who are either using or enquiring about the potential to use the BRAIN UK service, required as a consequence of providing a research tissue bank service. It sets out the data collected and how it is processed and secured.

5.1 Study Setting

BRAIN UK is based in the University of Southampton and is the central point for all enquiries and applications for tissue and/or data from researchers.

BRAIN UK is a collaborative study with a list of all Participating Centres and relevant contact details provided in Appendix D: Tissue Storage Centre Contacts. In summary, all centres participating in the study are NHS Neuropathology Centres, each with an estimated population catchment of approx.1-3 million. Currently 26/27 centres in the UK are participating in the BRAIN UK study. Centres' participation with BRAIN UK varies over time and this is usually mostly influenced by local staffing. The named Neuropathology contact is considered the local 'gatekeeper', with applications usually being sent to them in the first instance for them to consider the merit of the application and/or whether it conflicts with local requirements. Some centres rely on a lab manager to coordinate this activity. Typically the lab manager takes care of organising the tissue and/or data. There are three methods by which centres participate with identifying cases suitable for an approved study:

1. Centres can provide BRAIN UK with a minimal pseudonymised data set. This can then be incorporated on to the BRAIN UK database, see Figure 1. This allows searching of the archives to identify potentially suitable cases, with contact only then being required with the centre once cases have been approved for use in a study.
2. If suitable cases cannot be identified from the BRAIN UK database, BRAIN UK will approach a centre that has a known interest in the relevant type of cases and we will ask the local Neuropathology contact to organise a local search for the tissue;
3. For difficult to identify cases, where an applicant may require large numbers of samples or if the condition is extremely rare, we email all Participating Centres for their assistance in searching local archives.

The first approach is the one that we prefer as this allows us to make informed contact to centres, which allows us to use our contact's time more efficiently, with the third approach being the least preferred.

5.2 Data Accrual for the BRAIN UK

The BRAIN UK Information Governance[54] document, details the security measures and legal and ethical basis around the data accrual in more detail. Note, no participants are 'recruited' as BRAIN UK only uses residual diagnostic tissue from existing archived tissue samples and only information from pre-existing health records.

The data flow pathway for the accrual of data from the Participating Centres to BRAIN UK, as described in Figure 1, is summarised below. This is usually performed by a member of the local healthcare team.

1. Log−in to NHS laboratory computer system.
2. Query of computer system database to identify post mortem or brain biopsy cases.
3. Pertinent cases collated using a suitable format appropriate for transfer.
4. Data anonymised leaving laboratory number (resulting in linked anonymised data).
5. Anonymised data is encrypted and transferred to BRAIN UK.

Data from the Participating Centre is collated to create the BRAIN UK Database.

5.2.1 Sample Eligibility Criteria

Inclusion criteria

BRAIN UK encompasses donors from three distinctly different legal backgrounds:

BRAIN UK 1: All patients who have had tissues removed and archived by a Neuropathology service prior to 1st September 2006 as part of a post mortem examination (either Coronal/Fiscal Procurator or hospital/consented) in the UK, which are defined as part of an 'Existing Holding' under the Human Tissue Act.

BRAIN UK 2: All patients who have had tissues removed and archived by a Neuropathology service on or after 1st September 2006 as part of a post mortem examination (either Coronal/Fiscal Procurator or consented hospital examination) in the UK and who have given informed consent during life or for which informed consent has been given by their nominated representative or an individual in a qualifying relationship after death for the retention and use of their tissues for research purposes.

BRAIN UK 3: All patients who have had tissues or other samples (e.g. cerebrospinal fluid) removed either during surgery or in the course of a diagnostic procedure in the UK and whose samples have been archived by a Neuropathology service.

Exclusion criteria

Based on the categories above BRAIN UK excludes donors in the following way:

BRAIN UK 1: Where there is known evidence that consent has been refused (either by the patient during life or by a qualifying relative after death) for access to or disclosure from patient data or for the use of tissue for research purposes.

BRAIN UK 2: Where no recorded evidence of consent exists for the use of their tissues for research purposes.

BRAIN UK 3: Where there is known evidence that consent has been refused for access to or disclosure from patient data or for the use of tissue for research purposes.

5.2.2 Sampling

Currently 26(/27) NHS Neuropathology Centres take part in the BRAIN UK study. There are currently around 500,000 neuropathology specimens in these archives, with approximately 18,500 accrued per year. The distribution and number of post mortem cases available is listed in Appendix B. The distribution and number of living patient (biopsy) cases available is listed in Appendix C. The inclusion of 26/27 UK centres results in a comprehensive coverage of the spectrum of neurological disorders, as they do not discriminate what they collect and reflect the disease burden on society.

5.2.3 Collation of Data

Received data is collated and stored as described in the BRAIN UK Information Governance[54] document. In summary, BRAIN UK does not store identifiable data; it utilises linked anonymised data with the keys relating to patient identification held by Participating Centres. If potentially patient identifiable data is supplied for conversion by BRAIN UK, BRAIN UK staff will anonymise data at the earliest possible opportunity and convert to the necessary data (such as the calculation of the 'age at procedure') as soon as practicable with data (such as date of birth and date of operation) deleted after conversion. Data is only placed on the database when it has been converted.

The linked anonymised data is stored on a secure network drive, hosted by the University of Southampton with access restricted to BRAIN UK staff. User rights are minimised, firewall and antivirus/antimalware software provided, with regular and timely security patching and central access logging. There is full disk encryption of all PC's accessing BRAIN UK data using MS Bitlocker to mitigate against data loss through remnants left on accessing PC's. In addition, there are physical measures to prevent loss of accessing PC's such as limited room access and card activated magnetic locks at entrances to the adjoining corridor. To mitigate against data loss, 'snapshots' of the database are taken every day and are retained for a minimum of 3 months, with an offsite mirror. Annual audits will undertake an internal review of the system and associated risk register in conjunction with the University's IT Head of Information Security, in the spirit of ISO27001:2013 9.2.

The outcome of this activity is to produce a secure database of information: with linked anonymised data; with sufficient information to permit BRAIN UK to either identify tissue for approved studies or enquiries in order to support researchers in forming their research questions or grant applications; in a format that can be queried or interrogated readily by a BRAIN UK member of staff.

5.3 Data Interrogation and Dissemination

BRAIN UK interrogates the BRAIN UK Database using standard queries in order to either:

- Determine if a study is feasible/to help shape a study;
- Determine if cases are suitable for an approved study;
- Identify the cases to be used in an approved study.

With each of these queries the amount of information disseminated to the applicant reflects both the stage of enquiry and application to BRAIN UK. The types of information released at each of these stages is described below, with examples, but the same principles apply to each stage:

- Data is linked anonymised;
- The minimum data required to satisfy the request is released.

5.3.1 Data Disseminated to Determine Study Feasibility/Shaping a Study

Researchers often need data on cases to know:

- Whether a study is feasible using BRAIN UK tissue and/or data;
- How to shape a study based on the tissue available.

Researchers can obtain general information about the kind of material that is available from the BRAIN UK website, where some numbers of cases are listed against broad categories of disorders. They can also email expressions of interest in a particular disease process which BRAIN UK staff search the database and provide anonymised details about what is available. Using the anonymised dataset, researchers may then submit an application to BRAIN UK.

An example of this could be an email confirming that a brief search of the database confirms that BRAIN UK would have sufficient number of cases to support the researcher's request, such as for a relatively common tumour type, for example, a request for 150 paraffin embedded tissue from medulloblastomas.

An example in which more information would be required: a researcher wanted to know the feasibility of looking at the development of Alzheimer's disease in Down's Syndrome, from post mortem cases, which is a more unusual cohort than the example above. In this example, as the researcher was wanting to look at disease progression, both age and gender were considered important factors so the following is a representative extract of the information sent, demonstrating the range of information:

Diagnosis	**Age**
Down's syndrome. Alzheimer's disease. White matter calcification.	64
Head injury. Contusions. Extradural haematoma. Down's syndrome. Diffuse senile plaques.	37
Down's syndrome. Alzheimer type change	49
Down's syndrome	15
Twin Down's syndrome congenital heart diseaseTrisomy 21	2.1
Down's Syndrome. Coronal slices through the brain reveal that there is a small, old cystic infarct in the body of the right caudate nucleus at the level of the anterior putamen. There is a further larger infarct approx 2 x 0.5 cm in the thalamus on the left side. The cerebral cortex appears normal. The white matter is normal and brainstem and cerebellum appear normal.	27.8
This is a twenty week foetus terminated for a diagnosis of Down's syndrome.	0
Down's syndrome Spongiform change	

5.3.2 Data Disseminated to Determine Case Suitability for an Approved Study

Once researchers have their study approved, by BRAIN UK, they need data to consider relevant cases suitable for their study. They are likely to need more detail than above such as stratification by sex and age range and other variables important to their research. It is usual at this stage to provide an indication of the Participating Centres of origin for the tissue as researchers may have a preference for tissue from a single centre rather than multiple centres. Where relevant, this is provided to the researcher in an anonymised numerical form. This permits the researcher to be able to view the distribution of cases across centres. It may also be necessary to identify potential tissue for use as control material as it may not be possible to obtain pathologically 'normal' tissue.

An example in which more information would be required was supporting the study, *Multi-platform analysis of TSC Subependymal Giant Cell Astrocytoma (SEGA) to identify novel therapeutic approaches.* The availability of frozen tissue was an essential variable to the researcher. Given the difficulty of both obtaining the type of rare tumour and in frozen format, for which storage protocols may differ across different centres, when a single centre was identified as being able to support the research the researcher was made aware that a single centre supply was being pursued. Below is an example extract of the information sent, demonstrating the range of information supplied, with the important research variables supplied but without the laboratory numbers being supplied at this stage, with a 'Case' reference number being supplied instead. Researchers highlight cases that they want BRAIN UK to pursue for access from the Participating Centre.

Case	Age	Sex	Diagnosis	Frozen	Tissue available
1	61.3	M	Subependymoma/subependymal giant cell astrocytoma	Y	Small amount
2	19.4	M	Recurrent subependymal giant cell astrocytoma	Y	Yes
3	16.1	M	Subependymal giant cell astrocytoma (WHO grade I), hamartomatous vascular elements, thrombosis, infarction.	Y	Yes
20	26	M	Subependymal giant cell astrocytoma with areas of subependymoma		
25	28.6	F	Subependymal giant cell astrocytoma		
22	17.0	M	Recurrent subependymal giant cell astrocytoma		
23	43.4	M	Sub-ependymal giant cell astrocytoma (SGCA, WHO grade 1)		

5.3.3 Data Disseminated to Identify Cases to be used in an Approved Study

Once a researcher has identified that cases of interest could satisfy their study requirements, BRAIN UK checks for the availability of the tissue and whether a Participating Centre is able to support the request. In order to do this, the laboratory numbers of the cases are used to identify the cases, with the age, gender and diagnosis being supplied to ensure verification of the case. When a Participating Centre confirms their ability to support the study, the researchers are put in direct contact with the supplying centre and is then privy to the same linked anonymised data that BRAIN UK has supplied to the Participating Centre.

Building on from the previous section, as an example of supporting the study: *Multi-platform analysis of TSC Subependymal Giant Cell Astrocytoma (SEGA) to identify novel therapeutic approaches.* Below is an example extract of the information sent, with a 'Case' reference number now being replaced with the local laboratory number.

Lab Number*	Age	Sex	Diagnosis	Frozen	Tissue available
12345678	61	M	Subependymoma/subependymal giant cell astrocytoma	Y	Small amount
23456789	19	M	Recurrent subependymal giant cell astrocytoma	Y	Yes
34567890	16	M	Subependymal giant cell astrocytoma (WHO grade I), hamartomatous vascular elements, thrombosis, infarction.	Y	Yes
45678901	26	M	Subependymal giant cell astrocytoma with areas of subependymoma		
56789012	28	F	Subependymal giant cell astrocytoma		
67890123	17	M	Recurrent subependymal giant cell astrocytoma		
78901234	43	M	Sub-ependymal giant cell astrocytoma (SGCA, WHO grade 1)		

*Note, the actual laboratory numbers in this table are fictitious.

5.4 Researcher Application Process

The researcher application process is described by the flow chart, **Figure 2**. Researchers may use a dataset or the input received from an initial enquiry to BRAIN UK to determine the study's feasibility, see section 5.3.1 for details, to submit an application. Alternatively, they may apply directly, without a previous enquiry to BRAIN UK, in which case it may be necessary to perform a "Preliminary Search", as described in section 5.3.1, to ensure that the study needs could be met.

All applications are administered centrally through BRAIN UK. Applications are made using a standardised application form, available electronically[91]. The applications are subject to a review by BRAIN UK. On successful completion, relevant documentation is sent to supplying Participating Centres to reach a decision upon the ability to support an individual application.

5.4.1 Applicants

BRAIN UK does not treat applicants differently whether they are from the University of Southampton, are members of a Participating Centre, from elsewhere in the UK or abroad. In broad terms, any bona fide

[91] BRAIN UK Application Form

biomedical researcher may apply to BRAIN UK whether based in the UK or abroad. Commercial organisations, particularly pharmaceutical companies, play an important role in biomedical research for patient benefit and are regarded as “legitimate users”.

From our experience to date, most applicants originate from the UK. A proportion of applications originate from outside of the UK which, by definition, places such research outside of the scope of the Human Tissue Act 2004 and UK Research Ethics Committees. In order for an overseas application to be considered valid researchers will have to provide evidence that they have local Ethical Approval to undertake research on human tissue and make a declaration that they will adhere to local laws, policies and regulations in relation to the use, storage and disposal of tissue used for research. This aside, the same mechanisms are used to determine if an application from outside the UK warrants approval.

5.4.2 BRAIN UK Application Form

All documentation forwarded to BRAIN UK in support of an application will be held confidentially by BRAIN UK for a minimum period of five years after the closure of the study for the purposes of annual reports and audit.

The current version of the BRAIN UK Application Form[91] is provided on the BRAIN UK website, www.brain-uk.org. The application form gathers information from each research applicant and will contain:

1. Principal Investigator contact details
2. Details of where research will be taking place
3. Details of tissue and/or data required
4. Details of the proposed research study

As tissue samples are provided to researchers in a linked anonymised manner, in the vast majority of studies there is no feedback of results to participants. However, if in a specific study it is anticipated that data generated may have clinical significance for the participant and/or their relative, the mechanisms and protocols for disclosure should be established at the protocol planning stage. For a further explanation of what clinically significant information is and whether disclosure might be considered appropriate see Section 3.5 Discovery and Disclosure of Clinically Significant Information.

BRAIN UK has ‘generic ethical approval’ for the use of relevant material held by each Participating Centre. BRAIN UK, and the Participating Centres providing material, need to be satisfied that all research is of sufficient quality before releasing material. A list of criteria and conditions that would need to be satisfied has been provided by the UK REC granting permission for our previous approvals (latest ref. no.: 14/SC/0098). Under certain circumstances, the BRAIN UK Committee may consider that the proposed research does not satisfy those criteria or there are specific additional issues such that additional ethical approval may be required and this will be assessed on a case-by-case-basis (see Section 5.4.3 Mechanism for Determining Approval below). In such a situation then evidence of other ethical approval from a UK Research Ethics Committee will need to be submitted in support of any application.

It should be noted that BRAIN UK ‘generic ethics’ only applies in the UK. Outside the UK researchers need to make their own arrangements to gain equivalent ethical approval to study human tissue and this needs to be submitted in support of their application.

Please note that evidence of a study’s independent ethical approval will not automatically qualify for BRAIN UK support. All applications are dealt with on a case-by-case basis.

5.4.3 Mechanism for Determining Approval

Once a completed application with all relevant supporting documentation has been received by BRAIN UK the application is first checked by the BRAIN UK team to ensure completeness, feasibility of request, potentially within ethical remit of BRAIN UK, accessibility of the lay summary and whether the level of justification for the requested cases is sufficient. Prior to circulation to the wider BRAIN UK Committee, the BRAIN UK Director and/or Deputy Director check for acceptability of the proposed study.

The BRAIN UK Director (or in their absence the Deputy) considers each application independently and consistently in relation to the criteria listed below and needs to be satisfied that the application meets these criteria. The research proposal must:

1. Be within the fields of medical or biomedical research.
2. Have been subjected to a rigorous scientific critique and peer review.
3. Be appropriately designed in relation to its objectives.
4. Add something useful to existing knowledge (with the exception of student research below doctoral level).

A study may have received a peer review, for example, as part of a grant application, in which case BRAIN UK requests the supporting documentation as evidence, where available. Additionally, the BRAIN UK Committee assessment performs this peer review function and any feedback from the assessment is considered by the BRAIN UK Director and pertinent observations and suggestions are fed back to the applicant in an anonymised format, unless specifically requested by the reviewer, for example, if offering support to the study.

BRAIN UK aims to provide a rapid approval service. The BRAIN UK Committee is normally given one week to feed back any comments on an application. A definitive decision is usually provided to the applicant in the following week. A decision may be made that the applicant needs to provide further information or changes to the application before approval can be granted.

Successful Applications

If a study is 'approved by BRAIN UK it has been granted 'generic ethical approval'. A research project performed in the UK using tissue facilitated by BRAIN UK in accordance with these conditions will be considered to have ethical approval from the committee under the terms of this approval. In England, Wales and Northern Ireland this means that the researcher will not require a licence from the Human Tissue Authority for storage of the tissue for the duration of this project[92]. BRAIN UK supplies the applicant with a 'letter of approval' (Appendix J: Template Study Approval Letter, and associated relevant documentation, to evidence this to support any local research governance applications required to permit the study to take place in the hosting institution.

It is important to note that each Participating Centre has the ultimate right to veto the access to and subsequent use of their tissue archives for any particular study proposal regardless of the decision of the BRAIN UK Director.

Unsuccessful Applications

Those applications that do not meet the approval standards of the BRAIN UK review are not permitted to access the tissue archives through BRAIN UK. Such applicants will be informed in writing detailing the reasons for rejection and will be offered advice to enable re-submission if appropriate.

BRAIN UK may require any researcher to seek specific independent ethical approval for their project under certain circumstances (e.g. where research is likely to generate clinically significant data and this is felt too sensitive to be covered under a 'generic ethics' arrangement or where access to living relatives is required). Such applications should normally be made to a Research Ethics Committee able to grant generic approval and should be booked via the Central Allocation System.

[92] Human Tissue Authority (April 2017) Code of Practice and Standards E: Research https://www.hta.gov.uk/sites/default/files/Code%20E.pdf

5.4.4 BRAIN UK Approval

If cases have not already been identified, BRAIN UK will work with the applicant to identify suitable cases, as described in 5.3.2 Data Disseminated to Determine Case Suitability for an Approved Study. Access to the cases will then be negotiated with the relevant Participating Centres and the applicant will only be placed in contact with the centre once the cases have been confirmed as being suitable and available and the Centre is both prepared and able to support the study. The supplying Participating Centre will be provided with all documentation relevant to the ethical approval for the relevant study.

Arrangements concerning the shipping and the return of unused material are, ideally, included in the Material Transfer Agreement (a template is included in the Appendix H: Material Transfer Agreement). Funding to cover the retrieval, processing and transport of tissue will be recouped from a researcher's funding and this, as well as any other pertinent arrangements will be the prerogative of each Participating Centre.

It should be noted that:

- The favourable ethical opinion from BRAIN UK is only applicable to the study detailed in the approved application and is only valid if these conditions and those outlined in BRAIN UK Application Form, Appendix 1[91], are met.
- Tissue or data will be used solely for the purposes of the research study outlined in the approved application protocol and only by those named in the application (or local researchers working under the direction of named individuals).
- Tissue or data will not be passed on to third parties unless it is part of the approved application protocol or has the written permission of the supplying centre.
- Participating Centres, supplying tissue and/or data, may require involvement on a collaborative basis, especially if the request requires substantial effort from the Centre. Aspects such as co-authorship of any resultant papers are negotiated between the custodians of the originating archive, members of BRAIN UK and the applicant on a case-by-case basis. However, provision of samples with a specific diagnosis and associated data is typically regarded as sufficient intellectual input to justify co-authorship as the study could not be performed without well-characterised samples.

If any changes are required during the course of a study, they need to be submitted to BRAIN UK as an amendment, see Section 5.5.2 Amendments to the Researcher's Study.

5.5 During the Researcher's Study

The researcher study lifecycle process is described by the flow chart, Figure 3.

5.5.1 Annual Progress Reporting of the Researcher's Study

Successful applicants will be expected to complete an annual report of progress and inform BRAIN UK of any incidents in relation to the use of tissue in the study (a template is included in Appendix I: Annual Report to BRAIN UK). This is an important mechanism to help to determine if researchers are utilising tissues obtained from BRAIN UK Participating Centres appropriately and in line with the purposes defined within their applications. This is also achieved by researchers reporting formal outcomes of the results of their work such as through papers submitted to peer-reviewed journals and abstracts. It is important that all researchers maintain adequate records of the receipt, use and return of all tissues to enable audit trails to be evident.

Annual progress reports on all approved studies with a favourable opinion should be submitted to BRAIN UK when requested. For reasons of administrative efficiency, this is now done at the same time of year for all active studies. Applicants can contact BRAIN UK to request the due date of the report. Applicants are also invited to send outputs regularly throughout the year and details of cases received, in order to pre-populate the annual report for them. The due date for receipt of the report is 30 days following the request. Reports should continue to be submitted at least annually until the end of the study is notified. BRAIN UK, in

exceptional circumstances may request that more frequent reports be submitted, or may request an additional progress report at any time.

Where a progress report is not received by the due date, BRAIN UK will send a reminder. If the report is still not received after a further period of one month, BRAIN UK will consider what further action should be taken. This may take the form of a review of the favourable opinion, including possible suspension or termination, for the study.

These annual progress reports form the basis of information required to report on BRAIN UK's progress to the:
Study Sponsor, the University of Southampton
Health Research Authority NHS Research Ethics Committee
Human Tissue Authority
BRAIN UK Committee
British Neuropathological Society
Funders
Scientific community

5.5.2 Amendments to the Researcher's Study

Researchers may apply for their approved study to be amended whilst it is active. In the first instance, it is recommended that researchers contact BRAIN UK for advice. Applicants cannot start the proposed change to the study while waiting for approval of the amendment. The only exception would be for the management of urgent safety measures, however, BRAIN UK would at least expect to be notified of the requirement for an urgent change as soon as it was known to be required, but this has never been required to date.

To submit an amendment, an applicant must outline the proposed amendment in a covering letter and update the Application Form[91], highlighting any changes clearly. The BRAIN UK Director and/or Deputy Director will consider the request. For an amendment to be considered by BRAIN UK, the proposed change must be:

- In line with the original research question;
- Proportionate with the original request.

For example, a request for additional cases in order to validate findings. Approval of an amendment is typically within a week of receiving a valid amendment proposal. The decision may be that the applicant needs to provide further information or changes to the amendment before approval can be granted. Or, it may be considered outside of the scope of the original research question, in which case, the applicant would be asked to submit a fresh application to BRAIN UK.

If an amendment is 'approved' by BRAIN UK it has been granted an update to its 'generic ethical approval'. BRAIN UK will supply the applicant with a new 'letter of approval', and associated relevant documentation, to evidence this to support any local research governance applications required to permit the study to take place in the hosting institution. Additionally, any Centres that have already supplied the applicant with cases, will be updated with the relevant documentation, namely, the updated: 'letter of approval'; BRAIN UK Application; and amendment covering letter.

5.5.3 Discovery of Clinically Significant Information

All types of medical and biomedical research have the inherent capacity to reveal biological data and information that may have clinical or psychosocial implications for participants and/or their relatives. At times a study may, unexpectedly generate results of clinical significance. In this event, researchers should at least notify BRAIN UK and may also report to the supplying Participating Centre. For a further explanation of what clinically significant information is and whether disclosure might be considered appropriate see Section 3.5 Discovery and Disclosure of Clinically Significant Information.

5.5.4 Incident Management

The reporting of incidents is for the common good and the major concern is not to apportion blame, but to contain, then resolve the situation and prevent a future re-occurrence. Looking at what was wrong in the system helps organisations to learn lessons that can prevent the incident recurring. In line with the University of Southampton's Research Integrity and Governance Document on Management of Deviations and Serious Breaches of Good Clinical Practice and/or the Study Protocol[93] and the Health Research Authority[94] advice, the primary responsibility for investigating non-compliance with the protocol or Good Clinical Practice (or equivalent standards) and taking corrective action is placed with the Sponsor. It is not necessary to notify the Research Ethics Committee (REC) of minor protocol violations unless they constitute a 'serious breach'. It states that 'a "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-Clinical Trial of an Investigational Medicinal Products) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

In the UK, serious breaches are required to be reported to the relevant REC and should be notified as soon as possible of any breach of the approval conditions, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the tissue. Such incidents would also need to be reported immediately to the HTA.

Applicant and Researcher's Responsibilities

All BRAIN UK studies are required to have identified their research Sponsor and to have completed local Research Governance assessments prior to any research taking place. Any incidents should be reported to the local sponsor immediately and local staff should be able to advise on whether the breach constitutes a "serious breach" or a minor violation. It is imperative that researchers notify the Sponsor immediately as it is the responsibility of the Sponsor to notify the REC and relevant regulatory bodies of a serious breach in any study within 7 days of the matter coming to their attention. The report may be provided by the Principal Investigator or other representative of the Sponsor, copied to the Sponsor. Reports of serious breaches should give details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given and the REC informed what further action the Sponsor plans to take.

In addition, applicants (and their research team) must report a data breach immediately when it occurs, is threatened or is suspected, using local sponsoring organisation procedures. Failure of the applicant to report data breach incidents is a serious matter as it could leave your local sponsoring organisation exposed to repeated and more serious attacks/breaches as well as to the imposition of large fines. Certain types of breaches must be reported by the Data Protection Officer to the Information Commissioner's Office within 72 hours of becoming aware of the breach, therefore, it is important that you contain and respond immediately to the discovery of a data breach.

Researchers should also inform BRAIN UK of any serious breaches so it can evaluate if its governance arrangements are suitable or require improvement. Final outcomes of any breaches should be sent to BRAIN UK, in order to inform its sponsors to ensure adequate oversight of the BRAIN UK study.

[93] University of Southampton's Research Integrity and Governance Document on Management of Deviations and Serious Breaches of GCP and/or the Study Protocol Ver: 01
https://intranet.soton.ac.uk/sites/researcherportal/SiteAssets/Lists/Services1/EditForm/006%20Management%20of%20deviations%20and%20serious%20breaches%20of%20GCP%20and%20or%20the%20study%20protocol.pdf
[94] Health Research Authority Standard Operating Procedure for Research Ethics Committees Version 7.2 January 2017

5.5.5 Closure of the Researcher's Study

On completion of a study a researcher should notify BRAIN UK. The activity status of the study is also checked when requesting the annual report for BRAIN UK. On notification of closure researchers are sent:

- Request for a 'Closing Report'. This is very similar to the annual reports but seeks to identify an overall summary of the study, including whether the study achieved its objectives and the main findings.
- Study Closure Letter confirming that the Ethical Approval from the Southampton and South West Hampshire Research Ethics Committee 'B' under the terms of their approval for BRAIN UK has now terminated. And, a reminder of their obligations, under the Human Tissue Act[6,7], that data should not be passed onto third parties and to acknowledge the contribution of BRAIN UK and the NHS Trusts which supplied tissues in all resulting publications.
- The Participating Centres that supplied tissue are notified that the project is closed and are reminded of the applicant's responsibility to ensure that any remaining human tissue samples are appropriately managed. This email is copied to the PI of the project to ensure that lines of communication are open so that the applicant can appropriately manage the samples.

An example template for the Closing Report can be located on the BRAIN UK website. An example of the 'Study Closure Letter' is contained in Appendix K: Template Study Closure Letter. The information from the Closing Report is supplied to the BRAIN UK Committee for it to review at its Annual Committee Meeting. This is to gain oversight of the research taking place on cases encompassed by BRAIN UK and insight in to the utility of BRAIN UK.

6 Research Ethics Applying to BRAIN UK

The University of Southampton operates a process 'Ethics and Research Governance Online' (ERGO) which is an intranet-based online system designed to facilitate the process of gaining university ethics, governance and insurance approval and sponsorship for research studies conducted by staff and student researchers. BRAIN UK has an ERGO approved study reference 23425. BRAIN UK also has external ethical approval from the NHS Health Research Authority Research Ethics Committee.

The University Ethics Policy requires all research activity involving human participants to be registered on ERGO regardless of any other external approvals obtained. ERGO records all staff and student research activity and is a repository for essential study documents. This facilitates oversight by the Research Integrity and Governance (RIG) Team to ensure all the necessary approvals are in place, and that approved studies are conducted appropriately, thus ensuring compliance with legislation, regulation and adherence to best practice.

6.1 Research Ethics Committee (REC) Review & Reports

A favourable opinion for the operation of BRAIN UK has been obtained from South Central – Hampshire B REC (REC reference number 14/SC/0098) and continuing ethical approval is a pre-requisite for continued operation.
Substantial amendments for the operation of BRAIN UK that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
All correspondence with the REC will be retained.
An annual progress report for BRAIN UK is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
If BRAIN UK operations are terminated prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC within one year after the termination of BRAIN UK.

Regulatory Review & Compliance
Before any site can register cases into the BRAIN UK study, BRAIN UK will ensure that appropriate local 'Research and Development' (R&D) approvals are in place from Participating Centres. HRA and Health and Care Research Wales (HCRW) Approval is the process for the NHS in England and Wales that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA and HCRW staff, with the independent REC opinion provided through the UK Research Ethics Service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England and Wales. Studies led from England or Wales with sites in Northern Ireland or Scotland will be supported through existing UK-wide compatibility systems, by which each country accepts the centralised assurances, as far as they apply, from national coordinating functions without unnecessary duplication.

For any amendment to BRAIN UK, the Chief Investigator or designee, in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended. Document versions will be updated to facilitate tracking of version history of the document and SharePoint (a Microsoft tool that facilitates versioning, by which successive iterations of a document are numbered and saved).

If BRAIN UK wishes to make a substantial amendment to the REC application or the supporting documents, a valid notice of amendment will be submitted to the REC for consideration. The University of Southampton Research Integrity and Governance, in its role as sponsor will decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. This decision will be made in-line with the

HRA advice[94, 95]. If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

6.2 Peer review

The University of Southampton has a peer review process, performed by the Research Integrity and Governance team, which aims to facilitate and support researchers in undertaking clinical studies to meet the expectations and standards set out by legislation, frameworks and sponsor's procedures and guidance where integrity of data and patient safety are paramount considerations. Its policies[96] are within the UK Policy Framework for Health and Social Care Research[97].

In-line with the UK Policy Framework for Health and Social Care the Sponsor ensures that research proposals and protocols are scientifically sound (e.g. through independent expert review), safe, ethical, legal and feasible and remain so for the duration of the research, taking account of developments while the research is ongoing[96].

6.3 Protocol compliance

Reporting of breach incidents is for the common good and the major concern is not to apportion blame, but to contain, then resolve the situation and prevent a future re-occurrence. Failure to report breach incidents is a serious matter as it could leave the University exposed to repeated and more serious attacks/breaches as well as to the imposition of large fines. The University of Southampton Legal Services Department has a number of policies to provide specialist advice on Integrity, Ethics and Governance and Information Governance.

The University of Southampton Research Integrity and Governance policy Management of Deviations and Serious Breaches of GCP and/or the Study Protocol[98] describes the procedures for the recording, evaluation, management and reporting of deviations and serious breaches for non-commercial clinical research studies sponsored by the University of Southampton. In summary, it details the procedures that should be undertaken by the Research Integrity and Governance (RIG) Team on behalf of the Sponsor and sets out the expectations of the Sponsor on the Chief Investigator (CI), the investigational site team and the study management team in the event of a breach of protocol. The CI or designee is responsible for keeping records of all deviations and for reviewing and reporting serious breaches appropriately. The Sponsor or designee is responsible for ensuring serious breaches are reported to the REC. The CI, or any other member of the research team may identify a deviation or serious breach of the study protocol. They may also be identified through a monitoring visit, an audit, a BRAIN UK Steering Committee, Information Security Team or similar. Individuals external to the study team, including participants and members of the public may also report a deviation to the Sponsor or study team.

Information Governance sets out the way in which the University handles all of its information, in particular personal and special category (sensitive) information, from creation to deletion. It provides a framework for a compliance regime that includes privacy, access controls, and other compliance issues[99]. The University of

[95] NHS HRA Amending an approval (Aug 2018) https://www.hra.nhs.uk/approvals-amendments/amending-approval/

[96] University of Southampton, Research Integrity and Governance. Sponsorship Arrangements and Responsibilities. Ver 01. Sept 2018 https://intranet.soton.ac.uk/sites/researcherportal/SiteAssets/Lists/Services1/EditForm/University%20of%20Southampton_Sponsorship%20Arrangements%20and%20Responsibilities%20v1.0.pdf

[97] NHS HRA UK Policy Framework for Health and Social Care Research https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

[98] University of Southampton, Research Integrity and Governance. Management of Deviations and Serious Breaches of GCP and/or the Study Protocol. Ver 01. Dec 2018

[99] University of Southampton Legal Services Information Governance and Policies https://www.southampton.ac.uk/legalservices/policy-and-guidance.page

Southampton Data Protection Policy[100] includes how data breach incidents should be reported and handled both within the University and to relevant external bodies, such as the Information Commissioner's Office.

The University describes data breach incidents which must be reported as including those that:

- Pose a threat to personal data including special category (sensitive) personal data, for example, personal data sent to the wrong recipient, an unauthorised disclosure loss of portable computing equipment e.g. Laptop; Mobile phone etc. containing personal data.
- Pose a threat to privacy such as hacking or attempted hacking of systems containing personal data by staff, third-parties or outsiders and attempts to obtain personal data by deception (e.g. bogus phone calls, social engineering or e-mails); Actual or attempted unauthorised entry to a secure areas housing personal data.
- Breach confidentiality obligations such as disclosure of restricted or confidential information (especially passwords or other access control data) to unauthorised personnel.

6.4 Indemnity

Submission through the ERGO system will automatically ensure higher risk studies are forwarded to the University's RIG team, to arrange for University Sponsorship and insurance. As BRAIN UK is registered on ERGO it has been assessed and approved for Sponsorship and Insurance. This cover includes Professional Indemnity and Public Liability.

6.5 Access and Dissemination

Access to the final study dataset

The intention is that the BRAIN UK study will be enduring and as such the dataset will be continually accruing data. Given the sensitive nature there is currently no intention to provide access to the full dataset. Access to extracts of the dataset is described in Section 5.3 Data Interrogation and Dissemination. BRAIN UK follows the University of Southampton Research Data Management Policy[101] and in the event of study closure records would be retained for 30 years[102]. See BRAIN UK Information Governance[54] for further details.

Dissemination policy

BRAIN UK is a service to facilitate access to Biomedical Research and as such does not regularly produce novel research of its own. However, applicants to the service are encouraged to disseminate the findings of their research, see **Benefits of Research to Society** for further details.

The BRAIN UK service is promoted in the following ways:

- Regular attendance and presenting at scientific meetings, local, national and international;
- Acknowledgements of BRAIN UK support in outputs generated by studies (for e.g. scientific presentations and published scientific papers);
- Membership and involvement of the MRC Brain Banks Network;
- Presence on the UK Clinical Research Collaboration website;
- Own publicity, including website, leafleting and occasional interviews for radio and published media;

[100] University of Southampton. Data Protection Policy. May 2018
http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Information%20Governance%20Policies/Data%20Protection%20Policy.pdf
[101] University of Southampton Research Data Management Policy 2018-2019
http://www.calendar.soton.ac.uk/sectionIV/research-data-management.html
[102] University of Southampton Record Retention Schedule June 2018
http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Information%20Governance%20Policies/Record%20Retention%20Schedule%20Final%20June%202018.pdf

- 43% of our applications come from recommendations from other researchers, Participating Centres and committee members;
- 29% of our applications are from previous applicants.

In addition, BRAIN UK requires a lay summary of the applicant's research, to enable our lay members of the committee to engage with the review process; to be published on our website[103] to facilitate transparency within research; and to encourage and support collaborative work amongst research studies.

7 Acronyms

BNS	British Neuropathological Society
BRAIN UK	UK Brain Archive Information Network (long title)
CAG	Confidentiality Advisory Group
CNS	Central Nervous System
DPA	Data Protection Act
ERGO	Ethics and Research Governance Online
GDPR	General Data Protection Register
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HTA	Human Tissue Authority
MRC	Medical Research Council
MTA	Material Transfer Agreement
NHS	National Health Service
R&D	Research and Development
REC	Research Ethics Committee
RIF	Research Impact Factor

[103] BRAIN UK Lay Summaries https://www.southampton.ac.uk/brainuk/studies-supported/lay-summaries-home.page

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4	MRC Additional Terms and Conditions, June 2018. https://mrc.ukri.org/documents/pdf/mrc-additional-terms-and-conditions/
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9 Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
-	1.72	03/05/2016	C. Mitchell	Previously approved version under ethics ref: 14/SC/0098
-	2.0	01/04/2019	C. Mitchell	Preparation for new ethics application: updated to include GDPR changes, and amalgamation of documentation to ensure consistency and remove duplication.

10 Appendices

Appendix A: Impact of BRAIN UK

Applicants are questioned, in their annual report, about impact of BRAIN UK on their study and whether it would have taken place.
A: Yes, BRAIN UK support had VERY LITTLE impact on my study.
B: Yes, but it may have been more INCONVENIENT and limited my access to samples; I may have needed to redesign the study to proceed alone.
C: Yes, but it may have had a SIGNIFICANT effect on time, costs or outputs; I would have needed to redesign the study to proceed alone.
D: No, I could not have conducted this study without BRAIN UK.

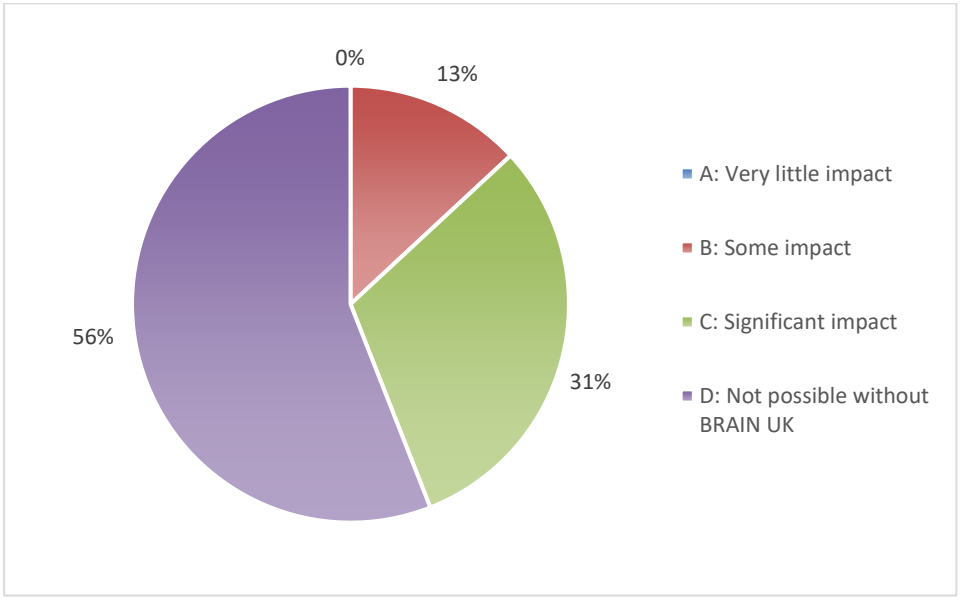

Figure 4. Summary of the impact of BRAIN UK on the studies it has supported. Data from 2011 to 2017. Overall, almost 88% reported that BRAIN had a significant impact on their study.

Appendix B: Distribution of Post Mortem Cases

The distribution of the number of post – mortem cases available for research at Participating Centres in the BRAIN UK network:

Participating Centre	Estimated Number of Cases
University Hospital Southampton NHS Foundation Trust	7,059*
Oxford University Hospitals NHS Trust	6,800
NHS Lothian	6,000
Nottingham University Hospitals NHS Trust	5,994*
NHS Greater Glasgow and Clyde	5,500
University College London Hospitals NHS Foundation Trust	1,331*
King's College Hospital NHS Foundation Trust	4,500
Royal Free London NHS Foundation Trust	4,400
Cardiff and Vale University Health Board	4,000
North Bristol NHS Trust	3,872*
Cambridge University Hospitals NHS Foundation Trust	1,297*
University Hospitals Plymouth NHS Trust	2,442*
Great Ormond Street Hospital for Children NHS Foundation Trust	945*
Imperial College Healthcare NHS Trust	765*
The Walton Centre NHS Foundation Trust	1,000
South Tees Hospitals Foundation Trust	270
Leeds Teaching Hospitals NHS Trust	*
Barking, Havering and Redbridge Hospitals NHS Trust	*
Sheffield Teaching Hospitals NHS Foundation Trust	*
Barts Health NHS Trust	*
Lancashire Teaching Hospitals NHS Foundation Trust	*
St George's Healthcare NHS Trust	*
Salford Royal NHS Foundation Trust	*
University Hospitals Birmingham NHS Foundation Trust	*
	58,470

* Currently unable to provide data.

Based upon current BRAIN UK 1 and BRAIN UK 2 databases and on questionnaires returned by Participating Centres December 2013.

Appendix C: Distribution of Biopsy Cases

The distribution of the total number of cases available for research in the putative BRAIN UK 3 database. (Based on data derived from questionnaires returned by Participating Centres December 2013).

Participating Centre	Current Surgical Archive	Additional Annual Surgical Cases
University Hospital Southampton NHS Foundation Trust	73,100	1,700
North Bristol NHS Trust	48,000	1,200
Great Ormond Street Hospital for Children NHS Foundation Trust	40,000	500
NHS Greater Glasgow and Clyde	32,000	800
University College London Hospitals NHS Foundation Trust	32,000	2,000
King's College Hospital NHS Foundation Trust	20,000	1,500
Nottingham University Hospitals NHS Trust	16,100	700
The Walton Centre NHS Foundation Trust	15,000	800
Cambridge University Hospitals NHS Foundation Trust	14,400	800
St George's Healthcare NHS Trust	13,200	550
Salford Royal NHS Foundation Trust	13,200	1,100
NHS Lothian	13,000	650
Cardiff and Vale University Health Board	12,000	400
University Hospitals Plymouth NHS Trust	8,500	500
South Tees Hospitals Foundation Trust	5,250	175
Barts Health NHS Trust	4,000	200
Imperial College Healthcare NHS Trust	3,600	300
Oxford University Hospitals NHS Trust	*	*
Royal Free London NHS Foundation Trust	*	*
Leeds Teaching Hospitals NHS Trust	*	*
Barking, Havering and Redbridge Hospitals NHS Trust	*	*
Sheffield Teaching Hospitals NHS Foundation Trust	*	*
Lancashire Teaching Hospitals NHS Foundation Trust	*	*
University Hospitals Birmingham NHS Foundation Trust	*	*
	363,350	13,875

Based upon questionnaires returned by Participating Centres December 2013.

* Currently unable to provide data.

Appendix D: Tissue Storage Centre Contacts

Below is a list of all centres participating with BRAIN UK and Neuropathologist contact.

Barking, Havering and Redbridge University Hospitals NHS Trust
ad int. Dr. Kathreena Kurian
Kathreena.Kurian@nbt.nhs.uk
01708 435 000
Queen's Hospital, Rom Valley Way, Romford, RM7 0AG

Barts Health NHS Trust
Prof. Silvia Marino
s.marino@qmul.ac.uk
020 7377 7000
Blizard Institute, Barts and The London School of Medicine and Dentistry, 4 Newark Street, Whitechapel, London, E1 2AT

Cambridge University Hospitals NHS Foundation Trust
Dr. Kieren Allinson
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01223 217 175
Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Level 3 Lab Block, Box 231, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ

Cardiff and Vale University Health Board
Dr. G Alistair Lammie
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Appendix E: Consent to Research in Participating Centres

BRAIN UK survey on consent to research practice for living patients in Participating Centres published: C. Mitchell, N.E. Bailey, H. Bulbeck, K. Hopkins, S. Price, W. Stewart, D. Hilton, J.A.R. Nicoll, K.M. Kurian. PO81 A Lack Of Consent To Donate Brain Tumour Tissue For Research Hampers Progress, *Neuro-Oncology*, Vol. 17, Issue suppl_8, November 2015, Page viii14, https://doi.org/10.1093/neuonc/nov284.70

A Lack of Consent to Donate Residual Tissue Hampers Progress

Mitchell C[1], Bailey NE[1], Bulbeck H[2], Hopkins K[3], Price S[4], Stewart W[5], Hilton D[6], Nicoll JAR[1], Kurian KM[7]

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[7]Department of Neuropathology, Southmead Hospital, Bristol, UK

Introduction

Brain tumour tissue can be difficult for researchers to access. Currently, NHS central nervous system biopsy archives hold around 400,000 stored samples, accruing a further 18,500 annually. *BRAIN UK* is a collaborative virtual brain bank, facilitating access to these under-utilised neuropathology archives for research. Without obtaining consent for research on residual tissue, it may not be possible to carry out testing on brain tissue samples using emerging diagnostic, prognostic or predictive tests which could improve disease management and access to new treatments.

Methods

24 UK neuropathology centres were surveyed on their consent for research on residual tissue processes, recording and rates.

Results

Figure 1: 23/24 (96%) centres responded to the survey about obtaining prospective informed consent to research:

- 16/23 (70%) obtain consent
- 1/23 (4%) were unsure
- 6/23 (26%) do not have a procedure for obtaining consent

Figure 2: of the 16 centres with procedures to obtain prospective consent, 9 provided quantifiable data on consent rates, 7 (44%) were unable to provide quantitative data:

- 6/9 (37%) have consent rates of 95-100%
- 3/9 (19%) we estimate consent rates of 10%

Figure 3: 19 centres provided quantitative or qualitative data regarding rates of consent:

- 7/19 (37%) have consent rates of 0%
- 6/19 (32%) have consent rates of 95-100
- 6/19 (32%) have varying rates of consent which we have estimated to be around 10%

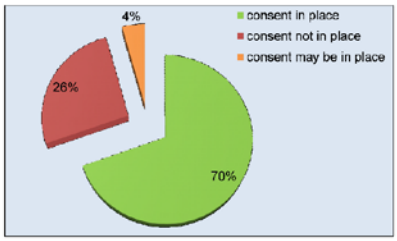

Figure 1. Percentages of centres prospective consent procedures in place, n=23.

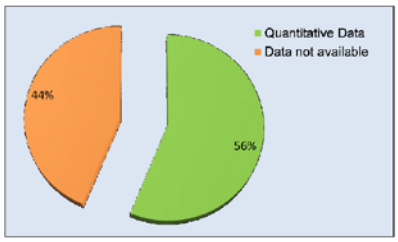

Figure 2. Percentages of centres, with procedures to collect prospective consent, with access to quantitative data on the rates of consent to research, n=16.

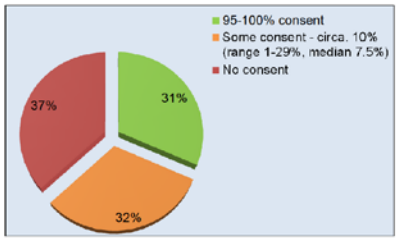

Figure 3. Overall picture of percentages of centres gaining consent to use residual tissue for research use, using both quantitative and qualitative data, n=19.

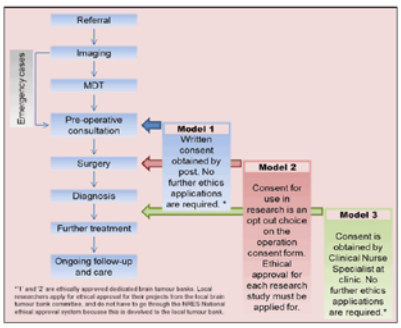

Figure 4. Variation in patient pathways (A lack of brain tumour tissue donation for research and genetic analysis hampers progress with the management and treatment of this disease (K Kurian)).

Conclusion

Consenting procedures and rates are very variable across the UK. In some centres consent rates are high but much less in others. We estimate that the overall current consent rate to be about 30%, which may reduce the number of samples available to research.

Robust systems for recording consent accurately in electronic records are not consistent across the NHS and not all centres have 'consent to research' procedures in place. Three different approaches to collecting consent in centres that are successful are illustrated in Figure 4.

Archived residual tissue could be a valuable research resource but could go unused due to lack of consent. This is despite research to suggest that patients are largely supportive of the use of their tissues in research and a fundamental legal and ethical right to determine what happens to their own bodies.

We are supporting *brainstrust* in leading a campaign to support both:

- Centres, with example consent forms and participant information leaflets
- Patients, with information on research and documentation to encourage a conversation with professionals.

Figure 5, *brainstrust* campaign

Without consent, research on tissue is limited and it may not be possible to investigate tissues thoroughly, such as correlating pathological and genetic findings with clinical outcomes and treatments.

This work is supported by

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Appendix F: Consent to Research for Surgical Patients

Example of a typical consent to research as part of a surgical procedure consent form from University Hospital Southampton.

Consent form 1

University Hospital Southampton NHS
NHS Foundation Trust

Patient agreement to investigation or treatment

Staff Use only:

For staff use only
Surname:
First names:
Date of birth:
Hospital no:
Male/Female:
(Use Hospital Identification label)

Special patient requirements..... Responsible healthcare professional.....
(e.g. other language/other communications method) Job Title:.....

Name of procedure or course of treatment **Side/site**..... (as appropriate)

(include brief explanation if medical term not clear)
.....
.....

Statement of Health Professional

(To be filled in by a health professional with an **appropriate knowledge of the proposed procedure**, as specified in the Trust's Consent Policy)

I have explained the procedure to the patient. In particular I have explained:
- The intended benefits of the procedure.....
.....
.....
- Any serious or frequently occurring risks from the procedure.....
.....
.....
- Any extra procedures which may become necessary during the procedure

☐ Blood product transfusion ☐ Radiological procedure ☐ Other procedure (please specify)
.....

I have discussed what the treatment procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of this patient.
- The following information leaflet/tape has been provided.....
(include version number/date as appropriate)

This procedure will involve:
☐ general and/or regional anaesthesia ☐ local anaesthesia ☐ sedation

Health professional's signature..... Date:.....
Name (PRINT): ..... Job Title:.....
Contact details (if patient wishes to discuss options later)
.....

☐ I have offered the patient information about the procedure but s/he has refused information.

Statement of the Interpreter (if appropriate)

I have interpreted the information above to the patient to the best of my ability and in a way in which I believe s/he can understand.
Interpreter's signature ..... Date.....
Name (PRINT).....

Copy accepted by patient: yes/no (please ring)

YELLOW COPY: CASE NOTES WHITE COPY: PATHOLOGY PINK COPY: PATIENT
(send to Pathology Business Unit SGH MP 8)

Statement of Patient

Please read this form carefully. If your treatment has been planned in advance, you should already have your own copy, which describes the benefits & risks of the proposed treatment. If not, you will be offered a copy now. Do ask if you have any further questions - we are here to help you. Please read this form carefully. **You have the right to change your mind at any time before the procedure is undertaken, including after you have signed this form.** You may ask for a relative, or friend, or a nurse to be present whilst the procedure is being explained and consent is obtained.
The training of doctors and other health professionals is essential to the continuation of the Health Service and improving the quality of care. Your treatment may provide an important opportunity for such training, where necessary under the careful supervision of a senior doctor. You may, however, decline to be involved in the formal training of medical and other students without this adversely affecting your care and treatment.
Please initial the boxes to indicate you have understood and agree to the statements below.

☐ **I agree** to the procedure (or course of treatment) described on this form.

☐ **I understand** that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.

☐ **I understand** that any tissue removed as part of the procedure or treatment may be used for diagnostic and therapeutic purposes as part of my care and may subsequently be stored as part of my Medical Records and may be of benefit to my subsequent care management.

☐ **I understand** that any surplus tissue may also be used for quality control/monitoring and/or public health surveillance purposes, where at the point of use my identity would not be known. The disposal of any surplus tissue would be done in a manner regulated by appropriate, ethical, legal and professional standards.

☐ **I agree** that any tissue removed as part of the procedure or treatment, which is then surplus to my own care, may be used for audit, teaching, and/or research. Any sample used for such purposes would be done in an anonymous way so that my identity at the point of use would not be known. All research studies would be subject to Research Ethics Approval and would be subject to national standards of practice.

☐ **I agree** to the use of photographs/video for the purpose of diagnosis and treatment.

☐ **I understand** that I will have the opportunity to discuss the details of anaesthesia with an anaesthetist before the procedure, unless the urgency of my situation prevents this. (This only applies to patients having general or regional anaesthesia.)

Female Patients only (when applicable); **I understand** my care may involve X-rays and that radiation should be limited during pregnancy. There is a chance I may be pregnant. ☐ Yes ☐ No

☐ **I understand** that any procedure in addition to those described on this form will only be carried out if it is necessary to save my life or to prevent serious harm to my health.

☐ **I have been told** about additional procedures, which may become necessary during my treatment. I have listed below any procedures that I do not wish to be carried out, without discussion with me.
.....
.....

Patient's own signature..... Date.....
Name (PRINT) .....
If the patient is unable to sign but has indicated his/her consent, a witness should sign below.
Signature:..... Date.....
Name (Print .....

Confirmation of Consent: to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance

On behalf of the team treating the patient, I have confirmed with the patient that s/he has no further questions and wishes the procedure to go ahead.
Signed:..... Date:.....
Name (PRINT) ..... Job title:.....
Important notes: (tick if applicable)
☐ The patient has withdrawn consent (ask patient to sign/date here) .....
☐ See also Advance Directive/Living Will (eg Jehovah's Witness Form)

Consent Form 1

Guidance to health professionals (to be read in conjunction with consent policy)

What a consent form is for

This form documents the patient's agreement to go ahead with the investigation or treatment you have proposed. It is not a legal waiver - if patients, for example, do not receive enough information on which to base their decision, then the consent may not be valid, even though the form has been signed. Patients are also entitled to change their mind after signing the form, if they retain capacity to do so. The form should act as an *aide-memoire* to health professionals and patients, by providing a check-list of the kind of information patients should be offered, and by enabling the patient to have a written record of the main points discussed. In no way, however, should the written information provided for the patient be regarded as a substitute for face-to-face discussions with the patient.

The law on consent

See the Department of Health's *Reference guide to consent for examination or treatment* for a comprehensive summary of the law on consent (also available at www.doh.gov.uk/consent).

Who can give consent

Everyone aged 16 or more is presumed to be competent to give consent for themselves, unless the opposite is demonstrated. If a child under the age of 16 has "sufficient understanding and intelligence to enable him or her to understand fully what is proposed", then he or she will be competent to give consent for himself or herself. Young people aged 16 and 17, and legally 'competent' younger children, may therefore sign this form for themselves, but may like a parent to countersign as well. If the child is not able to give consent for himself or herself, someone with parental responsibility may do so on their behalf and a separate form is available for this purpose. Even where a child is able to give consent for himself or herself, you should always involve those with parental responsibility in the child's care, unless the child specifically asks you not to do so. If a patient is mentally competent to give consent but is physically unable to sign a form, you should complete this form as usual, and ask an independent witness to confirm that the patient has given consent orally or non-verbally.

When NOT to use this Form

If the patient is 18 or over and is not legally competent to give consent, you should use Form 4 (form for adults who are unable to consent to investigation or treatment) instead of this form. A patient will not be legally competent to give consent if:

- they are unable to comprehend and retain information material to the decision and/or
- they are unable to weigh and use this information in coming to a decision.

You should always take all reasonable steps (for example involving more specialist colleagues) to support a patient in making their own decision, before concluding that they are unable to do so.

Relatives **cannot** be asked to sign this form on behalf of an adult who is not legally competent to consent for himself or herself.

Information

Information about what the treatment will involve, its benefits and risks (including side-effects and complications) and the alternatives to the particular procedure proposed, is crucial for patients when making up their minds. The courts have stated that patients should be told about 'significant risks' which would affect the judgement of a reasonable patient'. 'Significant' has not been legally defined, but the GMC requires doctors to tell patients about 'serious or frequently occurring' risks. In addition if patients make clear they have particular concerns about certain kinds of risk, you should make sure they are informed about these risks, even if they are very small or rare. You should always answer questions honestly. Sometimes, patients may make it clear that they do not want to have any information about the options, but want you to decide on their behalf. In such circumstances, you should do your best to ensure that the patient receives at least very basic information about what is proposed. Where information is refused, you should document this on page 1 of the form or in the patient's notes.

Pregnancy Disclaimer

If the patient has answered **Yes** the advice of a radiation professional should be taken before proceeding with treatment involving x-rays between nipples and knees.

Photographs and video recordings of patients

You must tell the patient wherever possible if this is going to happen and always seek written consent. If you are requiring consent to use photographs/video recordings/video conferencing for teaching/research and/or publication a specific Consent Form is available from Medical Illustration.

If staff have any general comments or queries related to this form, these should be directed either to the local Patient Advisory and Liaison Service or the Risk Management Department.

Appendix G: Consent to Research for Post Mortems

Example of a typical consent to research as part of a surgical procedure consent form from University Hospital Southampton.

University Hospital Southampton NHS
NHS Foundation Trust

Consent for post-mortem examination of an adult

Name of deceased:

Date of birth: Date of death:

Consultant / GP in charge of the patient:

Hospital number for deceased:

This form enables you to consent to a post-mortem examination of the body of the person named above. Please read it carefully with the person obtaining consent from you. For each section tick the relevant box to indicate your decisions and sign beneath each section.

☐ I confirm that I have had the opportunity to read and understand the information leaflet 'Guide to the Post Mortem Examination (Adult)'.

☐ I confirm that my questions about the post-mortem examination have been answered to my satisfaction and understanding.

Signed by……Name……

Part 1: Post-mortem examination

A post-mortem examination may be full or limited. The benefits and disadvantages of each will be explained to you. Please choose one of the following options.

Option 1: Consent to a full post-mortem examination

☐ I consent to a **full** post-mortem examination of the body of the person named above. I am not aware that he / she objected to this. I understand that the reason for the examination is to further explain the cause of death and study the effects of disease and treatment.

Option 2: Consent to a limited post-mortem examination

☐ I consent to a **limited** post-mortem examination of the body of the person named above. I am not aware that he / she objected to this. I understand that this may limit the information about the cause of death and effects of treatment.

I wish to limit the examination to:

☐ The head, including the brain
☐ The chest and neck
☐ The abdomen and pelvis
☐ Other (please specify) ……

……

Signed by……Name……

Version 4 (2014)

Part 2: Retention and future use of tissue samples

As part of a full or limited post-mortem examination tissue samples and small amounts of bodily fluids will be taken and used to determine the diagnosis and extent of the disease. Bodily fluids will usually be disposed of following a diagnosis. However, the tissue samples removed during a post-mortem examination can be stored for use in the future. The storage of the tissue samples and their later use require your consent. These samples can be valuable for review on behalf of the family if a need arises in the future, the education and training of healthcare professionals, research and other purposes. Please indicate whether you consent to this:

☐ Following the diagnosis, please dispose of the retained tissues in line with my wishes indicated below, **or**

☐ I consent to the tissue samples being stored for future use, **and**

☐ I consent to the tissue samples being used for the purpose of evaluating the efficacy of any drug or treatment administered to the deceased, or for review on behalf of the family if a need arises

☐ I consent to tissue samples being used for education and training relating to human health, quality assurance, public health monitoring or clinical audit

☐ I consent to the tissue samples being used for research that has been approved by an appropriate ethics committee

Please indicate one of the options below for the final disposal arrangements of tissue samples:

☐ I wish the hospital to dispose of any retained tissue samples

☐ I will make my own arrangements for lawful disposal of any retained tissue samples

Signed by……Name……

Version 4 (2014)

Part 3: Retention and future use of organs

As part of a full or limited post-mortem examination, it may be necessary to retain some organs for more detailed examination. This requires your consent:

☐ I consent to the retention, for more detailed examination, of the following organ(s):

……

……

Use and disposal of retained organs

After more detailed examination of organs removed during a post-mortem examination, they must be either stored for specified uses or disposed of in a lawful manner. You have the option of donating retained organs for research and / or medical education. Please indicate your wishes by choosing from the following options:

☐ I wish to have the organ(s) returned to the body prior to the funeral (this may delay the funeral taking place)

☐ I wish to donate retained organ(s) for research into related diseases, after which they will be disposed of lawfully

☐ I wish to donate retained organ(s) for education, after which they will be disposed of lawfully

☐ I wish the hospital to lawfully dispose of any retained organ(s), without them being used for research and / or medical education

☐ I will make my own arrangements for lawful disposal of any retained organ(s)

Signed by……Name……

Part 4: Other requirements of the post-mortem examination

In some cases there may be further requirements of the post-mortem examination, such as genetic testing of tissue samples. The person explaining about the post-mortem examination will explain these to you. Other requests or conditions which you would like to make:

……

……

……

Thank you for consenting to a post-mortem examination. You can change your mind about any of the decisions you have made, although there may be a short time limit for some of these. If you wish to make changes to anything you have consented to, or wish to withdraw your consent, please telephone …… as soon as possible and not later than…… Please do not hesitate to contact …… if you have any questions.

Signed……Name ……

Address……

……Tel no……

Relationship to the deceased ……Date ……

Details of person obtaining consent

Name ……Job title ……

Contact details……

Notes for person(s) obtaining consent

- I confirm that the person consenting has a full understanding of the post-mortem examination procedure

- I confirm that I have checked that the person consenting is the appropriate person for the purposes of the Human Tissue Act 2004

- I have discussed tissue samples being retained for future use and the potential uses for the tissue that is retained

- Consent is indicated by boxes which are ticked and signature of the person giving consent

- I have discussed any special requests or conditions concerning the post-mortem examination procedure

- Where appropriate, I have discussed the requirements of the post-mortem examination

  with…… **[insert name of pathologist]**

  Signed……Date……

- I have offered a photocopy of this form to the person giving consent

- If consent is subsequently withdrawn, either for the entire post-mortem examination, or for specific sections of it, each page of each copy of the form (or the relevant section(s)) should be clearly struck through. The person taking the withdrawal should also sign and date the form clearly, and note action taken to inform the mortuary (the date and time and member of mortuary staff informed).

Version 4 (2014)

Appendix H: Material Transfer Agreement

An example Material Transfer Agreement, as used by the University Of Southampton.

Draft, 11 September 2008

ACADEMIC – TO – ACADEMIC
HUMAN TISSUE TRANSFER AGREEMENT

The University of Southampton (the "**Supplier**"), an academic institution whose principal address is at Highfield, Southampton, SO17 1BJ, has collected and/or developed the materials known as

Insert description of materials: [.....] (the "**Original Materials**"), which may include human cells or tissues or other "relevant material" as defined in the Act.

Insert name of scientist: [.....] (the "**Recipient**"), who is an employee of

Insert name and address of scientist's Institution: [.....] (the "**Institution**"), an academic institution, whose principal address is at [.....],

Insert quantity of materials: wishes to acquire [.....] [vials] (the "**Quantity**") of the Original Materials for academic research relating to:

Insert description of academic research for which materials will be used: [..... ....] (the "**Project**"), which will be carried out at the following laboratory located at the Institution:

Insert laboratory address and insert term for which materials may be provided: [.....] (the "**Location**") for a period of [.....] year(s) (the "**Term**") on the terms shown below on pages [2 – 6]. The Institution agrees to be bound by and to comply with those terms in consideration of the Supplier making the Materials available to the Recipient and will ensure that the Recipient and the Co-workers comply with the Institution's obligations as if they were named as parties to this Agreement.

Agreed by the Parties by their authorised signatories:

For and on behalf of the University of Southampton	Read and understood by the Recipient	For and on behalf of **[**the Institution**]**
Signed	Signed	Signed
Print name	Print name	Print name
Title	Title	Title
Date	Date	Date

1 Supply of the Materials

1.1 *Supply.* If the Supplier has sufficient Original Materials at its disposal and is otherwise able, the Supplier will make the Quantity of the Original Materials available to the Recipient without cost, but the Institution agrees to reimburse the Supplier for any reasonable shipping and related costs that may be incurred when procuring, preparing and sending the Materials to the Recipient. Delivery of the Materials to the Institution's facilities will be at the Institution's risk.

1.2 *Ethics approval.* The Institution acknowledges that the supply of the Original Materials to the Recipient is conditional upon the Institution obtaining approval for the use of the Materials in the Project from an appropriately constituted research ethics committee. The Institution will provide the Supplier with a copy of such approval prior to the Supplier making the Original Materials available to the Recipient. The Institution confirms that the potential benefits of the Project outweigh any potential risk to the Donor(s).

1.3 *Data Protection.* If the Materials include Personal Data, the Institution will ensure that its registration under the DPA is sufficient for its use of the Materials in the Project prior to the Supplier making the Materials available to the Recipient. In addition, the Institution agrees to comply with all other provisions of the DPA applicable to its use of the Materials and any data and/or other information derived from their use.

1.4 *Receipt.* The Institution will provide the Supplier with written confirmation of the safe receipt of the Materials promptly after their delivery to the Institution's facilities. The Institution will ensure that such confirmation includes details of when and where the Materials were received by the Recipient and by whom and under what conditions the Materials were transported to the Institution's facilities.

1.5 *Location.* The Institution will store and use the Materials only at the Location. The Institution confirms that such Location is suitable for the Project and is compliant with the Act and all other applicable laws, approvals, rules, codes of practice and regulations.

1.6 *Return of Materials.* As between the Parties, the Supplier will retain custodianship of the Materials at all times and the Institution agrees to return or, if requested by the Supplier, destroy all remaining Materials and Modifications immediately:

(a) on termination of this Agreement;

(b) if the Institution is in breach of any term of this Agreement; or

(c) at any other time on the reasonable request of the Supplier.

1.7 *Disposal.* Except as may be reasonably required by the Project, the Institution will not destroy any Materials without the prior written consent of the Supplier and, the Institution agrees to comply with any reasonable instruction given by the Supplier in relation to the destruction of the Materials. If the Materials are exhausted or destroyed, whether during the course of the Project, in accordance with Clause 1.6 or otherwise, the Institution will provide the Supplier with written confirmation of the same.

2 The Recipient's use of the Materials

2.1 *Use.* The Institution will use the Materials and any Modifications only for the Project and will not use the Materials or Modifications for any commercial purpose or commercially sponsored research even if those purposes are being pursued in the Recipient's laboratory. The Institution agrees not to use any third party funding or materials in the Project without notifying the Supplier and ensuring that the terms imposed by any third party are consistent with the terms of this Agreement.

2.2 *Security.* The Institution will:

(a) keep the Materials secure at the Location and protected against loss, damage and contamination;

(b) keep the Materials clearly labelled as the property of the Supplier at all times;

(c) maintain complete and accurate written records to ensure that the Materials can be traced at all times and that details of all uses to which the Materials are put and any processes that are applied to them are documented;

(d) provide the Supplier with copies of the records maintained by the Institution under Clause 2.2(c) upon the Supplier's request;

(e) ensure that no one other than the Recipient and the Co-workers have access to the Materials and that the Recipient and the Co-workers are suitably qualified and trained to handle the Materials;

(f) ensure that it has in place all necessary safety procedures and practices to handle the Materials and that the Recipient and the Co-workers will comply with all safety requirements applicable to the Materials necessary for their well-being and that of others;

(g) ensure that all transportation, keeping, use and disposal of the Materials is in accordance with the appropriate containment level; and

(h) ensure that, if the Materials were obtained with the consent of the Donor, all use of the Materials is within the scope of that consent.

2.3 *Donor(s).* The Institution will not contact the Donor(s) or their medical advisor(s) without the prior written consent of the Supplier, which may require additional approval from a research ethics committee. If the Materials are made available to the Recipient in an anonymised form, the Institution will not, and will not seek to, link, decode or otherwise identify the Donor(s).

2.4 *Standards.* The Institution will use the Materials in accordance with good laboratory practice, all due skill and care and with dignity, sensitivity and respect. The Institution will comply with all applicable laws, approvals, rules, codes of practice and regulations governing the transportation, keeping, use and disposal of the Materials.

2.5 *No human use.* The Institution will not use the Materials, Modifications or any other material derived or generated through their use, in humans or in animals, in clinical trials or for diagnostic purposes involving humans nor expose the same to any material to be administered to any human or animal.

2.6 *No transfer.* The Institution will not sell, gift, charge, pledge, transfer, or otherwise supply or disclose the Materials or Modifications to any third party.

2.7 *No licence.* Except as expressly provided by this Agreement, no licence or other right to any of the Supplier's property or intellectual property is granted or implied by this Agreement.

3 Confidentiality obligations

3.1 *Ownership.* Confidential Information belongs to the Supplier. During the Term of this Agreement and for five (5) years thereafter, the Institution will not disclose to any third party nor use any Confidential Information for any purpose except the Project.

3.2 *Exceptions.* The obligations set out in Clause 3.1 do not apply to any information that the Institution can show by written record that:

(a) was known to the Institution before the information was imparted by the Supplier;

(b) is or subsequently becomes publicly known through no fault, act or omission on the part of the Institution;

(c) is received by the Institution without restriction on disclosure or use from a third party lawfully entitled to make the disclosure to the Institution without such restrictions;

(d) is developed by any of the Institution's employees and/or students who have not had any direct or

indirect access to, or use or knowledge of, the information imparted by the Supplier; or

(e) is required to be disclosed by the Institution to comply with the applicable laws or governmental regulations provided that the Institution, where possible, notifies the Supplier of such requirement prior to any such disclosure and limits the disclosure to the extent required by such law.

3.3 *Personal data*. Notwithstanding Clauses 3.1 and 3.2 above, if the Confidential Information contains any data that:

(a) constitutes Personal Data; or

(b) is otherwise protected either by law, an obligation of confidentiality owed to the Donor or otherwise;

the Institution agrees that it will not disclose any such data to any third party nor use the same for any purpose except the Project at any time and even after the Term of this Agreement.

4 Publication by the Recipient

4.1 *Acknowledgement*. The Institution will acknowledge the Supplier's contribution as the source of the Materials (and any other contribution that the Supplier may have made to the Project) in any Publication. The Institution will send the Supplier a copy of any proposed Publication, whether oral or written, prior to any Publication or submission for Publication, whichever is earlier. The Supplier's rights under this Clause 4 shall not affect the Institution's obligations under Clause 3.

4.2 *Publication*. The Institution agrees that it will not make any Publication that would disclose information that may allow the identity of the Donor to be deduced. The Institution acknowledges that data generated using the Materials may relate to the Donor, constitute Personal Data or otherwise be protected by law or an obligation of confidentiality owed to the Donor. The Institution agrees that it will not publish or disclose to any third party any such data.

4.3 *Data*. The Institution will make available, on the request of the Supplier, any data generated using the Materials, and the Supplier will be entitled to use all such data for academic research and educational purposes.

5 Arising intellectual property

5.1 *Notification*. If the Institution conceives, generates, or observes an Invention, then the Institution will promptly bring this to the attention of the Supplier on a confidential basis. The Institution agrees to obtain the consent of the Supplier, which will not be unreasonably withheld, prior to making any application to protect any Invention and prior to any commercialisation, transfer or grant of any rights to an Invention.

5.2 *Materials*. The Institution acknowledges that it may require a licence from the Supplier to use an Invention dependent on the Materials for purposes other than the performance of the Project and that the Supplier may be unable or unwilling to grant such a licence to its interest in the Materials.

5.3 *Supplier's share of revenue*. If any commercial revenues result from the Institution's use of any Invention or otherwise arise from the use of the Materials, the Supplier will be entitled to an equitable share of any such revenues that accrue to the Institution or any of its successors in title to any Invention.

5.4 *Supplier's right*. The Supplier will, at all times, retain the right to use all Inventions for academic research and educational purposes.

5.5 *Licence*. The Institution agrees that no Invention will restrict the Supplier's right to use, and to permit others to use, the Materials for any purpose.

6 No warranty or liability

6.1 *No warranty*. The Materials are experimental in nature, and the Supplier makes no representation and gives no warranty or undertaking in relation to them. As examples, but without limitation, the Supplier gives no warranty: (a) that it owns all necessary property, intellectual property, and other rights in the Materials and that their use will not infringe any rights owned by any third party; or (b) that the Materials are of merchantable or satisfactory quality or fit for any particular purpose, have been developed with reasonable care and skill or tested, for the presence of pathogens, infections, disease or otherwise, or are viable, safe, or non-toxic.

6.2 *No liability*. The Materials are made available by the Supplier free of charge as a service to the academic community and as such the Supplier and the Institution agree that the provisions of this Clause 6.2 are reasonable. The Supplier will have no liability to the Recipient, the Co-workers, the Institution, or any third party, whether in contract, tort, negligence, or otherwise, in relation to the supply of the Materials to the Recipient or their use or keeping by the Recipient or by any other person, or the consequences of their use, to the maximum extent permitted under applicable law. The Institution agrees that it will be wholly responsible for all claims and losses arising from such supply, use or keeping, including claims and losses arising from: (a) injury to the Institution's employees and third parties; (b) infringement of third-party intellectual property rights; and/or (c) the use of the Materials within or outside the scope of this Agreement.

7 General

7.1 *Definitions*. In this Agreement the following words have the following meanings:

(a) "**Act**" means the Human Tissue Act 2004 as from time to time amended.

(b) "**Confidential Information**" means the Materials and all information, including technical, patient, clinical, medical, scientific or commercial information, that may be provided by the Supplier to the Institution that: (i) in respect of information provided in documentary or by way of a model or in other tangible form, at the time of provision is marked or otherwise designated to show that it is imparted in confidence; (ii) in respect of information that is imparted orally, any information that the Supplier or its representatives informed the Institution at the time of disclosure was imparted in confidence; and (iii) any copy or part of any of the foregoing.

(c) "**Co-workers**" mean employees and students of the Institution who are authorised co-workers under the direct and immediate supervision of the Recipient and who have contractual obligations to the Institution that enable the Institution to comply with its obligations under this Agreement.

(d) "**Derivative**" means any derivative of the Materials.

(e) "**Donor**" means the person from whose body the Materials have come or about whom the Materials relate.

(f) "**DPA**" means the Data Protection Act 1998 as from time to time amended.

(g) "**Invention**" means any discovery, improvement or, invention arising out of the Project that incorporates or relates to the Materials or their use.

(h) "**Materials**" mean the Original Materials and (i) all materials, documents, and information that the Supplier may provide to the Institution under or in connection with this Agreement; (ii) any Derivatives and Progeny created by the Institution from or as a result of the use of the Materials; (iii) any of the foregoing contained or incorporated in any Modification; and (iv) any copy or part of any of the foregoing.

(i) "**Modification**" means any substance created by the Institution that contains or incorporates the Materials.

(j) "**Parties**" mean the Supplier and the Institution and "**Party**" means either one of them.

(k) "**Personal Data**" means "personal data" or "sensitive personal data" as defined in the DPA.

(l) "**Progeny**" means any unmodified descendent of the Materials.

(m) "**Publication**" means any report, publication, presentation, poster or other disclosure that mentions or describes work carried out using the Materials or any Modification.

7.2 *Amendment.* This Agreement may only be amended in writing signed by duly authorised representatives of each Party.

7.3 *No waiver.* No failure or delay on the part of either Party to exercise any right or remedy under this Agreement will be construed or operate as a waiver thereof, nor will any single or partial exercise of any right or remedy preclude the further exercise of such right or remedy.

7.4 *Entire agreement.* This Agreement sets out the entire agreement between the Parties relating to its subject matter and supersedes all prior oral or written agreements, arrangements or understandings between them relating to such subject matter. Each Party acknowledges that it does not rely on any representation, agreement, term, or condition which is not set out in this Agreement. Nothing in this Agreement limits or excludes either Party's liability for fraud.

7.5 *Survival.* The provisions of Clauses 1, 3, 4, 5, 6 and 7.5, will survive termination or expiry of this Agreement together with any other terms that by their nature or otherwise should reasonably survive termination or expiry of this Agreement.

7.6 *Third parties.* This Agreement does not create any right enforceable by any person who is not a party to it. Furthermore, no person except a Party to this Agreement has any right to prevent the amendment of this Agreement or its termination.

7.7 *Law and jurisdiction.* The validity, construction and performance of this Agreement will be governed by English law and will be subject to the exclusive jurisdiction of the English courts to which the parties hereby submit, except that a Party may seek an interim injunction in any court of competent jurisdiction.

Appendix I: Annual Report to BRAIN UK

Annual report that applicants are required to complete, can be obtained electronically.

BRAIN UK ANNUAL PROGRESS REPORT

To be completed and submitted by the Principal Investigator and emailed to brainuk@southampton.ac.uk. Continuation of your ethical approval for your project is dependent on the receipt of a completed progress form.

Please complete as many questions as you can (even if the project has not yet started).

1. Details of Chief Investigator

Name:
Address:
Telephone:
E-mail:

2. Details of study

Full title of study:
BRAIN UK reference number:
Date of favourable opinion:

3. Commencement and termination dates

Has the study started? Please put a cross in the relevant box.	Yes	No

If yes, what was the start Date?

If no, what are the reasons for the study not commencing?

If no, what is the expected start date?

Has the study finished?	Yes	No

If yes, what was the finish date of the study?

If no, what is the expected completion date of the study?

4. Summary of progress

Please provide a **brief** (1-2 paragraphs) summary of the project's activity during the year

Please provide details of all outputs using data derived from tissue sourced through BRAIN UK (please see "*Help* " tab for further details)

Please specify how you propose to share any data generated on the samples (please see "*Help* " tab for further details)

5. Amendments

Yes	No

Have any amendments been made to the study protocol during the year?
If yes, please give details below.

6. Collaborations

Yes	No

Was a collaboration suggested?
If yes, please give details below:

7. Serious breaches of the protocol

Yes	No

Have any serious breaches of the protocol occurred during the year?
If yes, please enclose a report of any serious breaches not already notified.

8. Discovery of clinically significant information

Yes	No

Have you discovered any clinically significant information during the year?
If yes, please describe what has been discovered and what has been done with the information so far.

9. Other issues

Yes	No

Are there any other developments in the study that you wish to report to *BRAIN UK*?
If yes, please describe the developments below.

Are there any ethical issues on which further advice is required?
If yes, please provide the details that you require ethical advice on.

Please add any other comments you wish to make that have not been covered.

10. The impact of BRAIN UK

Finally, we are looking for evidence of our impact, other than publication data, which we already record. We are looking at the impact of BRAIN UK in terms of the direct effect there would have been on your project if it had not been supported by BRAIN UK. Most applicants will have made use of the BRAIN UK generic ethics to work with human tissue and the network of contacts for obtaining tissue. Please indicate which of the following statements is most applicable.

Would you have been able to complete this study without BRAIN UK support? Please select the most appropriate

A: Yes, BRAIN UK support had VERY LITTLE impact on my study.	**A**
B: Yes, but it may have been more INCONVENIENT and limited my access to samples; I may have needed to redesign the study to proceed alone.	**B**
C: Yes, but it may have had a SIGNIFICANT effect on time, costs or outputs; I would have needed to redesign the study to proceed alone.	**C**
D: No, I could not have conducted this study without BRAIN UK.	**D**

Any Additional Comments:

11. Missing Information

Please provide the information requested below.

This informaton will then be added to the Project Summary Tab in preparation for next year's report.

Sample Costs

We are trying to get a better idea of actual costs involved in obtaining samples. Please tell us the costs (if

Declaration

Signature of Chief Investigator
(please either copy in your electronic signature or simply print your name in the box below):

Print name:

Date:

With the following summative data:

Project Info	
	Ref No
	Title
	Link to SharePoint (Login Req)
	Sponsor
Contact info	
	PI
	Department
	Institution
	email
	Telephone
Application	
	Date Received
	Application Status
	Date of Approval
	Approval Sent
Centres	
	Number of Centres
	Name of Centre/s
	Sent to Centre
Number of Cases	
Samples	
	Samples Received
	Supplying Centre
	Lab Number
	How samples supplied (please use drop down list)
	Sample Type (PM or Tumour)

Sample Costs		
	Number of Samples	
	Centre (if more than one centre, please copy information to empty cells below and complete separately.	
	Administration Costs (per batch)	
	Packaging Costs (per batch)	
	Transportation Costs (per batch)	
	Costs for samples (per batch)	
	Other Costs (please specify type as well as amount)	
	Total Cost	
Annual Review		
	Latest Annual Review Requested	
	Received	
	Study Start Date	
	Study End Date	
Summary		
Next Report Due		
Project status		
Amendments		
	Have there been any amendments?	
	Amendment Detail	
	Amendment Approved	
Collaboration		
	Was a collaboration suggested?	
Flag		
Current Status		
Notes		
After Project - samples returned/destroyed?		
How did you hear about BRAIN UK?		
BRAIN UK Impact		
	Would you have been able to complete this study without BRAIN UK support? Please select the most appropriate response.	
Data Sharing		
	Please specify how you propose to share any data generated on the samples	
Research Output		
	Overview	**Publication; Poster**
	Type	*Publications*
Sample Detail		
No.	*Supplying Centre*	*Lab Number*

Appendix J: Template Study Approval Letter

Template study approval letter sent to applicants on approval by BRAIN UK.

<PI Name>
<PI Address 1>
<PI Address 2>
<PI Address 3>
<PI Address 4>
<PI Address 5>

UK BRAIN ARCHIVE INFORMATION NETWORK
Director: Prof James AR Nicoll
Deputy Director: Dr David Hilton
Manager: Dr Clare Mitchell
email: brainuk@soton.ac.uk
Phone : +44 23 8120 5240
www.brain-uk.org

<Date>

Dear <PI Name>,

BRAIN UK Ref: XX/0XX – Study Title

After review of the information provided by you I am pleased to inform you that the above study has been granted approval by BRAIN UK. As this study conforms to the criteria laid down by the South Central – Hampshire B Research Ethics Committee (REC) it may proceed under the generic Ethical Approval given by this REC. A copy of these acceptance criteria is attached for your information and records.

I will forward the contact details for Participating Centres that are able to potentially provide you with tissue for your study once they have confirmed their participation. Please note that you must register your study with the relevant Research and Development office prior to being able to obtain tissue from any of these sites.

Once you have received the tissues, please email brainuk@soton.ac.uk confirming the lab numbers and supplying centre/s of the received samples. This allows us to enhance the service both in terms of improving the sample information held within BRAIN UK and by encouraging collaboration amongst researchers using similar samples. We will not share any details but may highlight that other research is being done either on the same samples or in the same area of research in order for you to consider if collaboration is appropriate.

Additionally, you are also obliged to provide BRAIN UK with annual updates concerning the progress of your study and to deliver evidence of the conclusion of your study. Any material published as a result of the use of tissue derived via BRAIN UK must also be acknowledged accordingly. Please do not feel that you must wait until the annual report to tell us about any publications or research output for this study; you can email details to brainuk@soton.ac.uk at any time and we will include these within a pre-filled annual report for your convenience.

Further information regarding these obligations is covered in greater detail in the attached Terms and Conditions which you have agreed to abide by. If you have any further questions or require further clarification then please do not hesitate in contacting BRAIN UK.

We would like to thank you for using BRAIN UK and we would like to wish you every success with your current and future research undertakings.

Yours sincerely,

Prof. James A R Nicoll
BRAIN UK Director

Mailpoint 825, Level F, Laboratory and Pathology Block, Southampton General Hospital, SO16 6YD

Appendix K: Template Study Closure Letter

Template study closure letter sent to applicants when BRAIN UK are notified of a study closure.

UNIVERSITY OF Southampton

BRAIN UK
Enabling research into neurological disease

PI
Address 1
Address 2
Address 3
Postcode
<Date>

UK Brain Archive Information Network
Director: Prof James AR Nicoll
Deputy Director: Dr David Hilton
Manager: Dr Clare Mitchell
email: brainuk@soton.ac.uk
Phone : +44 23 8120 5240
www.brain-uk.org

Dear <PI>,

BRAIN UK Ref: [Reference number] – [Study Title]

I am writing to advise that the above project has now been closed on the BRAIN UK database following its reported completion. As a result, the Ethical Approval from the Southampton and South West Hampshire Research Ethics Committee 'B' under the terms of their approval for BRAIN UK has now terminated.

Now that the project is closed:

- Please ensure that you acknowledge the contribution of BRAIN UK and the NHS Trust(s) from which such tissues originated in all resulting publications. Full details, including recommended wording are available in the Appendix (Condition 11).
- Please send a fully completed report to brainuk@soton.ac.uk as soon as possible. You should inform BRAIN UK whether the study achieved its objectives, the main findings, details of all outputs thus far and arrangements for data sharing. It is essential that we provide this information to our sponsor as part of BRAIN UK ethics approval. Please also provide details of any future outputs to brainuk@soton.ac.uk
- Human tissue or data must not be passed onto third parties unless it is part of a study protocol approved by BRAIN UK and with the express permission of the custodians of the originating archive (Appendix: Condition 4)
- Any human tissue that remains after the completion of a project should be processed as specified in the original Material Transfer Agreement (MTA) document. Where arrangements for samples at the end of the study have not been specified in the MTA, you should contact the supplying centre to ask if they would like the samples returned or if they would prefer that you destroy them. As part of the audit process, the return/destruction of samples must be appropriately documented. Where this is not possible, or it has been agreed with the originating archive, tissues, and derivatives thereof (e.g. stained sections) must be stored in premises licensed by the Human Tissue Authority or disposed of in accordance with Human Tissue Authority Codes of Practice. Recipients will also ensure that, where they lie outside of England, Wales and Northern Ireland, tissues supplied will be used in accordance with local laws and regulations. (Appendix: Condition 6)

We will email the centre/s that supplied tissue and/or data for this project to notify them that this project is now closed but it is the **responsibility of the applicant** to ensure that any remaining human tissue samples are appropriately managed after completion of the study. This request is in-line with Human Tissue Authority regulations and the Health Research Agency requirements for ending a research study. If you have any further questions or require further clarification then please do not hesitate in contacting BRAIN UK. We would like to thank you for using BRAIN UK and we would like to wish you every success with any future research undertakings.

Yours sincerely,

Prof. James A R Nicoll
BRAIN UK Director

Mailpoint 825, Level F, Laboratory and Pathology Block, Southampton General Hospital, SO16 6YD

Appendix L: BRAIN UK Approved Studies

List of approved BRAIN UK Studies. Further details can be found at www.brain-uk.org/studies-supported/lay-summaries-home.page.

Ref	Title
10/002	White matter disorders in children: from magnetic resonance to basic defect
11/001	Role of neutrophils in the pathogenesis of NMO
11/002	Pilot study comparing microglial markers in different neurological diseases known to be associated with inflammation
11/003	Pilot study – Microglia profile in schizophrenia
11/004	Response of stem cells in the human brain to acute hypoxic/ischaemic injury
11/005	Fight Alpers'
11/006	Comparative analysis of neuropathology in Huntington's disease brains
11/007	How do ageing processes contribute to Alzheimer's disease?
11/008	ADAM17 in subarachnoid haemorrhage
12/001	Pilot study to identify mast cells and basophils in brain
12/002	Neuropathology of autoimmune/limbic encephalitis associated with antibodies against voltage-gated potassium channels
12/003	Neuropathological examination of neurons, glial cells, axons and molecular factors in mood and affective disorders
12/004	Evidence for stem cell neuroprotection in genetic ataxias
12/006	The impact of mitochondrial DNA mutations on substantia nigra neurons
12/007	Regulation of microglial proliferation and its contribution to chronic neurodegeneration
12/008	Protein conformation changes in chronic traumatic encephalopathy and other tauopathies
12/009	Investigation into the impact of systemic inflammation due to infection on microglial phenotype and its contribution to Alzheimer's disease neuropathology
12/010	The brain in Sudden and Unexpected Death in Epilepsy (SUDEP): new insights from pathology
13/001	Are neurodegenerative diseases and gliomas inverse comorbidities?
13/002	Investigating inflammation of the normal appearing brain in patients with low-grade glioma
13/003	The role of c-Myc in choroid plexus tumours
13/005	UK brain bank for autism and other developmental disorders
13/006	Characterizing microglia/macrophage polarization in paediatric brain injury
13/007	CAA in subarachnoid haemorrhage
13/008	A post mortem study of progenitor cells following severe traumatic brain injury
13/009	CAA in autonomic dysfunction
13/010	Pilot study of cholesterol, lipids and LDL in Alzheimer's disease
13/011	DNA polymorphisms in mental illness (DPIM)
14/001	CAA and dystranglycanopathies
14/002	Age-modified forms of amyloid-β in a Drosophila model of neurodegeneration and in the brain of Aβ immunised Alzheimer's disease patients
14/003	Studying the role of TUBA8 (tubulin alpha 8) in brain disorders.
14/004	Pilot study: Expression analysis of candidate transcripts potentially involved in human brain tumourigenesis
14/005	Oligodendrocyte markers in bipolar disorder
14/006	Large scale genetic and epigenetic screen of chordoma
14/007	Pilot study: Expression of Bim in Huntington's Disease
14/008	An analysis of PPAR expression in human gliomas: its use as a novel diagnostic, prognostic and predictive biomarker
14/009	The role of Numb in the stability and activity of p53 in merlin-deficient tumours schwannoma and meningioma

14/010	Designing a glioma panel
14/011	Molecular and conformational signature of chronic traumatic encephalopathy
14/012	Identifying and characterising treatment-resistant subclones in glioblastoma multiforme
14/013	Functional characteristics of rare risk variants in TREM2 associated with Alzheimer's disease
14/014	Positive control tissue in direct and indirect immunohistochemistry, Western blot or other protein detection techniques
14/015	The role of Endogenous Retroviral proteins in the development of the tumours of the nervous system and as potential immunotherapy and/or drug targets
14/016	Molecular Characterisation of Childhood Craniopharyngioma and Identification and Testing of Novel Drug Targets
14/017	Electron microscopic study of CAA
15/001	Intratumoural Heterogeneity in GBM
15/002	Investigating cortical development in Trisomy 21
15/004	Possible ectopic Endothelin secretion in a patient with liver cancer who developed PRES
15/005	Dissecting the origins of central nervous system tumours exhibiting neuromesodermal differentiation
15/006	Identifying Circulating Tumour Cells in the Blood: An Analysis of their Diagnostic and Prognostic Significance in Correlation with Biopsy Findings
15/007	Role of c-Myc in choroid plexus tumours
15/008	Investigating the role of Astrocytes and Microglia in the development of Alzheimer's Disease in Down Syndrome
15/009	Assessment of expression and potential role of prmt5 and its upstream and downstream regulators in paediatric tumours
15/010	Brain inflammation and plasticity in schizophrenia and acute psychosis (amended title).
15/011	A pilot study analyzing the effect of driver mutations on the (phospho)proteome and microenvironment of meningiomas
15/012	Investigating the role of macrophages in schwannoma tumours of the PNS.
15/013	Exploratory study: use of MultiOmyx to investigate the pathology of Alzheimer’s disease
15/015	Examining the genomic landscape of rare brain tumour types
15/016	Molecular neuropathology of posterior pituitary/TTF-1-positive neoplasms
15/017	PPAR expression in glioblastoma as a putative prognostic biomarker (Extension to previous application BRAIN UK Ref: 14/008)
15/018	A morphological assessment of the white matter in CAA
15/019	Chronic traumatic encephalopathy (CTE) pathology in the brains of boxers
15/020	Studying the turnover of oligodendrocytes in Huntington's disease.
15/021	Investigation of astrogliosis and Lox expression in the Occipital Lobe of Bipolar Disease affected patients.
16/001	Investigation of the role of the c-MET proto-oncogene and the PI3K/AKT/mTOR pathway in brain metastasis.
16/002	Multi-platform analysis of TSC Subependymal Giant Cell Astrocytoma (SEGA) to identify novel therapeutic approaches.
16/003	Activation of the type 1 interferon response by nucleic acids.
16/004	Neuropathological Characterization of 'CTE'
16/005	Consensus diagnostic criteria of a novel tauopathy associated with anti-IgLON5 autoantibodies.
16/006	Identification of early onset cerebral amyloid angiopathy (CAA)
16/007	INSTINCT
16/008	Developing a Biomarker for Spinal Lipoma
16/009	Evaluating mTOR pathway hyperactivity in intractable epilepsy
16/010	Selective vulnerability in MND/FTD
16/011	Identification of novel therapeutic targets in malignant peripheral nerve sheath tumours (MPNST)
16/012	DNA/RNA instability in spinal muscular atrophy
16/013	Multi-species biofilm formation in senile plaques in Alzheimer’s disease: Contribution from oral bacteria
16/014	Effect of Hypothermia Treatment on Brain inflammation and Development in Neonatal Hypoxic Ischemia Encephalopathy

16/015	The development of a molecular methodology for improved detection of Isocitrate Dehydrogenase mutations in diffuse gliomas.
16/016	Epilepsy: What is the significance of the density of ectopic neurons in the white matter of temporal, parietal and frontal lobe, and are they normal or pathological?
16/017	Molecular pathology of infant gliomas
16/018	Determining the cell of origin of primary central nervous system lymphomas
17/001	Pathological study of two cases with SLC52A3 mutation
17/002	Identification of novel therapeutic targets and/or predictive biomarkers in brain gliomas
17/003	Molecular Pathology of Paediatric Gliomatosis Cerebri
17/004	Single-cell phenotyping technique applied to glioblastoma tumour samples as compared to normal brain tissue
17/005	Characterization and analysis of the brain tumour perivascular niche
17/007	Research and Innovation for Paediatric Low Grade Brain Tumours-Incorporating the SIGNAL and PINNACLE multicentre studies
17/008	Analysis of paediatric brain tissue by RAMAN imaging technology
17/009	Investigating the role of extracellular matrix in human neocortical development.
17/010	Characterisation of neuropathy and immune response following traumatic brain injury in children
17/011	Tau and A2AR expression in Alexander's disease
17/012	Defining changes in the tumour microenvironment of melanoma brain metastases following anti-PD-1 and anti-CTLA-4 antibody therapy
17/013	Establishing microglial phenotype in glioblastoma as a potential target for therapeutic intervention.
17/014	The Dynamics of Microglia in the Human Brain
17/015	Inflammatory and vascular changes after brain haemorrhage: a neuropathological assessment of human tissue
17/016	Understanding the mechanisms contributing to epileptogenesis in Alpers' disease
18/001	Role of c-Myc in choroid plexus tumours (Revised application to previous applications BRAIN UK Ref: 13/003 and 15/007)
18/002	Understanding the neural substrates of visuospatial memory and how this is affected by epilepsy and Alzheimer's Disease
18/003	Validation of prognostic markers and therapeutic targets in a large cohort of primary versus recurrent glioblastomas
18/004	Contribution of soft tissue tumours to DNA methylation-based sarcoma classifier
18/005	An Investigation of the Clinical Utility of Genetic and Epigenetic Profiling in Glioma
18/006	Study of Biological Abnormalities in Meningiomas
18/007	Charcot-Marie-Tooth Disease and related disorders: A Natural History Study
18/008	Characterising the role of chromatin regulator EZH2 in glioblastoma
18/009	Dissecting GBM invasion
18/010	Identification of Differentially Expressed Proteins and Genes Impacting Seizures and Risk of SUDEP in Dravet Syndrome
18/011	Investigation of cerebellar ataxia
18/012	How the matrisome drives human neocortex folding during development and neurodevelopmental disorders
18/013	Proteomic analysis of primary and recurrent glioblastoma – a pilot study
18/014	Whole Exome Sequencing of Primary Diffuse Large B Cell Lymphoma of the Central Nervous System
19/001	Molecular analyses of glial and glioneuronal tumours by DNA methylation profiling and next generation sequencing (NGS)
19/002	Molecular analyses of adult brain tumours by conventional molecular tests and DNA methylation profiling
19/003	Predicting recurrence/regrowth of non-functioning pituitary adenoma by a combination of patients' clinical, biochemical, radiological and immunohistochemical outcomes
19/004	Validation of histopathological findings in HTRA1 mutation carriers
19/005	Spatial subtyping of glioblastoma using in situ sequencing (ISS)

Appendix M: Participant Consent to Research Form

An example of a participant consent to research template that could be used where a centre doesn't have consent to research in place.

YOUR TRUST LOGO HERE

YOUR NEUROPATHOLOGY DEPT.
ADDRESS HERE

RESPONSIBLE PATHOLOGIST PHONE
RESPONSIBLE PATHOLOGIST EMAIL

PARTICIPANT CONSENT FORM

Title of Project:
Use of left over Tissue for Future Research

	Please tick box
1. I …… confirm that I have read and understood the information sheet for the use of left over tissue for research and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that sections of any of my medical notes from ***YOUR TRUST*** or elsewhere may be looked at and information taken from them to be analysed in strict confidence by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4. **Consent for storage and use in possible future research projects:** I agree that the left over tissue and the information gathered about me can be stored by the Neuropathology Unit at ***YOUR TRUST*** for possible use in future projects, subject to ethical approval.	☐
5. **Genetic research:** I understand that future approved projects utilising my left over tissue, may include genetic research aimed at understanding the genetic influences on tumours, but that the results of these investigations are unlikely to have any implications for me personally.	☐

Please sign and date

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking declaration	Date	Signature

Thank you for agreeing to participate in this research

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Appendix N: Participant Information Sheet

An example of a participant information sheet to accompany the consent to research template, in Appendix M: Participant Consent to Research Form, which could be used where a centre doesn't have consent to research in place.

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RESPONSIBLE PATHOLOGIST EMAIL

Participant Information Sheet

Use of Left Over Tissue for Future Research Use

We would like to invite you to permit the possible use of left over tissue for research. Before you decide we would like you to understand why research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the research if you wish. Ask us if there is anything that is not clear.

Thank you for reading this.

What is the purpose of this project?
Not all of the tissue that you will have removed as part of your procedure will be required to diagnose your condition. We wish you to consider using this left over tissue to support future research into the cause, diagnosis, treatment and outcome of disease. Some of these studies may include genetic research aimed at understanding the way in which genes (molecules instructing cell division and growth) influence the behaviour of these disorders. Researchers in ***YOUR TRUST*** and elsewhere will be able to access the tissue collection subject to ethical approval.

Why have I been chosen?
You are being asked to take part in this project because you are being investigated for a disorder of the nervous system (brain, spinal cord, nerves, or pituitary gland). Your management includes surgery during which tissue is removed routinely for access, diagnosis or treatment. We would like to ask you whether you would be willing to allow the left over tissue, that is no longer required, and any blood samples to potentially be used in research.

Do I have to take part?
NO, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. Your management and treatment will not be influenced in any way whether you wish to take part or not.

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What will happen to me if I take part?

- Participating in this study, by allowing the use of left over tissue to be used in research, will not affect your treatment in any way. The length of your operation and stay in hospital will not be affected and no additional surgery will be performed.
- We will ask you to give us permission (signed consent) to include samples removed as part of your surgery in our studies. It will not involve taking any tissue additional to that routinely removed for access, diagnostic or treatment purposes.
- Tissue will only be used for research once all diagnostic needs have been met.
- We will ask you for permission to consult your medical records at ***YOUR TRUST*** (or other relevant medical records elsewhere) for some information relevant to your illness. This information will include your age, gender, type and site of surgery, pathology diagnosis, radiological (X-ray) features, your medical treatment and the response to treatment. Any information passed to researchers would be anonymised.

To take part in this study, we will have all that we need for our research and will not need to contact you. Your tissue samples will be held under the care of the ***YOUR TRUST*** within the usual diagnostic archive, in accordance with Human Tissue Authority regulation.

What are the possible disadvantages and risks of taking part?
There are no disadvantages or risks to taking part.

What are the possible benefits of taking part?
There are no specific benefits to you directly, but the results of investigations using this tissue may help others with similar disorders.

What happens to tissue?
Tissue will be securely stored in NHS archives. In the future it may be allocated to an ethically approved project. However, not all samples will be used for research.

Will my taking part in this study be kept confidential?
YES. If you agree to take part in this study, only the relevant information mentioned above will be extracted from your records. Any information about you, released by ***YOUR TRUST***, will have personal details such as your name and address removed from it. The same will apply to the tissue samples used in any laboratory studies. The information and tissues will only be known by a research number, which will prevent researchers from knowing your identity.

What will happen if I don't want to carry on with the study?
Any unused tissue or blood stored in the ***YOUR TRUST*** diagnostic archive is stored or disposed according to the departmental diagnostic protocols. No further allocations will be made to research projects. Data from previously allocated tissue or blood may already exist and will remain associated with those projects anonymised to the researcher.

Will any genetic tests be done?
DNA derived from tissue may be examined for abnormalities, which may give information on the cause of a disorder. It is unlikely to produce results with a direct influence on you or your relatives.

What happens if something goes wrong?
The planned research will have no influence on your treatment. The storage of your tissue or blood for research carries no additional risks. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated, the normal National Health Service complaints mechanisms will be available to you.

What will happen to the results of the research study?
Results will be presented at conferences and published as scientific papers, but you will not be identified in any report or publication. Results obtained from your specimens are unlikely to include information of immediate clinical relevance, but should anything helpful be found, this will be conveyed to your treatment team.

Who is funding the research?
Future research studies utilising stored tissues will be funded by a variety of funds/charities.

Who has reviewed the study?
All research in the UK is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you very much for reading this information sheet.

Contacts for Further Information

APPROPRIATE CONTACT EMAIL, PHONE, WWW AND ADDRESS