UK Brain Archive and Information Network (BRAIN UK)

PROTOCOL

Version 1.71

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1. Title

United Kingdom Brain Archive and Information Network (*BRAIN UK*)

2. Glossary of Terms

Throughout this Protocol and associated documentation the three component arms of *BRAIN UK* will be referred to as distinct entities. This is in order to clarify the differing ways these are treated in law particularly within the Human Tissue Act 2004 and Human Tissue Act (Scotland) 2006:

***BRAIN UK* 1:** Refers to post mortem tissues archived before 1st September 2006 which are defined as part of an 'Existing Holding' under the Human Tissue Act 2004. In law, there is no mandatory requirement for informed consent for the use of this tissue for research purposes as long as such tissue is supplied in an anonymised format and that any research is subject to approval by a UK Research Ethics Committee.

This arm of *BRAIN UK* was granted Ethical Approval by Southampton and South West Hampshire B Research Ethics Committee on 7 May 2009 (**REC Ref: 09/H0504/68**).

***BRAIN UK* 2:** Refers to post mortem tissues archived on or after 1st September 2006. In law, there is a mandatory requirement for informed consent for the use of this tissue for research purposes.

This arm of *BRAIN UK* was granted Ethical Approval by South Central – Southampton B Research Ethics Committee on 11 October 2011 (**REC Ref: 11/SC/0395**).

***BRAIN UK* 3:** Refers to all residual tissue archived as the result of consented surgery on living patients. In law, there is no mandatory requirement for informed consent for the use of this tissue for research purposes as long as such tissue is supplied in an anonymised format and that any research is subject to approval by a UK Research Ethics Committee.

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5. Tissue Storage Centres

A list of all participating centres and relevant contact details are provided in *Appendix A: Tissue Storage Centre Contacts*.

6. Funding

Medical Research Council
20 Park Crescent
London
W1B 1AL
Reference: G1100578

This funding relates to the post mortem arms of *BRAIN UK* (i.e. *BRAIN UK* 1 and *BRAIN UK* 2).

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This funding relates to the surgical arm of *BRAIN UK* (i.e. *BRAIN UK* 3).

7. Sponsorship and Indemnity

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8. Background

Neurological and psychiatric diseases represent an increasing social and economic burden for developed nations such as the United Kingdom[1]. The progress towards effective therapy is being met with increasing frustration at the lack of translational success from animal and cell line models of neurological disease to the human disease itself[2]. This has highlighted the 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, and most rare neurological disorders are not provided for in this way. There exists an opportunity to benefit from the extensive archival collections of human brain tissue held by neuropathology services around the UK and to exploit such holdings for high quality research to gain a better understanding of the aetiology and progression of a range of neurological diseases and disorders and to 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 contribute towards the improvement of public health in the UK and beyond through improved therapeutic and medical practice.

Neuropathology (defined as the identification, characterisation and diagnosis of neurological disease based on the analysis of tissue) has existed as a distinct speciality in the United Kingdom for several decades. Neuropathology services are located in approximately 30 NHS Neuroscience centres, each with a catchment population of 1 to 3 million people. After the macroscopic and histological analysis of human tissue derived from a post mortem examination or surgical biopsy has been completed it is archived with appropriate consent according to guidelines published by the Royal College of Pathologists[3]. This archive of pathologically verified residual tissue represents a potentially valuable resource for research purposes especially as it can be readily linked to relevant clinical data. *BRAIN UK 1* has previously undertaken a systematic attempt to organise and utilise this national resource for research purposes by facilitating access to post mortem archives held prior to the enactment of the Human Tissue Act 2004 (as applied to England, Wales and Northern Ireland), and the equivalent Human Tissue (Scotland) Act 2006. Tissues archived prior to enactment of this legislation (*i.e.* before 1st September 2006) are defined as 'Existing Holdings' which can be used, without explicit consent, for the purposes of ethically approved research provided that

any material is anonymised to researchers[4]. In addition *BRAIN UK 2* has now also augmented *BRAIN UK 1* by making available all post mortem archives collected after enactment of the above legislation (i.e. on or after 1st September 2006). These may be used for ethically approved research where informed consent (or 'Authorisation' in Scotland) can be demonstrated for this purpose. There is therefore a large amount of archived post mortem tissue now available to the research community that is of great potential value in increasing our understanding of neurological disease.

It is the purpose of this protocol and the supporting documentation to augment the use of these post mortem archives by making all residual tissues derived from living patients as part of a consented surgical procedure available for research purposes *i.e.* to extend *BRAIN UK* to incorporate a 'surgical' arm (*BRAIN UK 3*). The removal, storage, use and disposal of such tissues are currently regulated by the Human Tissue Authority which was established by the relevant legislation described above although such regulatory authority is likely to change in the future due to governmental reorganisation of this and associated bodies[5]. Like the use of post mortem-derived 'Existing Holdings' (which do not require consent for research purposes provided that such research is approved by a registered UK Research Ethics Committee and that tissues released to researchers are in an anonymised format) the Human Tissue Act 2004 (and the equivalent in Scottish Law) makes tissue derived from surgical procedures on the living available for research subject to the satisfaction of the same caveats.

For our previous application relating to the use of 'Existing Holdings' for research purposes we undertook a limited pilot survey of five regional neuropathology services (Southampton, Plymouth, Oxford, Bristol and the Corsellis Collection) representing approximately 20% of the UK population. These preliminary data revealed 28,000 cases as being potentially available which extrapolated linearly to approximately 150,000 cases throughout the UK. Additional approaches have indicated that an additional 4,500 cases per annum are available UK-wide on a prospective basis. In its current state, as of the date of this Protocol, *BRAIN UK 1* and *BRAIN UK 2* encompass approximately 67,000 cases with an additional 4,500 cases anticipated to be added on an annual basis (see *Appendix G* for a summary of this data). These post mortem collections consist predominantly of formalin-fixed paraffin embedded tissue which is ideal for the study of disease phenotypes in terms of morphological and protein expression analyses. Although arguably less powerful than the use of fresh tissue, this type of resource is also, through continuing technical advances, becoming increasingly amenable to the extraction of nuclear and mitochondrial DNA and RNA for the study of the genetic influences on disease as well as the identification of infectious agents (*e.g.* viruses, bacteria and fungi) and the concomitant genetic study of such organisms.

One major benefit of these post mortem collections is that they comprehensively cover the spectrum of neurological disorders, contain large numbers of common disorders, and provide useful numbers of rare disorders and non-diseased tissues suitable for control studies. These collections are of great value and the importance of the collection continuing to grow in order to ensure that current patterns of disease are accurately reflected in the archive has now been realised. In many cases when autopsy brain tissue is subjected to neuropathological examination, whether from Coronial or Hospital autopsies, consent is given from the relatives for subsequent research use. This continuing collection will usefully supplement the existing holdings maintaining numbers of rare conditions and allowing the correlation of pathology to be made with current investigations[6,7] (*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[8] (*e.g.* FUS and TDP-43 related diseases).

In addition to the collection and characterisation of post mortem archives *BRAIN UK* is now in receipt of funding to further extend to include all residual tissue specimens archived as a consequence of surgery upon living patients, A directed Pilot Study of 29 NHS Neuropathology centres indicated approximately 450,000 archived cases with an additional 17,500 cases per annum available on a prospective basis (see *Appendix H* for a summary of this data). This particular collection (i.e. *BRAIN UK 3*) will potentially provide a greater depth and quality of neurological tissue for research applications and in particular will be of greatest benefit to investigations relating to tumours of the central nervous system and adnexa.

This proposal to create a comprehensive national database of neuropathology tissue archives throughout the UK has the full support of the British Neuropathological Society (BNS) and now the brain cancer charity '*brainstrust*'. The importance of such an initiative has been reiterated by bodies such as the Medical Research Council (through the creation of the UK Brain Banks Network of which *BRAIN UK* is a member[9]) 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[10].

9. Aims and Objectives

The current initiative aims to establish an overarching model to the UK Brain Archive and Information Network (*BRAIN UK*) in order to include all tissue specimens (both post mortem and surgically derived) archived both retrospectively and prospectively to maximise the potential to be gained from this valuable tissue resource for research into neurological diseases. The availability of high quality, well-characterised human brain tissue should form an essential and integral part of any systematic translational health research strategy for the UK. In contrast to established conventional brain banking facilities *BRAIN UK* acts as a 'virtual brain bank' with the tissue samples being retained in the departments of origin. This approach has been successfully used by the Confederation of Cancer Biobanks[11] and the Cancer Research UK Bio-Specimen Biorepository[12] and has a number of advantages over conventional brain banking facilities:

- 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 and relatively low maintenance costs as existing facilities are utilised,
- Participating centres maintain full custodianship of tissue samples.

A linked anonymised electronic database has been created which currently is searchable by *BRAIN UK* staff on request by potential research applicants. The ultimate aim is to make it available, in a fully anonymised format, to the research community via the website of the British Neuropathological Society and through our own website (http://www.brain-uk.org/). The database, hosted by the University of Southampton, includes details of disease categories, together with the number of cases available, the tissue formats available and limited demographic data (sex and age at death). Access to archived tissue is negotiated directly between the initiators of a research study and the local custodians of that tissue, once the relevant study has been approved by *BRAIN UK*.

It is a primary aim of *BRAIN UK* to attempt to gain generic Ethical Approval for all research utilising tissue archived by participating centres. *BRAIN UK* has previously received favourable opinions relating to post mortem archives (References: 09/H0504/68 and 11/SC/0395) and 'generic Ethical Approval' from the Southampton and South West Hampshire Research Ethics Committee B and its successor body the South Central – Southampton B Research Ethics Committee for researchers through the *BRAIN UK* application process but, should this not be forthcoming on this occasion, Ethical Approval should be obtained by the researcher in question as a prerequisite for access. It is intended that the technical and administrative costs incurred by the retrieval, processing and transportation of tissues will be met by the researcher's grant funding.

Letters of invitation to participate in this initiative have been sent to neuropathology centres and, at the time or writing, support has been received from 25 out of a total of 30 approached.

10. Patient Eligibility

10.1 Inclusion Criteria

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 (*i.e.* as part of an 'existing holding').

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.

10.2 Exclusion Criteria

BRAIN UK 1: All patients who have had tissues removed and archived as part of a post mortem examination (either Coronal/Fiscal Procurator or hospital) in the UK 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: All patients who have had tissues removed and archived on or after 1st September 2006 as part of a post mortem examination (either Coronal/Fiscal Procurator or consented hospital examination) in the UK where consent has been refused (either by the patient during life or by their nominated representative or an individual in a qualifying relationship after death) or no recorded evidence of consent exists for the use of their tissues for research purposes.

BRAIN UK 3: All patients who have had tissues removed either during surgery or in the course of a diagnostic procedure 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.

11. Consent, Privacy and Confidentiality

***N.B. BRAIN UK* does not itself seek consent. However, that consent for research use has already been obtained is a pre-requisite for inclusion of cases in *BRAIN UK 2*. Consequently, issues relating to consent are discussed in more detail within this section and within *SOP 2: Data Confidentiality Policy* (see Appendix C).**

11.1 Consent for the Use of Human Tissue for Research[13]

The Human Tissue Act 2004 and The Human Tissue (Scotland) Act 2006 place 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 disorders, or the functioning, of the human body' is one. Therefore, in order for post mortem human tissues archived 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.

'Informed Consent' (or 'Authorisation') may be obtained from adults in life or from their nominated representatives or an individual in a qualifying relationship after death. Informed Consent from children defined as an individual under 18 years of age (or aged under 16 years of age in Scotland) may be given if such an individual is considered competent to do so ('Gillick

competency'). Evidence of Informed Consent should ideally be given in a written format and should be clearly documented as part of the individual's medical record.

Participating centres have protocols and procedures in place to obtain and record Informed Consent as part of their compliance with the Human Tissue Act 2004 (and the Scottish equivalent), Human Tissue Authority Codes of Practice and Human Tissue Authority Licensing obligations.

However, the legal position differs relating to residual tissue archived after a diagnostic or therapeutic procedure (e.g. surgery) on a living individual. In this case, consent for storage or use of the tissue for research is not a legal requirement, provided that the 'researcher is not in possession, and not likely to come into possession of information that identifies the person from whom it has come' (i.e. tissue and concomitant clinical information is provided in an anonymised format) and that 'the material is used for a specific research project with ethical approval'.

In summary, the composite arms of *BRAIN UK* deal with the issue of informed consent in the following manner:

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:

i. Tissue is supplied to the researcher in an anonymised format and;
ii. The intended research is subject to approval by a UK Research Ethics Committee

In line with the spirit of the relevant legislation and guidance, if it is known, or comes to be known that there is a request for tissue **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.[14]

The above principles also apply to *BRAIN UK* 3.

BRAIN UK 2: Informed consent (either from an individual during life or an individual in a qualifying relationship after death) is a mandatory requirement for tissue to be used for a 'Scheduled Purpose' of which research is one.

11.1.1 Consent for Hospital Post Mortem Examinations[15]

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.

11.1.2 Coroner's (or Procurator Fiscal's) Post Mortem Examinations[15]

Informed Consent is not required for post mortem examinations that have been ordered as part of a Coroner's (or Procurator Fiscal's) examination into an individual's cause of death. However, for the continued storage and use of human tissues derived from such investigations archived 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 Informed Consent is a mandatory requirement.

11.1.3 Consent from Children[16]

The archives maintained by Participating Centres will invariably contain residual tissue derived from children, infants, neonates and foetuses.

Under the Human Tissue Act 2004 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 so) then this obligation passes to those with parental responsibilities (as covered by the Children Act 1989).

Participating Centres will, as part of their Human Tissue Authority Licensing conditions, have processes and procedures in place in order to provide information to the patient and their families and agents and to collect and record such informed consent in writing where mandated by law for the collection and storage of tissue for research purposes.

10.1.4 Adults with Lack of Capacity to Consent[17]

The archives maintained by Participating Centres will invariable contain residual tissue derived from adults lacking the capacity to consent as defined by the Mental Capacity Act 2005 and the equivalent Adults with Incapacity (Scotland) Act 2000.

As argued in Section 11.1.3 Participating Centres will, as part of their Human Tissue Authority Licensing conditions, have processes and procedures in place in order to provide information to the patient and their families and agents and to collect and record such deemed consent in writing where reasonable.

11.2 Human Tissue Authority Licensing

BRAIN UK 1 and *BRAIN UK 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 2004. 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 2004 and the Human Tissue Authority Codes of Practice. Model consent forms are available on the Human Tissue Authority website:

http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/modelconsentforms.cfm

BRAIN UK 3: Diagnostic archives (i.e. tissues taken from the living as part of a surgical or diagnostic procedure and then archived) do not need to be stored under an HTA licence. Diagnostic tissue can only be released for research under the following circumstances:

- When the patient has given consent for use of their tissue in research (the preferable scenario); or
- When the tissue will be released to the researcher in a non-identifiable form; and
- When the tissue will be used in a project that has approval by a recognised Research Ethics Committee

11.3 Consent for the Use of Patient Data

Informed Consent for access to and disclosure from the medical records of both the living and deceased is not covered by the Human Tissue Act 2004 (and the Scottish equivalent), but by the National Health Service Act 2006 (see Section 10.3 below). Consent for access to and disclosure from the computerised laboratory records of patients fulfilling the inclusion criteria with tissue(s) will not be sought in the first instance for the following reasons:

1. Approaching relatives following bereavement could cause distress and harm especially if the nature of the bereavement related to a distressing condition or incident.

2. Given the potential number of cases available the absolute requirement for consent would severely limit the size and scope of the database within available resources and diminish its potential benefits to the research community and the UK as a whole.

3. The intended use of linked anonymised ('pseudonymised') data renders the probability that any individual could be identified by the recipient of such data to be extremely small. For practical purposes, this data may be considered as anonymous thus there is no concomitant requirement for consent[18, 19].

11.4 Section 251 National Health Service Act 2006

For the reasons cited above it is felt that obtaining individual consent for access to and disclosure from the medical records of the deceased would be both impracticable and disproportionate. The implementation of measures to maintain patient anonymity and the common law duty of confidentiality (see Section 12 – Methods) and given that this initiative would potentially facilitate 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.

As part of our previous applications (Refs: 09/H0504/68 and 11/SC/0395) we have received conditional exemption from Section 251 support from the National Information Governance Board for Health and Social Care Ethics and Confidentiality Committee (NIGB-ECC) (Reference: ECC 3-06(k)/2009). Previous guidance and advice from the Approvals Manager of the NIGB-ECC have been utilised to create the necessary processes and procedures to obtain Section 251 support should this become a mandatory requirement (see Section 12.3).

12. Methods

N.B. Expansions of this section are contained within the following policy and standard operating procedure documents:

SOP 1: Policy for Access to Archival Tissue Holdings of Participating Centres (see Appendix B)
SOP 2: Data Confidentiality and Security Policy (see Appendix C)
SOP 3: Information Technology Security Policy (see Appendix D)
SOP 4: Data Extraction Policy (see Appendix E)
SOP 5: Policy for the Disclosure of Clinically Significant Information (see Appendix F)

12.1 Database Development, Management and Responsibilities

The database and all files (both electronic and paper) relating to it will be managed on a day-to-day basis by the designated Data Co-ordinators. These individuals will have core responsibility for undertaking procedures and arrangements for data collection, data anonymisation (where not already performed), data storage and data security. Data generated

or accrued as part of this initiative will be accessible to only the Data Co-ordinators and the Chief Investigators until the creation of a secure fully anonymised database is complete. (Please see *SOP 1: Policy for Access to Tissue Archival Holdings of Participating Centres, Section 3* for further details).

12.2 Data Collection

12.2.1 Sources of data

Relevant data will be obtained from the computerised archives of each neuroscience centre participating in the *BRAIN UK* initiative. Where such records prove incomplete, reference will be made to paper records (*e.g.* pathology reports and autopsy reports) held by the same departments.

12.2.2 Frequency of data extractions

The frequency of any data extraction will be dependent upon the size of the participating centre in question and the potential number of applicable cases they are able to collect but it is intended to poll each participating centre for an update of the cases they maintain on at least a quarterly basis.

12.2.3 Types of data

Computerised laboratory records from participating centres will be accessed and data pertinent to the study will be accrued. These data will consist of:

(i) Disease/diagnostic category,

(ii) Systemised Nomenclature of Medicine Clinical Terms (SNOMED CT) number or equivalent,

(iii) Laboratory/Specimen/Post mortem number (dependent upon local practice and custom),

(iv) Specimen format (*e.g.* formalin-fixed paraffin-embedded tissue, formalin-fixed wet tissue, frozen tissue, cerebrospinal fluid, whole blood, plasma, serum, unstained slides, stained slides, tissue microarrays),

(v) Location,

(vi) Custodian contact details (contact name, telephone number, fax number, e-mail address, full postal address),

(vii) Matched clinicopathological data availability (*e.g.* pathology reports and autopsy reports),

(viii) Simple demographic data (*e.g.* sex, age at death, age at time of tissue sampling).

12.2.4 Linked anonymised (pseudonymised) data

The inclusion of a specimen laboratory number (or equivalent) will by definition make the data stored on the database linked anonymised ('pseudonymised')[19] in nature. From feedback we have received from those centres interested in participation there was a common feeling that the inclusion of laboratory numbers would make it more efficient for them to locate specific tissue(s) and medical data of interest for subsequent research activities. Although a laboratory number is potentially a personal identifier, the key relating to core personal details (*e.g.* patient name, date of birth, address, NHS number) will be held and maintained only by the participating host centre in question. No inference about the identity of an individual represented by a particular laboratory number can therefore be reasonably or easily deduced by the Data Co-ordinators or others. The data is therefore linked anonymised which is

considered as anonymised for practical purposes when the key to patient identity is not held by the researcher as is the case here and that there is neither compromise to patient privacy nor a common law requirement to seek consent for their use under these circumstances [18,19].

12.3 Data Anonymisation

Ideally, and in the first instance, the removal of identifying information from accrued data will be performed within the originating organisation by a Healthcare Professional prior to it being disseminated as linked anonymised data to the Data Co-ordinator. However if, due to time or cost constraints, this could not be performed by the data custodians then data collection and anonymisation would be performed by the Data Co-ordinators. The Data Co-ordinators would take all measures to anonymise the data as soon as is practical resulting in a linked anonymised data set. As nominated individuals would have this task this would present minimal risks of personal data being disclosed inappropriately and it would greatly reduce any scope for the infringement of the common law duty of confidentiality. This measure makes potentially sensitive personal data available to the least number of individuals possible and greatly reduces the scope for legal or ethical objection. The Data Co-ordinators would be bound by a duty of confidentiality as *per* the relevant policies produced by the University of Southampton and would be liable to the sanctions set out in such policies should inappropriate breaches of data security or confidentiality occur for whatever reason.

In order for the Data Co-ordinators to gain access to pertinent data it will be ensured that relevant administrative and managerial approvals have been sought at the participating centre in question (*e.g.* Honorary Contract, Research Passport) and that an evidence-based application to the National Information Governance Board for Health and Social Care Ethics and Confidentiality Committee (NIGB-ECC) is made on a case-by-case basis as the requirement to do so arises.

Shifting the burden of creating anonymised or linked anonymised data sets onto hospital pathology departments could be onerous and may create a reason for a centre not to become involved with this initiative. As comprehensive nationwide coverage is a primary goal of this initiative we consider that providing time resources to participating centres will make their involvement more likely, and will provide a more representative and enduring data and tissue resource than would otherwise be the case.

12.4 Data Transfer

Linked anonymised data will be transferred from the site of origin to the central electronically by using an encrypted Zip file and the use of the University's 'Dropoff' service (https://dropoff.soton.ac.uk) for secure transmission of the file. With the password for the zip file being communicated via another medium; telephone, post or email to an alternative email account used for the 'Dropoff' process.

It must be stressed that the 'Dropoff' service provided by the University of Southampton not be confused with the commercially available 'DropBox' which is wholly unsuitable for this purpose.

Given historic and high profile security lapses in a range of UK governmental and organisational settings concerning the loss of sensitive data, measures maintaining the security of data during its transport or transfer from the originating site to the core database are considered to be of utmost importance. Therefore protocols for the safe and secure transportation or transfer of data have been developed in line with the recommendations of best practice contained within the NHS Information Security Management Code of Practice[20]. The bulk extraction and transfer of data will also only occur once the specific authorisations of the Participating Centres have been received in line with the NHS Information Governance Framework[21].

12.5 Data Storage

The *BRAIN UK* database will not store any patient identifiable information either electronically or in a written or printed format. *BRAIN UK* data will be stored electronically, by the provision of a folder, on networked SAN storage dedicated to University research data in secure University data centre. By storing the data on networked storage, risk of theft or loss of data on the client PCs is minimised. Further encryption and securing of the client PCs minimises further risk of loss of data via data remnants, swapfile contamination and orphaned temporary files.

12.6 Data Security

12.6.1 Password protection

The System shall be accessible from any staff University PC with permitted access control with access permissions set and verified to permit only those with authorised user access. Network logins ensure access by authorised staff: project staff, project supervisor and authorised iSolutions staff under supervision (ISO27002:2013 9.2.3) with access restricted by Active Directory permissions to authorised staff and minimal set of senior trusted administrators. (ISO27002:2013 9.4.1). The system will only be accessed by *BRAIN UK* Data Co-Ordinators on a routine basis and will be made available to the *BRAIN UK* Director (Professor James A. R. Nicoll), his deputy (Dr David Hilton) upon request**.**

There will be enforced regular robust password changes 9ISO27002:2013 9.4.3), review of user access rights at regular intervals (ISO27002:2012 9.2.5) and review of access permissions on a regular basis and following exceptional events such as termination of employment (ISO27002:2013 9.2.5).

12.6.2 Electronic file back-up

The *BRAIN UK* database and the database relating to the application process contain valuable sensitive data. It is considered best practice to ensure that these files are maintained on a networked SAN storage dedicated to University research data in a secure University data centre. Backups of the data will be automated via functionality inherent in the networked storage, providing a minimum of 90 days snapshots of the data for recovery purposes, and mirrored to an offsite secure University data centre for business continuity purposes.

(Current configuration provides snapshots every 2 hours, retained for one month, and offsite replication every 6 hours, retained for 3 months)

12.6.3 Encryption

Current encryption guidance for NHS organisations can be found in "Guidelines on use of encryption to protect person identifiable and sensitive information", and we would expect any electronic solution for the handling of patient identifiable / sensitive data to comply with this guidance as a minimum.

User access will be via Windows based PCs provided by iSolutions. By storing the data on networked storage, risk of theft or loss of data on the client PCs is minimised. Further encryption and securing of the client PCs minimises further risk of loss of data via data remnants, swapfile contamination and orphaned temporary files. *BRAIN UK* employs full disk encryption of all PCs accessing *BRAIN UK* data using MS Bitlocker as per iSolutions policy (ISO27002:2013 10.1.1) with central recovery keys for MS Bitlocker having restricted administrator access (ISO27002:2013 10.1.1)

Data will only be transferred using an encrypted Zip file (AES-256 encryption; many Zip programs offer this functionality) with the password for the zip file shall be communicated via another medium. Data required to be physically transported will us an encrypted USB drive

that conforms to NHS-approved standards (FIPS-140-2; 3-DES or AES, to 256-bit strength. Kingston Technology DataTraveler Locker 4GB 256-SHA is a typical approved device).

12.6.4 Data Protection Act 1998

Procedures and protocols relating to the Data Protection Act 1998 are dealt with in detail within *SOP 2: Data Confidentiality and Security Policy* (see Appendix C).

12.7 Research Uses of Database

Currently the BRAIN UK database is offline as described above. It is accessible to researchers indirectly by their e-mail queries to BRAIN UK staff who search the database on their behalf. However, it is our ultimate aim to make the *BRAIN UK* database available to the UK research community in a fully anonymised format using the website of the British Neuropathological Society (http://bns.org.uk/) as a portal and will be hosted by the University of Southampton. Basic and superficial content will be available to browsers (*e.g.* disease category, number of specimens available UK-wide, tissue format, sex, age range represented and number of participating centres holding relevant material) and functionality will be incorporated to enable browsers to undertake queries relating to sex and age if such variables are important to their intended research. It is important to note that no laboratory numbers will be presented on the website under any circumstances.

It is envisaged that the *BRAIN UK* database will be used as a means of facilitating high quality research by enabling researchers to determine which archive(s) contain those tissues of interest to their future and on-going investigations.

12.8 Applications from External Researchers

Once a researcher has identified relevant tissue pertinent to their research they are at liberty to make an application for access to tissue held by Participating Centres. This will be achieved via the use of a standard application form which will be submitted to *BRAIN UK* electronically with a signed paper copy being submitted by post. The application form will provide contact information, details of where the research is to be conducted and details of the types and quantities of tissue required. Each application will be supported by documentary evidence of a favourable ethical opinion (where applicable, otherwise the applicants will be seeking the cover of the BRAIN UK ethical approval), a declaration that sufficient funding is available, favourable peer-review (if available, otherwise the *BRAIN UK* Director has sufficient expertise to provide this), sponsorship and the study protocol (please refer to *SOP 1: Policy for Access to Tissue Archival Holdings of Participating Centres* for additional details).

Once all documentation has been received, each application will be considered against standard criteria (see *SOP 1: Policy for Access to Tissue Archival Holdings of Participating Centres, Section 3.3.1* for further details) and a decision relating to granting access to the *BRAIN UK* network of participating centres will be made by the *BRAIN UK* Committee. This decision making process will be based upon whether the proposed research reaches a minimum threshold in terms of quality and design. Each application will also be disseminated to participating centres holding tissue of potential use for their opinion and it is important to note that each centre has the ultimate right to veto the use of their archive regardless of any decision made by *BRAIN UK*.

Once a favourable opinion has been received researchers will be put in contact with participating centres and vice versa. It is the responsibility of each participating centre and researcher to ensure that supply arrangements are in place to ensure the storage, use and disposal of the samples in accordance with the HTA Codes of Practice (*i.e.* a 'Material Transfer Agreement'), the terms of the ethical approval and any other conditions required by the participating centre supplying relevant material. In addition, it is the sole responsibility of the researcher to ensure that local R&D approvals have also been attained prior to undertaking any work. Costs incurred due to the retrieval, processing and transportation of tissue will be met by the investigator's grant fund.

The process of applying for access to the *BRAIN UK* network of participating centres will require that personal information of applicants will be held for a period of 5 years for the purposes of audit and to enable annual reports to be drafted. As a consequence, the Data Protection Act 1998[22] will apply therefore *BRAIN UK* will adhere to the letter and spirit of this legislation to maintain data security and to ensure that all data is processed fairly and lawfully. All policies and guidance relating to Data Protection published by the University of Southampton will be implemented and adhered to.

12.9 Ethical Approval

BRAIN UK will, in the first instance, be applying for 'generic ethical approval' for the use of archived tissue at participating centres for the purposes of supporting research. This has been granted as part of our previous applications (Refs: 09/H0504/68 and 11/SC/0395). If forthcoming, this would enable most research to be conducted without the requirement for individual researchers to obtain their own ethical approval and would greatly facilitate the process of neurological research. However, there may be occasions when *BRAIN UK* may feel it is appropriate for a particular study to receive additional scrutiny from a UK Research Ethics Committee. This would apply in particular to research requiring access to relatives of the deceased, broad access to clinical notes and medical histories and to research that has an above 'minimal' risk of generating data that would have clinical significance for the surviving relatives of a donor. Applying for such additional ethical approval would be the sole responsibility of the researcher and evidence of a favourable opinion would need to be submitted in support of an application (see *SOP 5: Policy for the Disclosure of Clinically Significant Information* for further details).

12.10 Submission of Research Data

All researchers utilising tissue obtained from the *BRAIN UK* network of participating centres are obliged to submit the outcomes of their research to the *BRAIN UK* Director in the form of fully acknowledged papers and abstracts. In addition, at the end of their studies researchers will be encouraged to submit the new data generated by their studies to *BRAIN UK*. This would ultimately create an enriched data set which would further facilitate future research and promote collaboration.

12.11 Offer to Disclose Clinically Significant Data

It will be the policy of *BRAIN UK* not to offer to disclose research data to the donors or relatives of the deceased/donors except in rare and exceptional circumstances. This decision has been based upon the following reasoning:

1. The tissue held is diagnostically verified therefore, for diseased tissues, there would be reduced scope to discover additional information of clinical pertinence. For instance, if an individual had died of Huntingdon's disease, it is probable that family members at risk would already have been identified and received appropriate counselling and testing. It is therefore assumed that the value of outcome has been determined and that subsequent life choices (*e.g.* reproductive decisions) would have been addressed.

2. Many neurological and psychiatric diseases and disorders remain incurable and there is limited scope in terms of effective curative therapy. Therefore the likelihood of an effective clinical outcome would remain low for most research particularly that relating to neurodegenerative disorders and dementias.

3. In terms of study context, there would be no existing relationship between participants in the *BRAIN UK* network and the relatives of donors nor would it be likely that one would exist in the future. This would indicate, as a consequence, that to approach relatives would be inappropriate. However, if researchers were to pursue living individuals (either donors or their relatives) in terms of gaining additional clinical information as part of their study, this would require the additional approval of a UK Research Ethics Committee and this undertaking would be the sole responsibility of that researcher.

Importantly, in the unlikely event that research yields data of a clinically significant nature, such as a modification or change to the diagnosis, the details should be made available to both *BRAIN UK* and the NHS Trust from which the relevant sample originated so that a decision can be reached over whether to offer to disclose such data to the living relatives of that donor or the donor themselves in the case of a biopsy. If so, the question will be considered by the *BRAIN UK* Committee which will seek appropriate advice and discuss the possibility of disclosure with the relevant NHS Trust. In this event, the final decision to disclose will lie with the NHS Trust from which the relevant tissue was obtained for research purposes. The process and means of such a disclosure will follow the policies and guidelines of the particular NHS Trust in question and would ultimately be decided by them as they would be in possession of the 'key' which would link to the identity of the relevant patient.

The principles regarding this process are elaborated upon in *SOP 5: Policy for the disclosure of Clinically Significant Information*.

13. Statistical Analysis

The data stored on the database will be utilised for simple data analysis to exemplify the content of the database (*e.g.* diagnostic categories represented, the number of specimens, types of holdings at each individual site). The representation of data will be through the use of simple tables or diagrams *e.g.* pie charts, bar charts.

14. 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[23], the Kennedy Report[24], the Campbell Report[25] and the Redfern Report[26]). 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 2004 (and the Human Tissue (Scotland) Act 2006) 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.

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. Despite its fundamental importance to the research sector, the Human Tissue Act 2004 (its Scottish equivalent) and the associated HTA Codes of Practice are but a single aspect relating to research. Other relevant legislation such as the Data Protection Act 1998 and the National Health Service Act 2006 are also pertinent in relation to how patient data is handled and processed in such a way to protect the rights to privacy and confidentiality of research participants. This section will summarise the legal and ethical background to the establishment of BRAIN UK and the subsequent moulding of our intended procedures and protocols.

The data of interest in the compilation of the BRAIN UK database is to be derived from the medical records (primarily the computerised laboratory records) of the both living and deceased individuals. The principles and requirements of the Data Protection Act 1998 does not apply to the deceased[22] meaning that there is an immediate difference in the legal obligations regarding the storage and use of data dependent upon its status. 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 have a claim arising from the patient's death and only applies to records created since 1st November 1991[27]. More recently, there has been an indication that access may also be facilitated via the Freedom of Information Act 2000 and this has subsequently been clarified to conclude that the duty of confidence is not absolute and may be waived if consent to do so is given by the individual, or disclosure is required as a legal duty or it is in the public interest to do so[28]. The Bluck case[29] initially indicated that disclosure may

be exempted under Section 41 of the Freedom of Information Act 2000 but as a consequence of the relevant clarification by the Information Commissioner's Office (ICO) this position was rejected as disclosure of patient information would not have been in the public interest in this instance. Additionally, disclosure of such information, where there may be interference of the rights of surviving family members (so-called 'survivor privacy'), may be potentially prevented under Section 44 of the Human Rights Act 1998. This legislation applies to living individuals and so there is a degree of ambiguity regarding the deceased and this has been exemplified by a change in the advice of the ICO indicating that this legislation should not act as a statutory bar. Although greater clarity regarding access to the medical records of the deceased for research purposes has been forthcoming in the recent past there still remains a grey area exacerbated by a lack of formal legal obligations to confidentiality that apply to the deceased[30].

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[31], it is felt that the intended nature and scope of this initiative would make it insupportable in terms of available time and resources to undertake obtaining consent for access to and disclosure from the medical records of the deceased. In addition, given the extrapolated volume of surgical cases available now and into the future, to obtain consent on a case-by-case basis would greatly diminish the power of the initiative and greatly restrict the scope, coverage and depth of the proposed database. Therefore, it is proposed that, as obtaining consent would be onerous and disproportionate, an approach will be made to the National Information Governance Board for Health and Social Care Ethics and Confidentiality Committee (NIGB-ECC) to seek permission for disclosure under Section 251 of the National Health Service Act 2006 using procedures developed in line with advice and guidance received after discussions with the Approvals Manager of the NIGB-ECC.

In addition, there are ethical considerations pertaining to approaching the families of the deceased or living donors as this has the potential to cause harm or distress 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. With regards to the potential passage of time, it may also be difficult to locate family members to obtain consent due to migration or, indeed, death.

It is accepted that during the process of accessing the medical records and the anonymisation of any subsequent data that individuals may be privy to personal identifying information. It is intended that linked anonymisation will occur as soon as is practicable and that this process will either be undertaken by the original custodians of the data or, if they are not able to, by nominated *BRAIN UK* staff. In exceptional circumstances, when a specific research study requires additional information to be obtained from the hospital records and the staff of the participating centre and BRAIN UK are unable to extract this information the research team may do this after the necessary approvals of the NIGB-ECC for 'Section 251 support' have been sought and local data custodians have also granted relevant management approvals. This greatly minimises the access to such sensitive information and greatly reduces the scope for inappropriate dissemination of this information. In addition, there are contractual mechanisms and safeguards in place that would bring forward sanctions should there be a breach of confidentiality or an inappropriate disclosure of information.

We therefore feel, as safeguards are to be rigorously implemented concerning the security and confidentiality of any data accrued, that the proposal does not represent any significant or unmanageable risks to the well-being or security of the families of the deceased or to those still living. Also, given that the future research that could be facilitated by this initiative has the potential to be of benefit to such individuals, as well as society as a whole, we feel that this initiative will very much be in the best interests of the future health and well-being of the population of the United Kingdom and beyond. Disclosure of relevant patient information would therefore be in the public interest, be proportionate to need and would balance with the rights of the individuals concerned and their families whilst maintaining trust in what is a confidential service.

Finally, it should be considered that all autopsy tissue encompassed by BRAIN UK stored since the commencement of the Human Tissue Act 2004 (*i.e.* on or after 1st September 2006) is obtained with the permission of the patient (during life) or of their nominated representative or from an individual in a qualifying relationship for research use. However, at present this tissue is often not used for this purpose as the local centres may not be participating in relevant research. By making knowledge of this extremely important tissue resource widely available to the research community in a searchable format there is a much greater likelihood of such archived diagnostically-verified tissue being used for research that could benefit society as a whole in the future[32]. It is important to emphasise this in relation to cases of uncommon disorders where a single centre is unlikely to have sufficient cases to undertake a useful research project.

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Appendices

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Appendix B

SOP 1: Policy for Access to Tissue Archival Holdings of Participating Centres

SOP1e.doc

Appendix C

SOP 2: Data Confidentiality Policy

SOP2e.doc

Appendix D

SOP 3: Information Technology Policy

SOP3e.doc

Appendix E

SOP 4: Data Extraction Policy

SOP4e.doc

Appendix F:

SOP 5: Policy for the Disclosure of Clinically Significant Information

SOP5e.doc

Appendix G

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
The Corsellis Collection (West London Mental Health NHS Trust)	8,500
University Hospital Southampton NHS Foundation Trust	7,000
Oxford University Hospitals NHS Trust	6,800
NHS Lothian	6,000
Nottingham University Hospitals NHS Trust	6,000
NHS Greater Glasgow and Clyde	5,500
University College London Hospitals NHS Foundation Trust	4,500
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	3,900
Cambridge University Hospitals NHS Foundation Trust	1,400
Plymouth Hospitals NHS Trust	1,200
Great Ormond Street Hospital for Children NHS Foundation Trust	1,000
Imperial College Healthcare NHS Trust	1,000
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	*
	66,970

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

** Currently unable to provide data.*
***Participating Centre has agreed to a 'supply and demand' relationship with* BRAIN UK*.*

Appendix H

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
Plymouth Hospitals 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	*	*
The Corsellis Collection (West London Mental Health NHS Trust)	**	**
	363,350	**13,875**

Based upon questionnaires returned by Participating Centres December 2013.

** Currently unable to provide data.*
***The Corsellis Collection does not maintain a diagnostic or surgical archive.*

Appendix I

The following is a list of research projects applications received by *BRAIN UK:*

BRAIN UK Reference	Study Title	Status
10/001	PML pathogenesis	Withdrawn
10/002	White matter disorders in children: from magnetic resonance to basic defect	Approved
11/001	Role of neutrophils in the pathogenesis of NMO	Approved
11/002	Pilot study comparing microglial markers in different neurological diseases known to be associated with inflammation	Approved
11/003	Pilot study – Microglia profile in schizophrenia	Approved
11/004	Response of stem cells in the human brain to acute hypoxic/ischaemic injury	Approved
11/005	Fight Alpers'	Approved
11/006	Comparative analysis of neuropathology in Huntington's disease brains	Approved
11/007	How do ageing processes contribute to Alzheimer's disease?	Approved
11/008	ADAM17 in subarachnoid haemorrhage	Approved
12/001	Pilot study to identify mast cells and basophils in brain	Approved
12/002	Neuropathology of autoimmune/limbic encephalitis associated with antibodies against voltage-gated potassium channels	Approved
12/003	Neuropathological examination of neurons, glial cells, axons and molecular factors in mood and affective disorders	Approved
12/004	Evidence for stem cell neuroprotection in genetic ataxias	Approved
12/005	PML Pathogenesis	
12/006	The impact of mitochondrial DNA mutations on substantia nigra neurons	Withdrawn
12/007	Regulation of microglial proliferation and its contribution to chronic neurodegeneration	Request for additional information
12/008	Protein conformation changes in chronic traumatic encephalopathy and other tauopathies	Request for Protocol modification
12/009	Investigation into the impact of systemic inflammation due to infection on microglial phenotype and its contribution to Alzheimer's disease neuropathology	Approved
12/010	The brain in SUDEP: new insights from pathology	Approved
13/001	Are neurodegenerative diseases and gliomas inverse comorbidities?	Approved
13/002	Investigating inflammation of the normal appearing brain in patients with low-grade glioma	Approved
13/003	The role of c-Myc in choroid plexus tumours	Approved
13/004	Translation of novel findings for dentatorubropallidoluysian atrophy: from *Drosophila* to mice and human beings	Request for Protocol Modification
13/005	UK brain bank for autism and other developmental disorders	Approved
13/006	Characterizing microglia/macrophage polarization in paediatric brain injury	Approved
13/007	CAA in subarachnoid haemorrhage	Request for additional information
13/008	A post mortem study of progenitor cells following severe traumatic brain injury	Request for additional information
13/009	CAA in autonomic dysfunction (1)	Request for additional information
13/010	Pilot study of cholesterol, lipids and LDL in Alzheimer's disease	Approved
13/011	DNA polymorphisms in mental illness (DPIM)	Request for additional information
14/001	CAA in autonomic dysfunction (2)	Review

Appendix J

Sample *BRAIN UK* Study Acceptance Letter.

Acceptance Letter Template 040214 v1_0.pdf

Appendix K

BRAIN UK study application flowchart.

Application flowchart 040214 v1.0.pdf

Appendix L

BRAIN UK Terms and Conditions

Terms and Conditions 040214 v1_0.pdf

Appendix M

Systems Level Security Policy (SLSP)

SLSPe.docx