

UK Meningitis Study:

Epidemiology and outcomes in meningitis in the UK

- A prospective, observational, cohort study.

Version 7.2

25/11/2015

Meningitis Research Foundation Reference Number: 0904.0

The Royal Liverpool and 
Broadgreen University Hospitals
NHS Trust



i. General Information

This document describes the 'UK Meningitis Study: Epidemiology and outcomes in meningitis in the UK – a prospective observational cohort study' study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but centres entering patients for the first time are advised to contact the coordinating centre (Brain Infections UK, University of Liverpool) to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the Chief Investigator via the Liverpool Brain Infections Group (LBIG) at the Institute of Infection and Global Health (IGH).

ii. Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol.

iii. Contact Details – Institutions

Sponsor:	Study Management and Monitoring:	Co Sponsor
University of Liverpool, Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 794 8373	Brain Infections UK Liverpool Brain Infections Group University of Liverpool Ronald Ross Building 8 West Derby Street Liverpool L69 7BE Tel: 0151 795 9670 Fax: 0151 795 5528	Royal Liverpool and Broadgreen University Hospitals Trust Research and Development Department 4th Floor Linda McCartney Building Royal Liverpool Hospital Liverpool L7 8XP 0151 706 3702

iv. Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Co-Sponsors:	Chief Investigator (CI):
<p>Alex Astor Head of Research Support – Health and Life Sciences University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL</p> <p>Tel: 0151 794 8739 Email: sponsor@liverpool.ac.uk</p> <p>Heather Rogers Research Governance Manager Research and Development Department 4th Floor Linda McCartney Building Royal Liverpool and Broadgreen University Hospitals Trust 0151 706 3702</p> <p><i>Heather.Rogers@rlbuht.nhs.uk</i></p>	<p>Prof Tom Solomon FRCP PhD, MRC Senior Clinical Fellow Head, Liverpool Brain Infections Group Department of Clinical Infection, Microbiology and Immunology, Director, Institute of Infection and Global Health, Ronald Ross Building 8 West Derby Street Liverpool L69 7BE</p> <p><i>tsolomon@liv.ac.uk</i></p>
<p>Study Manager (including data management and statistics):</p>	<p>Medical Expert who will Advise on Protocol Related Clinical Queries (If other than CI):</p>
<p>Dr Fiona McGill MRCP DTMH DipHIVMed Clinical Research Fellow, Brain Infections UK Department of Clinical Infection, Microbiology and Immunology Institute of Infection and Global Health Ronald Ross Building 8 West Derby Street Liverpool L69 7BE</p> <p><i>Fiona.mcgill@liv.ac.uk</i></p> <p>0151 795 9606</p>	<p>Dr Fiona McGill MRCP DTMH DipHIVMed Clinical Research Fellow, Brain Infections UK Department of Clinical Infection, Microbiology and Immunology Institute of Infection and Global Health Ronald Ross Building 8 West Derby Street Liverpool L69 7BE</p> <p>fiona.mcgill@liv.ac.uk</p> <p>0151 795 9606</p>

v. Collaborators

Name	Department	Nature of Collaboration
Prof Tony Marson	<i>Division of Neurosciences</i> University of Liverpool	Expertise in running multi-centre studies
Professor Gus Baker	<i>Division of Neurosciences</i> University of Liverpool	Assistance with neuropsychological assessments
Dr Antonieta Medina Lara	Senior Health Economist Health Economics Unit University of Liverpool	Assistance with economic analyses and quality of life assessments.
Professor Carolyn Young	Walton Centre for Neurology and Neurosurgery NHS Trust	Expertise on evaluation of different scores for assessing outcome
Dr Gina Pinchbeck	Senior Lecturer in Equine Epidemiology, Department of Animal and Population Health, School of Veterinary Science, University of Liverpool	Study design and statistical analysis

vi. Co-Applicants

Name	Department
Dr Nicholas Beeching	Consultant Infectious Diseases Physician Department of Infectious Diseases Royal Liverpool University Hospital
Dr David McKee	Consultant Neurologist Department of Neurology Manchester Royal Infirmary
Dr Ed Wilkins	Consultant Infectious Diseases Physician North Manchester General Hospital Manchester
Dr Paul Klapper	Consultant Clinical Scientist Manchester Royal Infirmary Manchester
Dr Ian Hart	Consultant Virologist Royal Liverpool Hospital Liverpool
Dr Bahram Ebrahimi	Senior Lecturer Dept of Functional and Comparative Genomics. University of Liverpool

vii. Definitions

Co-Applicant

This is an additional applicant to the principal applicant or principal investigator or chief investigator in a grant application. They will normally be an investigator who will make a significant contribution to, and have part ownership of the project.

Co-Investigator/Local collaborator

This is a person who will assist the principal investigator in carrying out the study at the separate research sites.

Collaborator

A collaborator will be involved in the study as a whole and will, normally, have been involved from early on in the inception. They may or may not be paid. They would be an individual who will supply technical advice, reagents, samples or data for the project, but who would not normally be involved in the day-to-day execution of the project (unlike applicants and co-applicants). Collaborator involvement should be governed by appropriate legal agreements, e.g. material transfer agreements, confidentiality agreements and/or consultancy agreements.

Principal Investigator

This is an individual who will have responsibility for ensuring the correct and safe conduct of the study at a research site.

Study Management Group

This is a group of researchers in the institute of the Chief Investigator who will be responsible for the day to day running of the study. They will meet approximately every 3 months. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

Study Steering Committee

The role of the Steering Committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Study Steering Committee should agree the study protocol and any protocol amendments and provide advice to the investigators on all aspects of the study. A Study Steering Committee may have members who are independent of the investigators, in particular an independent chairperson. Decisions about continuation or termination of the study or substantial amendments to the protocol are usually the responsibility of the Study Steering Committee

viii. Glossary

ABNAS	<i>Aldenkemp and Baker Neuropsychological Assessment Score</i>
AE	<i>Adverse Event</i>
AR	<i>Adverse Reaction</i>
ASM	<i>Aseptic Meningitis</i>
BIUK	<i>Brain Infections UK</i>
BIUKCC	<i>Brain Infections UK Co-ordinating Centre</i>
CI	<i>Chief Investigator</i>
CRF	<i>Case Report Form</i>
CSF	<i>Cerebrospinal Fluid</i>
CTU	<i>Clinical Trials Unit</i>
GP	<i>General Practitioner</i>
HIT	<i>Headache Impact Test</i>
IDSMC	<i>Independent Data and Safety and Monitoring Committee</i>
IEC	<i>Independent Ethical Committee</i>
LREC	<i>Local Research Ethics Committee</i>
MREC	<i>Multi-centre Research Ethics Committee</i>
PI	<i>Principal Investigator</i>
PIS	<i>Patient Information Sheet</i>
PISC	<i>Patient Information Sheet and Consent</i>
R&D	<i>Research & Development</i>
SAE	<i>Serious Adverse Event</i>
SAR	<i>Serious Adverse Reaction</i>
SBM	<i>Suspected Bacterial Meningitis</i>
SM	<i>Study Manager</i>
SMG	<i>Study Management Group</i>
SUSAR	<i>Suspected Unexpected Serious Adverse Reaction</i>
SSC	<i>Study Steering Committee</i>
TB	<i>Tuberculosis</i>
TMS	<i>Total Morbidity Score</i>
UAR	<i>Unexpected Adverse Reaction</i>
VM	<i>Viral Meningitis</i>

Table of Contents

i.	General Information.....	2
ii.	Statement of Compliance	2
iii.	Contact Details – Institutions	3
iv.	Contact Details: Individuals	4
v.	Collaborators.....	5
vi.	Co-Applicants.....	6
vii.	Definitions	7
viii.	Glossary.....	8
1	PROTOCOL SUMMARY.....	13
1.1	Substantial Amendment 17 (01/05/2015)	Error! Bookmark not defined.
2	BACKGROUND INFORMATION	15
2.1	Introduction and rationale	15
2.2	Potential Risks and Benefits.....	16
2.2.1	Potential Risks.....	16
2.2.2	Potential Benefits.....	16
3	SELECTION OF CENTRES / CLINICIANS	17
3.1	Centre/Clinician Inclusion Criteria.....	17
3.2	Centre / Clinician Exclusion Criteria.....	17
4	STUDY POPULATION.....	18
4.1	Inclusion Criteria.....	18
4.2	Exclusion Criteria	18
4.3	Patient Transfer and Withdrawal	18
4.3.1	Patient Transfers	18
4.3.2	Withdrawal from Study.....	18
5	ENROLMENT	19
5.1	Screening	19
5.2	Algorithm of diagnostic criteria.....	22
5.3	Enrolment.....	23
6	ASSESSMENTS AND PROCEDURES.....	24
6.1	Baseline Tests.....	24
6.1.1	Amendment (05/04/2012)	25
6.1.2	Substantial Amendment 12 (03/09/2013)	25
6.2	Summary of Investigations	26
6.3	Schedule for Follow-up.....	27

6.3.1	Primary Acute Outcomes	27
6.3.2	Recurrence	27
6.3.3	Longer term outcomes	27
6.4	Other Assessments	28
6.4.1	Meningitest	28
6.4.2	Headache Impact Test (HIT) TM	28
6.4.3	Quality of Life and Health Economics	28
6.4.4	Neuropsychological Screening Assessment – ABNAS.....	28
6.5	Loss to Follow – Up.....	29
6.5.1	Amendment 12 (3/9/2013)	29
6.6	Study Closure.....	29
6.6.1	Extension (14/01/2015).....	29
6.6.2	Non-substantial amendment 19 (25/11/2015)	29
6.7	Schedule	30
6.8	SUB-STUDIES	31
6.8.1	Qualitative study on outcomes important to patients.	31
6.8.2	Retrospective study to calculate the prevalence of viral meningitis in the NW of England 31	
6.8.3	Biomarkers of infection (led by Dr Mike Griffiths)	31
6.8.4	Proteomics.....	34
6.8.5	DNA Sampling (led by Dr Mike Griffiths)	35
6.9	Substantial Amendment 12 (3/09/2013)	37
6.9.1	Qualitative study investigating themes in investigating a case of acute meningitis.....	37
6.9.2	Molecular studies to improve diagnostics in aseptic meningitis.	38
6.9.3	Immunology of aseptic meningitis	40
6.10	Gifting of samples.....	41
7	STATISTICAL CONSIDERATION.....	42
7.1	Outcome Measures	42
7.1.1	Primary	42
7.1.2	Secondary	42
7.2	Sample Size	42
7.3	Analysis Plan.....	43
8	Safety Considerations.....	44
8.1	Terms and Definitions	44
	National Research Ethics Service (NRES) Definitions.....	44
8.2	Severity / Grading of Adverse Events	44

8.3	Follow-up after Adverse Events.....	45
8.4	Reporting Procedures	45
8.4.1	Non serious AEs	45
8.4.2	SAEs	45
8.5	Responsibilities – Investigator	45
8.6	Responsibilities – BIUK Coordinating Centre.....	46
8.7	Safety Reports	46
9	ETHICAL CONSIDERATIONS.....	47
9.1	Ethical Considerations.....	47
9.1.1	Patients lacking capacity.....	48
9.2	Ethical Approval	48
9.3	Informed Consent Process	48
9.3.1	Deferred Consent	49
9.4	Study Discontinuation.....	49
10	REGULATORY APPROVAL.....	50
11	STUDY MONITORING	51
11.1	Risk Assessment.....	51
11.2	Source Documents.....	51
11.3	Data Capture Methods	51
11.3.1	Case Reports Forms.....	51
11.4	Monitoring at Brain Infections UK	52
11.5	Clinical Site Monitoring.....	52
11.5.1	Direct access to data	52
11.5.2	Confidentiality	52
11.5.3	Quality Assurance and Quality Control of Data	52
11.6	Records Retention.....	53
12	INDEMNITY	54
13	FINANCIAL ARRANGEMENTS.....	55
13.1.1	Substantial Amendment 17 (01/05/2015).....	55
14	STUDY COMMITTEES	56
14.1	Study Management Group (SMG)	56
14.2	Study Steering Committee (SSC)	56
14.3	Other contributors.....	56
15	PUBLICATION	57
16	PROTOCOL AMENDMENTS.....	58
16.1	Version 1 (28/06/2011).....	58

16.2	Version 2.1 (28/07/2011)	58
16.3	Version 3 (20/04/2012).....	58
16.4	Version 3.1 (14/05/2012)	58
16.5	Version 3.2 (13/06/2012)	58
16.6	Version 4 (5/07/2012).....	58
16.7	Version 5 (17/09/2012).....	58
16.8	Version 5.1 (21/02/2013)	58
16.9	Version 5.2(19/03/2013)	58
16.10	Version 6 (03/09/2013).....	58
16.11	Version 7 (06/05/2014).....	58
16.12	Version 7.1 (19/08/2014)	59
16.13	Version 7.2 (25/11/2015)	59
17	REFERENCES.....	60
18	APPENDICES	63
	Appendix A: Patient Information Sheets and Consent Forms	63
	Appendix B: Quality of Life Questionnaire.....	74
	Appendix C: A-B Neuropsychological assessment scale.....	75
	Appendix D: Participating Sites	76

1 PROTOCOL SUMMARY

Title: UK Meningitis Study: Epidemiology and outcomes in meningitis in the UK – A prospective, observational, cohort study.

Population: A study looking at adults admitted to hospitals in the UK with suspected meningitis.

Inclusion Criteria

- a. 16 years or over
- b. Suspected Meningitis AND either
 - i) Have had or are going to have a lumbar puncture
OR
 - ii) If Lumbar puncture is contraindicated: the clinician has a strong suspicion of meningitis AND positive blood culture for bacterial pathogen consistent with meningitis OR radiology consistent with meningitis AND being treated as meningitis.

Exclusion Criteria

1. Patients with indwelling ventricular devices (EVD, VP shunts etc...) or iatrogenic meningitis
2. Patients in whom a lumbar puncture is contraindicated (except see b(ii) above)

Number of Sites: 35-45

Study Duration: 2 years extended to 5 years

Objectives:

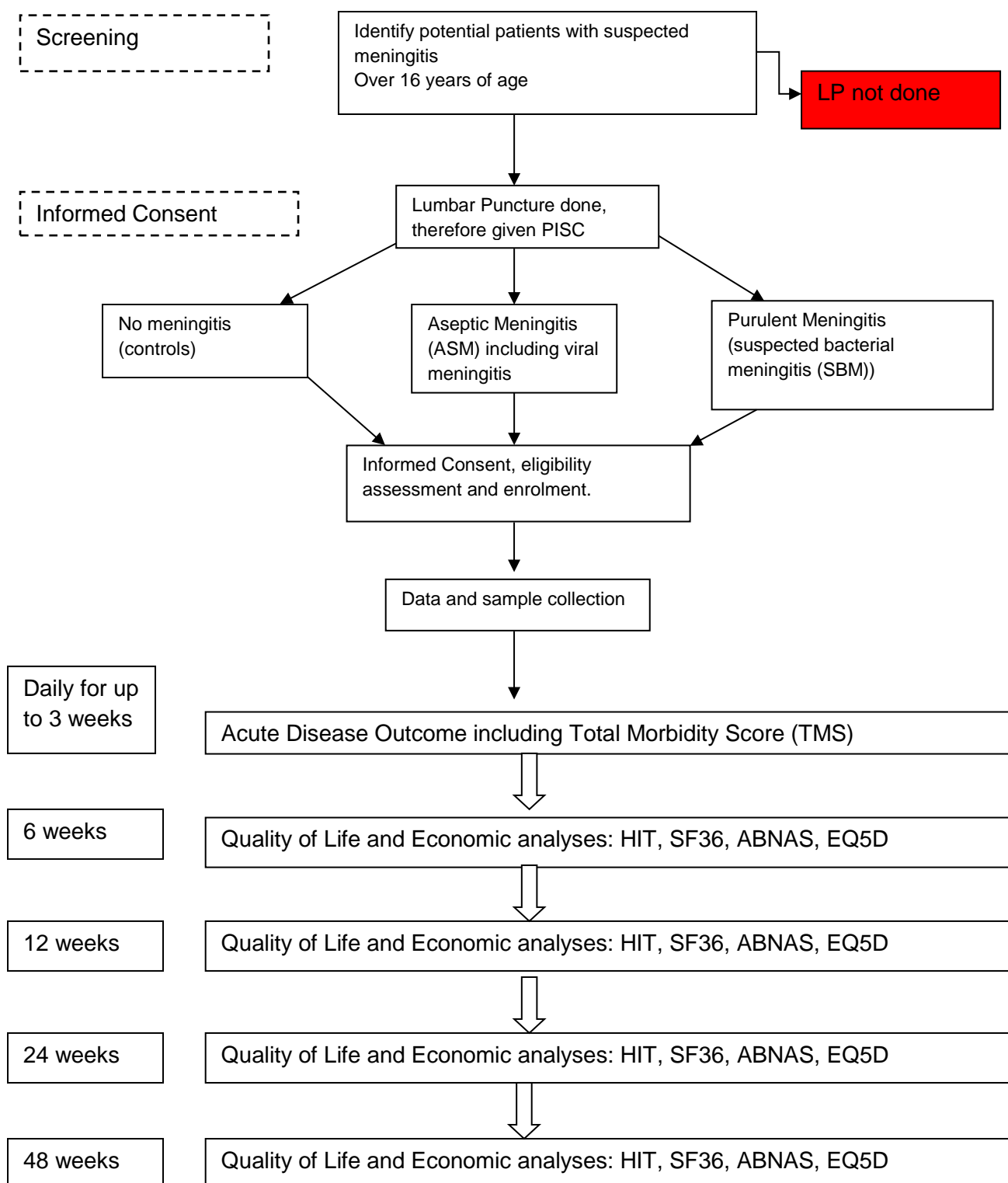
Primary:

- To determine the prevalence of viral meningitis in adults hospitalised with suspected meningitis and how much of viral meningitis is attributable to herpes viruses, and other viruses.

Secondary:

- To examine the clinical and laboratory features, time to symptom resolution, neurological complications, neuropsychological sequelae, and recurrences in viral meningitis
- To compare these features and outcomes with those in bacterial meningitis and non-meningitic controls
- To prospectively evaluate the *Meningitest* – an algorithm for predicting viral or bacterial aetiology in meningitis
- To determine the number of people with aseptic meningitis being offered an HIV test and the proportion of these that are positive.
- To determine and describe the causes of aseptic meningitis in our region.
- To determine the costs to the NHS and to the patients.
- To determine the impact on the patient's quality of life.
- To evaluate the use of certain outcome measures in viral meningitis (HIT, ABNAS).
- To use these epidemiological and disease burden data to design a phase III study of aciclovir / valaciclovir in herpes meningitis.
- To evaluate new genomic and proteomic approaches in the diagnosis of meningitis.
- To evaluate new diagnostic techniques and methods
- To identify themes and barriers amongst clinicians and laboratory staff that may be associated with implementing new diagnostic tests for meningitis.

Schematic of Study Design



1.1 Substantial Amendment 17

Some patients will be sent an additional questionnaire 2 years after discharge to monitor the significant differences observed at the 48 week time point. From May 2015, the TMS and follow-up questionnaires will no longer be given, or sent, to new patients enrolled on the study.

2 BACKGROUND INFORMATION

2.1 Introduction and rationale

Despite bacterial meningitis attracting more attention and research, viruses are the second commonest notified cause of meningitis in the UK (after *Neisseria meningitidis*) (1). Moreover, the actual incidence of viral meningitis is likely to be much higher than that which is notified (2, 3). Nearly 3000 cases of viral meningitis were recorded in the UK during 2009-10 (3). Studies from similar countries in Europe show an incidence in adults of 7.6 per 100,000 (4, 5). Traditionally enteroviruses have been shown to cause most cases of viral meningitis. However a recent study has shown that, in adults, the herpes viruses (herpes simplex virus (HSV) types 1 and 2, and varicella zoster virus (VZV)) are as common as enteroviruses(5). In this study from Finland (5) HSV-2 is shown to be the most common of the herpes viruses.

HSV -2 is primarily acquired sexually, and therefore occurs more frequently in adults. Individuals are often asymptomatic at the point of transmission of HSV-2 (6) and as the seroprevalence of HSV-1 decreases, primary infection with HSV-2 will increase.

There are many outstanding issues and unanswered questions with regard to viral meningitis.

- Sequelae

Although viral meningitis has largely been considered a benign self-limiting illness, recent data suggest otherwise (2, 7). One study has shown that more than a year after their illness, patients with viral meningitis had impaired global cognitive ability, short term memory and executive function compared with normal controls (8). Other patients have neurological complications, such as radiculitis (especially with VZV), or recurrences: it is now clear that the vast majority of Mollaret's recurrent meningitis is due to HSV-2 (7).

- Cost to the Health service

Studies from the USA have shown the large economic burden of viral meningitis (9). Equivalent figures for the UK are not available. However the full economic burden may go beyond the hospital costs, because of the potential subsequent effects on the patient and their family.

- Treatment

There is currently no consensus for the treatment of herpes virus meningitis. In particular there has not been a Cochrane review, hence the need for a study to assess this. Some clinicians treat patients with intravenous aciclovir (or its oral pro-drug valaciclovir), because studies have shown it is effective in encephalitis caused by HSV (10, 11). Indeed in some centres all patients with aseptic meningitis are treated this way, whether or not HSV infection is proven. In contrast other physicians discharge patients without treatment, because there is no evidence for efficacy, and the drug has rare but important side effects, such as renal failure. The use of aciclovir in the treatment of herpes virus meningitis has been identified by experts in the field as a key question that needs addressing by a randomised study (2, 12).

This current study is planned as a preliminary study to produce outcome data needed for the design of such a study.

- Need for improved diagnostics

As aseptic meningitis often results in no pathogen identified it may prevent patients receiving prompt appropriate medical management and may lead to poor utilisation of drugs, i.e. antibiotics and aciclovir. Further work by our group is planned with respect to evaluating newer genomic and proteomic approaches to diagnosis. This is outlined in section 6.8.3

Objectives

- 1) To determine the prevalence of viral meningitis in adults and how much is attributable to herpes viruses, and other viruses.
- 2) To examine the clinical and laboratory features, time to symptom resolution, neurological complications, neuropsychological sequelae, and recurrences in viral and bacterial meningitis, and non-meningitis controls.
- 3) To prospectively evaluate the *Meningitest* – an algorithm for predicting viral or bacterial aetiology in meningitis
- 4) To determine the number of people with aseptic meningitis being offered an HIV test and the proportion of these that are positive.
- 5) To determine and describe the causes of aseptic meningitis in our region.
- 6) To determine the costs to the NHS and to the patients.
- 7) To determine the impact on the patient's quality of life.
- 8) To evaluate the use of certain outcome measures in viral meningitis (HIT, ABNAS).
- 9) To use these epidemiological and disease burden data to design a phase III study of aciclovir / valaciclovir in herpes meningitis.
- 10) To evaluate new genomic and proteomic approaches in the diagnosis of HSV and other viral causes of meningitis.
- 11) To evaluate new diagnostic techniques and methods
- 12) To identify themes and barriers amongst clinicians and laboratory staff that may be associated with implementing new diagnostic tests for meningitis.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

Risks include loss of confidentiality. Good Clinical Practice should ensure this does not happen. Physical risks are limited to those of the extra venepuncture including bruising. The extra blood tests will, where possible be done at the same time as routine venepuncture to minimise this risk. There are no other potential physical risks to the participants as this is an observational study. The clinical care is directed by the responsible physician. There may be psychological risks as participants recall the impact their illness has had on their quality of life.

2.2.2 Potential Benefits

Whilst there may be psychological benefits for the individual patients taking part in an observational study, most of the benefits from this study will be for the future.

- We will have a more comprehensive knowledge of the natural history of viral meningitis.
- There are also potential benefits in knowing the long term outcomes of this illness.
- This work will lead on to a randomised treatment trial.
- There will be future benefits in increasing diagnostic possibilities with the proteomics and genomics work.

3 SELECTION OF CENTRES / CLINICIANS

The centres selected for potential inclusion are acute NHS trusts that take either general medical, acute medical or geriatric patients. Each PI will have current GCP status.

3.1 Centre/Clinician Inclusion Criteria

- a. Local R&D approval and SSA
- b. Receipt of Material Transfer Agreement (MTA)
- c. Receipt of evidence of completion of (a) & (b)
- d. Completion and return of 'Signature and Delegation Log'.
- e. 2 page CV to accompany all research personnel recorded on the 'Signature and Delegation' log

3.2 Centre / Clinician Exclusion Criteria

- a. Not meeting the inclusion criteria

4 STUDY POPULATION

4.1 Inclusion Criteria

- a. 16 years or over
- b. Suspected Meningitis AND either
 - i) Have had or are going to have a lumbar puncture
 - ii) If Lumbar puncture is contraindicated: the clinician has a strong suspicion of meningitis AND positive blood culture for bacterial pathogen consistent with meningitis OR radiology consistent with meningitis AND being treated as meningitis.

4.2 Exclusion Criteria

- a. Patients with indwelling ventricular devices (e.g. EVD, VP shunts etc...) or iatrogenic meningitis.
- b. Patients in whom a lumbar puncture is contraindicated (unless strong suspicion of bacterial meningitis as above).
- c. **In Scotland only** patients who do not have capacity are also excluded.

4.3 Patient Transfer and Withdrawal

In consenting to the study, patients are consented to study follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations and complete an end-of-study evaluation.

Subjects may withdraw from the study or follow up at any time. Data already collected will still be used in the final analysis unless otherwise requested by the participant/consultee.

Two written attempts and one phone call will be made to follow up patients before a patient is defined as lost to follow up.

4.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating study centre and for this study centre to take over responsibility for the patient. Brain Infections UK (BIUK) should be notified in writing of patient transfers.

If a patient moves out with the area and we are notified of the change of address every effort will be made to continue the follow up.

4.3.2 Withdrawal from Study

Patients who withdraw from the study for other reasons have previously consented to follow-up in the study. Data up to this time can be included in the study if anonymised.

5 ENROLMENT

5.1 Screening

Screening criteria

- a) Over 16 years of age
- b) Suspected meningitis

Patients will be screened from participating hospitals when they have suspected meningitis (see definitions).

They will be allocated a screening number (including the site number) e.g. 01001 for site number 01, screening number 001.

They can be considered for inclusion in the study either by the admitting clinical teams (on clinical suspicion of meningitis), or by the diagnostic microbiology services (when they receive a CSF sample for analysis).

E.g.

Screening point 1:

A clinician identifies a patient that meets the inclusion criteria.

Screening point 2:

A laboratory identifies a CSF sample that is received in the microbiology department. The patient can then be screened for eligibility with regard to the inclusion criteria and clinically suspected meningitis.

Enrolment should occur within the same admission as the above tests are done.

A screening register or log will be required at each site and reasons for non-inclusion will be listed in the screening log. Screening log will be kept at site and at coordinating centre.

Definitions

SUSPECTED MENINGITIS

Illness for 3 weeks or less with:

Headache and one or both of:

- neck stiffness
- photophobia

*except for those with very sudden onset severe headache (defined as no pain to maximal pain within one minute).

OR

Other patients with symptoms in whom the clinician feels a lumbar puncture is needed to diagnose/exclude meningitis

MENINGISM

Headache with neck stiffness and/or photophobia

CSF ≤ 4 leukocytes per ml of CSF**.

(NB some of these patients may have positive microbiology/virology)

ASEPTIC MENINGITIS

Suspected Meningitis (as above), AND

Negative Cerebrospinal fluid (CSF) microscopy and culture for bacteria (or negative PCR for bacteria if on antibiotics prior to CSF sampling), AND

CSF white cell count of 5-1000 leukocytes per ml of CSF** (with a lymphocyte predominance unless total leucocyte count < 20)

and a CSF / Plasma glucose ratio of $> 40\%$ (if paired glucose taken).

WITH NO IMPAIRMENT OF CONSCIOUSNESS

(NB this group may be further subdivided into infective and non infective causes. If there are significant numbers of migraine in this group then they may also be separated out for purposes of analyses.)

PROVEN VIRAL MENINGITIS

Suspected meningitis, AND

CSF white cell count of >4 leukocytes per ml of CSF**

Positive CSF PCR for viral pathogen (or intrathecal antibody).

POSSIBLE VIRAL MENINGITIS

Suspected meningitis AND

CSF white cell count >4 leukocytes per ml of CSF**

AND laboratory detection of organism outside the CNS (e.g. stool, throat, genitals etc...).

PURULENT MENINGITIS (suspected bacterial meningitis)

Suspected Meningitis AND

CSF WCC 20-1000 leukocytes per ml of CSF** and predominantly polymorphonuclear cells,
OR

CSF WCC >1000 (any predominant cell type)

AND

CSF/plasma glucose ratio <40%(if paired glucose taken).

PROVEN BACTERIAL MENINGITIS

Suspected meningitis

AND

CSF with >4 leukocytes per ml of CSF**

AND

Detection of appropriate bacterial pathogen from blood or CSF (culture, nucleic acid detection or serology)

Some patients who are admitted and have a lumbar puncture for suspected meningitis may turn out to have encephalitis. This would be defined as(13):

ENCEPHALITIS

Altered consciousness for >24 hours (including lethargy, irritability or a change in personality)

With 2 or more of the following

- Fever or history of fever (≥ 38 degrees Celsius) during the current illness
- Seizures and/or focal neurological signs (with evidence of brain parenchyma involvement)
- CSF pleocytosis (>4 leukocytes)
- EEG suggesting encephalitis
- Neuroimaging suggestive of encephalitis (CT or MRI)

WITH NO OTHER CAUSE FOUND.

***A bloody tap will falsely elevate the CSF white cell count and protein. To correct for a bloody tap, subtract 1 white cell for every 700 red blood cells/mm³ in the CSF, and 0.1 g/dl of protein for every 1000 red blood cells(14).*

CONTROLS

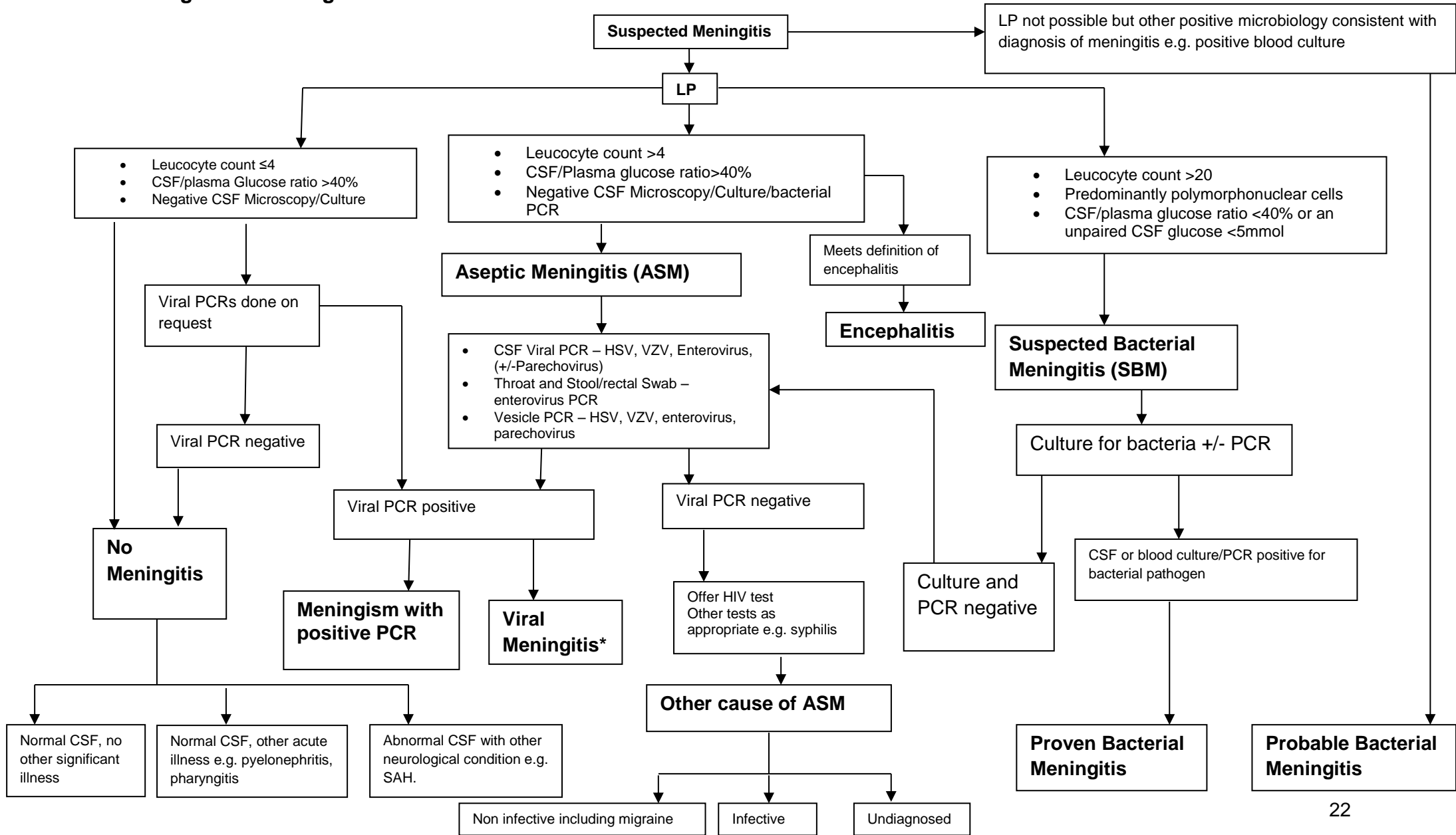
Our control group will be the group of patients who have had a lumbar puncture for suspected meningitis but are subsequently found not to have meningitis i.e. the LP shows no features of viral, bacterial or aseptic meningitis (less than or equal to 4 leukocytes/ml).

Information will be obtained on discharge diagnosis and follow up will be as for the meningitis cases. The control group will be further subdivided into:

- a) Those who have a normal CSF and no other significant illness (as determined by members of the study management team) causing their symptoms
- b) Those who have a normal CSF but have a significant systemic illness contributing to their symptoms e.g. pyelonephritis, pharyngitis, HIV seroconversion illness etc...
- c) Those who have a normal CSF leukocyte count but abnormal CSF in other ways indicating another neurological condition causing their symptoms e.g. subarachnoid haemorrhage.

All definitions may need to be further refined as the study goes on.

5.2 Algorithm of diagnostic criteria



*Unless only stool/rectal swab positive = Probable Viral meningitis

5.3 Enrolment

After screening if a patient is eligible to enter the study they can be approached by the local healthcare team, unless they have been discharged by the time they are identified as being eligible, in which case a letter may be sent, from the research team, inviting them to take part in the study.

After the initial approach if a patient is keen to participate they will be reassessed to ensure eligibility, and given a patient information sheet (PIS). Informed consent will be taken after the patient has had time to read the PIS and ask any questions. Consent will be taken by the local collaborator (or deputy), or a member of the research team.

If a patient is recruited in the emergency setting it may be necessary to defer consent for the extra blood samples (see section [6.8.3](#) and [9.3.1](#)) in order to a) get them taken in a timely manner and b) taken with the rest of their routine blood samples. Written consent will be obtained from either the patient or a consultee as soon as is feasible, and preferably within 48 hours. If a patient does not give written consent at this time the samples will be destroyed.

The participant contact detail form, consent form and enrolment form will be filled in at site and a copy faxed back to Brain Infections UK co-ordinating centre (BIUKCC) at the University of Liverpool. The patient's screening number will be used on all these forms. Once the enrolment form is received at BIUKCC a subject ID number will be allocated from the electronic database (OpenClinica™). A confirmation form confirming entry into the study will then be faxed back to the site. (If there is no secure fax available then a phone call can be made from the site to enrol a patient and the subject ID given verbally over the phone and all the forms can be sent by secure e-mail (nhs.net) or post). The confirmation form will have both the screening number and subject ID on it. Once the subject ID has been allocated the CRF can be completed. The completed paper CRF will then be faxed back to Brain Infections UK and data inputted into the electronic database centrally. If sites prefer they may input data directly onto the OpenClinica™ database having been given a password and training from the Brain Infections UK Data team.

The fax machine at Brain Infections UK Coordinating Centre is located in a locked office and is deemed a 'safe haven' fax by the data protection office.

The clinical care of the patient will be under the direction of the responsible clinician and involvement in the study will not alter that. Broad spectrum antibiotics may be started while awaiting the results of a CT (if indicated) and/or lumbar puncture, for patients in whom bacterial meningitis is clinically suspected.

Brain Infections UK Fax number: 0151 795 5528

Note the office is open Mon - Fri, 9a.m. - 5p.m. (excluding bank holidays)

Forms can still be faxed out of hours but they are unlikely to be responded to until the next working day.

6 ASSESSMENTS AND PROCEDURES

6.1 Baseline Tests

All patients will be asked if they have ever had a history of mouth or genital ulcers (if not already documented in the notes). And if they currently have any ulceration.

Opening Pressure will be recorded if LP is done in the lateral position.

CSF will be sent for

- Microscopy and Culture
- Protein
- Glucose

Further investigations:

Patients with **Aseptic Meningitis**

- Viral PCR - HSV 1 and 2
VZV
Enteroviruses
Parechoviruses (if routinely done by the treating centre).
Any other PCR that is deemed clinically appropriate in discussion with the clinical virologist/microbiologist (e.g. CMV, EBV in immunocompromised patients)
- HIV serology if no cause found
- Other investigations at the discretion of the responsible physician.

The viral CSF panel is what is regarded as 'good practice' amongst infection specialists and it has been shown that diagnosing viral meningitis reduces length of antibiotics and length of hospital stay and in turn brings a large cost saving.(15)

Patients with **Suspected Bacterial Meningitis**

- Meningococcal and Pneumococcal PCR on CSF (with consideration of 16S PCR if culture and meningo/pneumo PCR are negative – in discussion with local microbiologist).
 - PCR may be done routinely or only if culture negative depending on local practice.

If consented to all participants will have a small sample of CSF stored for future work on genomics/proteomics and other possible future studies. Participants will also be asked for permission to extract and sequence host and viral DNA from their specimens. (See section 1.1 for details of sub-studies.)

All participants will have **blood** tested for

- FBC, clotting, U and E's, LFTs, CRP, glucose ^(must be taken within 4 hours of LP)
- Blood Cultures
- Clotted sample to send for HSV type specific serology if HSV PCR on CSF positive
- Extra sample for gene expression, proteomic studies and other future studies. (see section 1.1)

Other Samples

In those with **Aseptic Meningitis**

- Throat swab and stool/rectal samples will be tested for enterovirus PCR
- Any oral or skin lesions present will be swabbed for HSV, VZV
- Any genital lesions will be swabbed for HSV PCR. *(if the PCR is negative for HSV in genital lesions the sample should then be referred (within the laboratory) for the CSF PCR panel as this is more sensitive, to exclude false negatives from the genital PCR.)*
- Any vesicle fluid present will be tested for HSV, VZV, enterovirus and parechovirus (if available locally).

Again these samples are considered to be good practice and are reiterated in the Health Protection Agency's Standard Operating Procedure 48 (The investigation of viral encephalitis and meningitis.)

In those with proven **HSV meningitis**

- If self reported genital lesions present swab as above.
- HSV type specific serology at time of presentation
 - If type specific serology is IgG negative then further follow up type specific serology will be requested at 6 months to document seroconversion.(this can be done by the research nurse or fellow at the patient's home)
- If no genital lesions self reported participants will be asked to self swab for asymptomatic genital HSV infection as follows:
 - Men – swab penile skin and perianal area.
 - Women – swab vaginal, vulval and perianal area.

(Different swabs can be used for the different areas but all the swabs will be put into the same vial of transport medium.)

In order to find out if there is a link between genital HSV infection and undiagnosed aseptic meningitis we will also ask **all patients in the aseptic meningitis** group to take genital swabs, as above. We will advise these patients that if their swabs return positive we will contact them and suggest self referral to a local sexual health clinic. Currently the relationship between viral shedding and incidence of meningitis is unknown. We know from enterovirus infection of the CNS that we can find the virus outside of the CNS when it is not demonstrable in the CSF.

If a patient lacks capacity genital swabs will NOT be taken unless clinically indicated.

To facilitate in collection of the appropriate samples we will, where they are in place, use the pre – prepared lumbar puncture packs which are being rolled out in the northwest region for investigating patients with suspected meningitis. This follows previous work that showed patients were not having appropriate testing done.(16)

Those classed as having suspected bacterial meningitis can be treated with broad spectrum antibiotics in accordance with local policies and/or the British Infection Association Guidelines (17). Virological investigations will not be performed, but they will remain in the study for the comparative analyses of different pathogens, and disease burden, as described below.

All patients with confirmed meningitis (bacterial, viral or aseptic) will be offered an HIV test in line with local policy and national HIV testing guidelines(18).

6.1.1 Amendment (05/04/2012)

All patients when enrolled should have a sample of blood taken for storage/serology if they consent to having extra blood samples taken. If the patient is later shown to have HSV meningitis this can be used to test for type specificity. If they have another diagnosis the sample can be stored if the patient has consented to having their samples stored and used in the future.

6.1.2 Substantial Amendment 12 (03/09/2013)

All patients will consent to gifting any leftover samples (blood and CSF) to the University of Liverpool for further work on diagnostics.

6.2 Summary of Investigations

		All patients	Controls	Aseptic Meningitis	HSV Meningitis	Suspected BM
Sample	Test					
CSF	Opening Pressure	X				
	Microscopy and Culture	X				
	Protein	X				
	Glucose	X				
	CSF Viral PCR panel			x		
	Meningococcal/ Pneumococcal PCR +/- 16S PCR					X (If microscopy /culture negative.)(according to local protocol)
	4.5ml CSF for genomics	X (if consented to)				
3-5ml CSF for DNA sampling	X(if consented to)					
Blood	FBC	X				
	Clotting	X				
	U and E's	X				
	LFTs	X				
	CRP	X				
	Glucose	X				
	Blood Cultures	X				
	Serology	X				
	HSV type specific serology				X	
	HIV serology			X	X	X
HSV type specific serology (at 6 months).				X (If initial type specific serology negative)		
4.5ml EDTA blood for proteomics (SST)	X (if consented to)					
18.5ml for genomics	X(if consented to)					
18ml for DNA sampling	X(if consented to)					
Throat swab	Enterovirus PCR			X		
Stool/rectal swab	Enterovirus PCR			X		
Lesions (oral, skin, genital)	HSV PCR, VZV PCR			X		
Vesicle Fluid (if present)	HSV, VZV, enterovirus and parechovirus PCR			X		
Self taken genital swab (see text)	HSV PCR			X	X	

 Samples to be taken over and above what would be routine practice.

All samples may be stored (if consented to), anonymously, for future research studies.

6.3 Schedule for Follow-up

6.3.1 Primary Acute Outcomes

6.3.1.1 Time to fever resolution

Temperature will be assessed 6 hourly for the first 48 hours, and thereafter 12 hourly (unless it is clinically necessary to do more frequently). Time to fever resolution will be recorded in days, (temp <37.5 for > 24 hours) for patients febrile on or after admission. (This will be recorded as the time between admission and the first temperature of <37.5 – after which the temperature remained less than 37.5 for > 24 hours.)

6.3.1.2 Resolution of Acute Morbidity

The Total Morbidity Score (TMS) (see below) will be assessed daily until a participant has a score of 0 for seven consecutive days. This score has been used on viral meningitis previously (19), and ranges from 0 to 21. Resolution of acute morbidity (using the TMS) including time to first symptom score of zero, and time to headache score of 0, has been used in previous studies of viral meningitis (19, 20).

The Total Morbidity Score. *This is the sum of the scores for the following six individual symptoms: headache, nuchal rigidity, photophobia, myalgia, fever, and nausea/vomiting. Each symptom/sign, other than headache, is ranked by the subject on a four-point scale (0=absent and 3=severe). Headache is ranked on a seven-point scale (0-6). It, therefore has a range from 0-27. This self-completed questionnaire takes less than five minutes to complete.*

In current hospital practice, many patients with meningitis are discharged before these symptoms are completely resolved. For these patients assessment will continue at home. Participants will be given a thermometer and asked to record their oral temperature daily and their TMS on a pre-prepared form. They will be given a postage paid envelope to return the data (anonymously).

Patients will be contacted by a member of the study team to ensure the forms are completed and returned after 21 days.

6.3.1.3 Morbidity index

In addition to the TMS we will also assess the co-morbidity of the participants using the Charlson Index(21) which has been validated previously and uses a scoring system to predict 10 year survival. This will help us compare outcomes with regard to co-morbidities.

6.3.1.4 Clinical Relapse

Clinical Relapse will be defined as

- A recurrence of fever, after fever resolution, with no other cause found. Fever is defined as one recording above 38.5 or 2 consecutive readings >38 (at least one hour apart)
- A recurrence of headache (with a score of 3 or more on the TMS) following resolution accompanied by at least one other score of >0 for 2 or more consecutive days.(19)

Clinical relapse will be defined within the first 3 weeks following admission to hospital.

6.3.2 Recurrence

Recurrence of viral meningitis will be defined as a recurrence of clinical symptoms, with CSF pleocytosis at least four weeks after complete symptom resolution (i.e. a TMS of 0).

Participants will be asked to contact the research team if they are readmitted to hospital with similar symptoms after they are discharged from hospital.

6.3.3 Longer term outcomes

Longer term exploratory analyses will be conducted on the HIT, SF-36 and ABNAS (see below) to assess their suitability as outcome measures in future studies of viral meningitis. The SF-36 and ABNAS will be compared with published normative data. Professor Carolyn Young from the Walton Centre, who is an expert on validation and implementation of rating scores will provide advice on evaluation of the different scores.

Patients will also be asked to document if they have had any episodes of genital lesions throughout the follow-up period. All patients will be asked and this will enable us to compare the rate of genital recurrence in those patients with HSV-2 meningitis with the other groups of meningitis and controls. A separate questionnaire will be sent to record this to be returned anonymously with the other questionnaires.

6.4 Other Assessments

6.4.1 Meningitest

We will prospectively evaluate the 'meningitest'(22). This is a screening tool to improve the empirical diagnosis of viral or bacterial meningitis using initial blood and CSF parameters. This has previously been piloted retrospectively by members of our group(16).

6.4.2 Headache Impact Test (HIT)™

This will be used to assess the impact headaches have on a person's ability to function on the job, at home, at school and in social situations. This tool which is particularly suitable for assessing the long term morbidity, has been developed for migraine and chronic headache (<http://www.headachetest.com/>) (23). We will compare between the groups of patients with viral meningitis and other types of meningitis. If there is a significant group of patients with migraine then they will also be used as a comparator group. Post LP headache will be defined as either a) new onset headache or b) worsening of headache following lumbar puncture which is worse on being vertical and eased on lying down with no other cause found.

6.4.3 Quality of Life and Health Economics

6.4.3.1 Quality Of Life Assessment - SF36

Quality of Life will be assessed using a generic health status measure, the SF36 (24) and the EQ-5D(25). The SF-36 assesses health status across eight domains: physical and social function, roles physical and emotional, mental health, energy/vitality, pain and general health; it also includes a 'transition' question (assessing perceived change in health status over time). It is a self-completion questionnaire, that been validated for use across a range of conditions of ill-health (24); and UK normative data are available, and takes between 5 and 10 minutes to complete. In addition, in order to obtain utilities for the economic analysis the EQ-5D will be used. The EQ-5D is a standardised non-specific multidimensional self completed questionnaire that describes and values health states, expressing results in a single index value of quality of life. It is based on a descriptive classification of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels 'no problem', 'some problem' and 'extreme problem'; death and unconscious health states are added creating a total of 245 health states for the evaluation. We will also include a single-item global quality of life question.

6.4.3.2 Economic Analyses

We will examine the total costs incurred by the NHS of providing care for patients with viral meningitis. The EQ-5D as mentioned before will be used for expressing the health outcomes as cost per Quality Adjusted Life Years (QALY). The cost analysis will follow the ingredients approach; costs and benefits will be discounted at 3.5%. Quantities will be reported separately from prices. Patients and carers will be asked to answer a socio-economic questionnaire to assess the costs incurred by them (non-medical direct costs, indirect costs, and accompany person costs).

Both of these analyses (SF36 and EQ5D) will be led by Dr Antonieta Medina Lara, Senior Health Economist.

6.4.4 Neuropsychological Screening Assessment – ABNAS

Neuropsychological function will be assessed with the ABNAS (Aldenkamp and Baker Neuropsychological Assessment Schedule). This is a patient completed assessment of cognitive impairment and function based on everyday activities, that takes approximately 5 minutes to complete (26). This has been used in epilepsy and a range of other conditions with neuropsychological impairment, and has normative data available, but has not been used previously in meningitis. (Prof GA Baker, Prof of Neuropsychology, Liverpool is advising on this aspect of the study.)

6.4.5 Amendment 09 (17/09/2012)

Early analysis has shown that there is no difference between the control patients and the viral meningitis patients (n=20 in each group). Therefore, it is postulated that as our control patients are patients that have been hospitalised a more 'healthy' control group is needed. Therefore, we will ask the participants when they are filling in the questionnaires to also give a pack of questionnaires to a relative/friend/neighbour to also fill in and return. Data on age and gender will be collected on these healthy controls.

The HIT, SF-36, ABNAS, and EQ-5D will be performed at 6, 12, 24 and 48 weeks after discharge. Each of these is a patient self-completed questionnaire which collectively will take twenty to thirty minutes to complete. It is important to obtain these serial evaluations so that we can determine the best endpoint for the subsequent treatment study.

6.4.6 Substantial Amendment 17 (01/05/2015)

Some patients will be sent an additional questionnaire 2 years after discharge to monitor the significant differences observed at the 48 week time point. From May 2015, the TMS and follow-up questionnaires will no longer be given, or sent, to new patients enrolled on the study.

6.5 Loss to Follow – Up

Two written attempts and one phone call will be made to follow up patients before a patient is defined as lost to follow up.

6.5.1 Amendment 12 (3/9/2013)

An interim analysis of the questionnaire responses has shown various areas in need of change:

1) Patient will be contacted by telephone at 6 weeks and one year if they have not responded to the questionnaires to ask for their responses over the phone. This will, hopefully, increase the response rate.

Time off work was an important area that had not been considered, therefore:

2) An additional thank you letter will be sent with the final set of questionnaires with a question enquiring about the amount of time spent off work.

3) A question will be added to the economic questionnaire to enquire about amount of time spent off work.

The HIT questionnaire was confusing for patients who have never suffered headaches.

4) A statement will be added to the covering letter that states 'if you do not suffer from headaches please tick NEVER for all the questions on the HIT'. This is because some patients are doing this and some are leaving blank and some are not returning the questionnaires.

6.6 Study Closure

Study recruitment will finish one year after the study period begins. The study will close when all the follow up from those patients has been achieved – approximately one year after that.

6.6.1 Extension (14/01/2015)

The study was extended until 31 December 2015

6.6.2 Non-substantial amendment 19 (25/11/2015)

The study was extended until 01 October 2016.

6.7 Schedule

	Who?	Baseline	Post LP	Daily for 3 weeks from admission	6 weeks (+/- 1 week)	12 weeks (+/- 1 week)	24 weeks (+/- 1 week)	48 weeks (+/- 1 week)
Consent Form	LC/RN	X						
Assessment of eligibility criteria	LC/RN	X						
Review of medical history	RN	X						
Ask re oral/genital ulcers (if not documented in medical history)	RN	X						
Check routine bloods taken (FBC, clotting, U and E's, LFTs, CRP, glucose, blood cultures)*,	RN	X						
Throat Swab for enterovirus PCR	CT							
Blood for proteomics and genomics (SST and PAXgene™ tube to be supplied by BIUK)	CT/RN	X						
Stool sample for enterovirus PCR	CT/RN	X						
If oral/genital/skin lesions present. Swab of oral/genital/skin lesion for HSV/VZV PCR Any vesicles present should have fluid sent for HSV, VZV, enterovirus and parechovirus PCR	CT	(X)						
Lumbar puncture***	CT	X						
If no self reported/documentated genital lesions. Self taken genital swab for HSV if CSF positive for HSV. Women – vulval, vaginal and perianal swab. Men – perianal and penile skin swab.	RN/Patient		(X)					
Meningitest performed	RN/RF		X					
Charlson Index	RN/RF	X						
TMS	Patient/RN/RF			X				
HIT	RN/RF				X	X	X	X
ABNAS	RN/RF				X	X	X	X
EQ5D	RN/RF				X	X	X	X
SF36	RN/RF				X	X	X	X

(X) If appropriate

* If not performed already these should be taken

** One for HSV type specific serology if needed and one for proteomics and genomics work

***Opening pressure, protein, glucose, cell count, microscopy and culture, PCR as appropriate for cell count/clinical judgement, stored

sample for proteomics/genomics. LC= Local collaborator, CT= Clinical team, RN = Research Nurse, RF= Research Fellow

6.8 SUB-STUDIES

6.8.1 Qualitative study on outcomes important to patients.

We will take a selection of participants (c. 20) with proven herpes meningitis and follow them up with a semi-structured questionnaire to generate a hypothesis on what outcomes should be evaluated with respect to viral meningitis. Help will be sought for this from the department of public health and policy in the University of Liverpool. In order to do this consent will be taken from all patients to allow future contact.

Amendment 14 (6/5/2014) – In addition to recruiting patients who have been enrolled in the UK Meningitis study for the qualitative study I will also utilise links with the Meningitis Research Foundation (MRF). Often patients contact the MRF following an admission to hospital and are keen to take part in research. Currently this can only happen if the hospital they were in happens to be part of the study. However, for the qualitative study they could be interviewed without being part of the rest of the study. I will utilise the MRF and any patients recommended to me via them. I will not include any patients who directly approach me by other means but only through the MRF.

6.8.2 Retrospective study to calculate the prevalence of viral meningitis in the NW of England

In addition to our prospective study, in order to corroborate our results we will also be asking all centres in the North West to participate in a retrospective study.

All laboratories will be asked to provide retrospective data on CSFs they have received in the preceding 2 years from patients over the age of 16. Data to be collected will be:

- Age
- Gender
- CSF
 - o WCC
 - o Percentage lymphs
 - o Percentage neuts
 - o Percentage other
 - o RCC
 - o Pathogen identified (if any)
- Clinical diagnosis from notes (if not available from the laboratory system).

Most of this data should be easily obtainable from the laboratory information system (LIS) and shouldn't take longer than 10mins per patient.

This data will then be compared with population data – found on the census website or the SHA's website – in order to determine the incidence. We will also be able to compare trends in incidence over the years and with our prospective study.

6.8.3 Biomarkers of infection (led by Dr Mike Griffiths)

Investigation of aseptic or lymphocytic meningitis using conventional techniques often results in no pathogen being identified (5, 27). This can prevent patients receiving prompt appropriate medical management and may lead to poor utilisation of drugs, i.e. antibiotics and aciclovir. Thus there is a need to improve diagnostics.

We aim to use a molecular approach to improve diagnosis via the detection of gene 'building-blocks' (transcripts) generated by the patient during acute illness.

These 'building blocks' are generated by the patient's immune cells in response to illness. Examining the patterns of these responses, called gene-expression profiling, can help characterise the underlying immune process and the insult causing it. We will employ gene-expression profiling methods, already used by our group(28-30), to examine the patients' gene-expression responses (in blood and cerebral spinal fluid (CSF)) between different classes of central nervous system (CNS) infection (e.g. viral or bacterial meningitis) or the pathogen causing it (e.g. Herpes Simplex virus (HSV) or Enteroviruses). Because the host gene-expression profile reflects the reaction of immune cells in response to infection, we will also collect leukocytes, key immune cells, from the blood and CSF to help understand which immune cells are involved in generating the host response patterns.

We will collect samples on all patients with suspected meningitis. Utilising patients that are later confirmed to have a definite diagnosis (i.e. a pathogen is detected), we will examine gene-expression responses between these patients to identify gene-expression patterns that delineate between different classes of CNS infection. Later, we will then use these gene-expression signatures to differentiate classes of CNS infection where no pathogen is recovered.

The blood and CSF samples will be collected in PAXgene™ tubes (to be supplied by BIUK). These tubes stabilise the transcripts when out of the body. The samples will be collected at the time of routine venepuncture and LP (where the patient is recruited prior to LP). Leukocytes from venepuncture will be collected into CELL PREPARATION TUBES (2x8mls) Leukocytes from CSF will be collected into LiHeparin tubes. These tubes facilitate separate of leucocytes from the rest of the biological samples (<http://www.bd.com/vacutainer/products/molecular>).

Amendment AM08

Interim analysis has shown that the samples are being collected several days after admission (median 3 days). Due to prompt and correct usage of antibiotics, the information we will be able to gather from these samples will not help us in our aim of differentiating acute viral meningitis from acute bacterial or indeed meningitis from non meningitic illnesses. In order to try and improve this we will obtain samples as close to admission as possible. Preferably, with the admission bloods/lumbar puncture (LP). Due to the emergency nature of suspected meningitis bloods/CSF may be taken for RNA analysis at the same time as the routine bloods/LP (BUT NOT PROCESSED) without written informed consent. Informed consent will be deferred until the patient is more stable and settled in hospital. If consent is not given the samples taken will be DESTROYED.

The patient information leaflet will reflect the fact that samples may have already been taken and the consent form will also include an optional section on consenting to use samples already taken specifically for research purposes.

Key Questions

Can analysis of the human host response (examining RNA transcripts) during acute infection be used to help differentiate between different types of CNS infection (e.g. viral or bacterial meningitis)?

Can analysis of the human host response (examining RNA transcripts) during acute infection be used to help differentiate between different types of CNS pathogen causing meningitis (e.g. HSV or enterovirus meningitis)?

Statistical Analysis

This sample-size estimation utilises the model described specifically for micro-arrays by the Department of Bioinformatics and Computational Biology, MDAnderson Cancer Centre, University of Texas (<http://bioinformatics.mdanderson.org/MicroarraySampleSize>). The model assumes that on the log scale the expression of each gene is normally distributed and that measurement of each gene is independent of the next.

Pilot data used to inform the current sample size calculation: We have previously undertaken a pilot gene-expression study among patients with two types of neuro-infection (Tuberculous and bacterial meningitis; 18 and 16 patients respectively in each group). The study identified over 200 highly discriminatory transcripts with > 2 fold differential transcript abundance between the two groups. Individually re-testing a sub-set of the transcripts (n=20) identified on the arrays via RT-PCR the differences in transcript abundance between infection classes were confirmed. The mean standard deviation in gene-expression (across both groups) was 0.72 in the study (Griffiths, MJ. unpublished data).

The sample size needed to identify a 2x fold change in gene-expression between the two patient groups, accepting an average standard deviation in gene-expression of 0.72, a 5% false detection rate (i.e. a per-gene significance level alpha of 0.05) and 80% power, will be 9 (in each arm).

In another study that collected research samples during clinical indicated venepuncture being undertaken by our group in Nepal, more than 90% of those patients approached consented to participate in the study. Previous clinical studies undertaken on the infectious diseases wards in Royal Liverpool University Hospital (e.g. PIVOT, genetic susceptibility to *C. difficile* infection) have demonstrated a similar high willingness to participate (80-90%). Taking a conservative estimate that 20% participants may not consent then we will still recruit sufficient participants. Additional patients will be used towards developing a validation set of patients.

Sample collection

Two blood samples will be taken during admission one on recruitment and one 3-5 days later (or at discharge if this occurs sooner). These will be taken, where possible at the same time as routine venepuncture. If possible two further samples will be taken during convalescence; one at three months and one at 12 months. This will only happen if the patient is being followed up and will need to be assessed on a case by case basis. The blood samples will be 18.5 ml in total; 2.5ml will be collected into PAXGENE for RNA extraction, and the rest will be collected into heparin for leukocyte separation.

If a patient is enrolled in the study prior to having a lumbar puncture an extra 4.5 ml of CSF will be collected whilst collecting the other clinically indicated samples. The LP will not be carried out purely for research reasons. LP samples will be collected into RNA stabilisation and leukocyte separation medium. The study team will also be able to collect left over samples taken for clinical reasons, for example serum or CSF. This will only be done if the samples are surplus to clinical requirements. Convalescent blood samples will only be collected in patients followed up by the physician.

Sample processing

	Biological Fluid	Tube/Purpose	Volume	When			
				Recruitment	d3-5	3/12	12/12
In sites that can either process and	Peripheral Blood	1x PAXgene RNA tube	2.5mls	X	X	X	X
		2x CPT tube	16 mls	X	X	X	X

store leukocytes or transfer them to another site that can within 8 hours	CSF	1xPaxgene RNA tube	2.5mls	X			
		Lithium Heparin	2 mls	X			
In sites that can't process leukocytes or transfer samples within 8 hours.	Peripheral Blood	1x PAXgene RNA tube	2.5mls	X	X	X	X
	CSF	1xPaxgene RNA tube	2.5mls	X			

All tubes utilized will be compatible with blood and CSF collection systems currently in use within the hospital(s).

RNA: Venous blood or CSF will be collected into PAXGENE tubes (2.5mls). Samples will be stored at room temperature for 2 hours then stored at -70c in open racks (to avoid differential freezing). Total RNA will be extracted in sample batches following the manufacturer's protocol.

Leukocytes: Leukocytes from venepuncture will be collected into CELL PREPARATION TUBES (CPT) (2x8mls). These tubes facilitate separate of mononuclear leucocytes from erythrocytes and plasma. Leukocytes from CSF will be collected into LiHeparin tubes. The samples will be processed within 8 hrs of collection. Separated leukocytes will have a cryo-protectant added (DMSO) and then be stored. Leucocyte samples will only be collected where research personnel are available to support leucocyte processing and storage or where a site is able to get them to another site that can within the 8 hours. All samples will be stored in -80°C freezers. All storage of material containing cells will be fully compliant with the human tissue act (HTA).

This substudy will be funded by FSF funding from the Liverpool Biomedical Research Centre.

6.8.4 Proteomics

In addition to the genomics work we will also build on the proteomics work that our group are already involved in.

Previous studies have demonstrated the power of linking protein and RNA expression methodology (31). Known proteins predicted to be differentially regulated by the transcriptomic studies can be measured, if secreted, in the corresponding plasma using ELISA or cytokine bead array (CBA) approaches (the latter allows us to screen for large number of target proteins in a relatively small volume of sample). Where antibodies to the protein are not available we may also consider 'tagging' target proteins and undertake quantification of the tagged proteins via Mass spectrometry.

In addition, in a selective sub-group of patients we will utilise SELDI mass spectrometry profiling, which enables rapid proteomic assessment of all protein peaks. Peaks of interest in particular diagnostic groups will be identified with the aid of dedicated software. The putative identification of peaks will be made by interrogating the publicly available databases with molecular masses of interest using tools available at www.expasy.ch (TagIdent, Findmod, Findpept) and/or Protein Prospector (<http://prospector.ucsf.edu/>)

Using these techniques we can compare the proteomic profiles of different groups of patients, such as

- those with viral meningitis with good outcomes,
- those with poorer outcomes and
- controls.

Our group are already collaborating with the University of Manchester, Liverpool School of Tropical Medicine and UCH in London where these techniques are already being used. Professor Levin (a co-applicant in this study) has extensive experience of these techniques.

Much of the work done previously on protein expression in viral meningitis has been done on viral meningitis as a group. We will be able to separate out the different causes of viral meningitis and compare between viruses as well as with our non-meningitic controls and others with undiagnosed causes of aseptic meningitis.

An extra sample of blood will be taken for this work; again this can be taken at the same time as routine venepuncture.

The CSF for the proteomics will be obtained from any leftover CSF.

6.8.5 DNA Sampling (led by Dr Mike Griffiths)

6.8.5.1 Background

All individuals are naturally exposed to range of viruses and bacteria during their life. However, in some the pathogen exposure can lead to devastating infection within the central nervous system. Infections are controlled by the body's immune system. The success of the immune response in preventing development of infection is influenced by inheritable factors of resistance and predisposition in the patient (genetic background of the patient) and the pathogen (genetic background of the pathogen).

These inheritable factors are based on DNA. DNA is the basic "instruction book" for the cells that make up our bodies and other living organisms including bacteria and some viruses. The DNA of a person is more than 99% the same as the DNA of any other unrelated person. But no two people have exactly the same DNA except identical twins. Differences in DNA are called genetic variations. These variations explain some of the physical differences, e.g. shape of your nose, among people, and partly explain why some people get diseases, e.g. meningitis while others do not.

Sometimes these variations have been shown to predispose to a variety of related, but different diseases(32).

We want to examine these factors in patients who are diagnosed with aseptic meningitis compared to individuals who haven't suffered meningitis or suffered less severe meningitis.

Control human sequences will be obtained from global and UK DNA data-bases (e.g. Wellcome Trust Case Control Consortium; MRC UK Biobank). Pathogen sequence data will be compared between samples from different body sites e.g. cerebral spinal fluid and genital lesions or from patients' with less severe brain infection.

Better understanding of these inheritable factors will help the design of new treatments against brain infections in the future.

6.8.5.2 Key Objectives

- To identify differences in the frequency of polymorphisms in human DNA sequences among patients with confirmed CNS infections compared to controls.
- To identify differences in the frequency of polymorphisms in pathogen recovered from cerebrospinal fluid compared to blood and/or genital lesions among patients with confirmed CNS infection.

6.8.5.3 Patient recruitment

All patients will be given the option of consenting to this part of the study. If they do not wish to have their DNA sampled they can still be part of the main study. Anybody who meets the eligibility criteria can consent to DNA sampling.

6.8.5.4 Statistical analysis

Human DNA study.

The initial study will look at genetic risk associated with the syndrome of aseptic meningitis. Based on the sample size calculation in section 7.2 we expect in excess of 220 patients with aseptic meningitis.

The sample size calculation assumes marker allele is the same as the disease allele, marker allele is present in 10% of the population and has 100% penetrance ($D'=1$). It also assumes there will be 1:4 ratio of cases to controls, a study power 80% and significance 95%. Controls will be obtained from the Wellcome Trust Case Control Consortium (containing a bank of up to 4500 DNA sample from control subjects).

Based on genotype relative risk of between 2.25 and a multiplicative genotypic risk model, the study will require 218 patients diagnosed with aseptic. Sample size estimation utilised the genetic power calculator (<http://pngu.mgh.harvard.edu/~purcell/gpc>).

Pilot Pathogen DNA study

Currently, the largest study of HSV sequence diversity in clinical samples looked at 28 patients and only examined selected regions of the viral genome (33). Based on advances in genome sequencing we are now able to sequence the whole-genome which may identify new areas of sequence diversity in the Herpes Simplex virus (34). We therefore intend to undertake a pilot study sequencing whole-genome pathogen DNA in the collected samples and use the resulting levels of sequence diversity to estimate the sample size required to do a full study.

6.8.5.5 Sample Collection

In consenting patients we will take an extra 3-5 ml of CSF (the exact volume will depend on whether or not the patient is also have CSF taken for leukocyte analysis (see section 6.8.3)). We will ensure no more than the maximum recommended amount of CSF is taken in total (15-17ml)(35). The CSF will be to sequence the pathogen in its entirety. 18ml of blood in EDTA tubes will be taken for the human DNA analysis.

This study will also be funded by FSF funding.

6.9 Substantial Amendment 12 (3/09/2013)

Following interim analysis of the data from the Meningitis NorthWest study (predecessor to UK Meningitis Study) it was discovered that up to 40% of patients with proven meningitis never have a pathogen identified. Therefore, further funding was successfully obtained from the National Institute for Health Research to look into this further.

6.9.1 Qualitative study investigating themes in investigating a case of acute meningitis

One reason pathogens are not found in cases of meningitis is that diagnostic tests and investigations are not performed in a standardized way in cases of meningitis.

Using the already established network of centres (and new ones in the UK Meningitis Study), **semi-structured interviews will be carried out** with clinicians who have recently treated a potential case of meningitis. The clinicians will be identified following cases that are enrolled into the UK Meningitis study. To ensure that the actual work and decisions made by clinicians is captured as accurately as possible, I am proposing to interview clinicians, face to face, as soon as possible after they have treated such patients. The interviews will be carried out to understand the decisions and management of each case.

Additionally, **focus groups** with laboratory staff will explore the acceptability of the introduction of novel technologies for meningitis.

Following local research governance approval identification of the clinicians would be done via the research team recruiting the patients. Clinicians who may be potential participants will be sent a letter of introduction and an information sheet as soon as local governance is obtained in order to ensure that they are aware of the research, can ask relevant questions, and have enough time to consider their participation. This can be sent via a trust wide e-mail. The research nurses within each of the sites will be notified of this component of the Fellowship to ensure that there is clear communication and understanding of the research. The relevant research nurse will be contacted to determine the name of the clinician who initially looked after the patient. They will then be contacted via a letter, information sheet, and completion of a brief 'profile' questionnaire. If possible there will also be a brief follow up phone call. If the participant is agreeable a time and location convenient for them to carry out the interview will be arranged.

Semi-structured interviews will be undertaken and will last between 30 and 45 mins.

Informed consent will be used to ensure participants understand the research and consent to take part. The interviews will explore participants' previous training, speciality, and management of meningitis – using the recent case as an exemplar. Additionally, the introduction of a 'blanket' test all potential causes of meningitis will be discussed to understand any barriers to implementation.

Clinical Staff

To ensure maximum variation 30 semi-structured interviews will be carried out with the medical staff. The clinicians interviewed will be stratified according to speciality and level of seniority, doctors within the first 4 years post qualification (foundation and core medical

trainees); and more senior specialist trainees (ST3 and above). If possible consultant interviews will also be carried out. In addition the interviews will be carried out in both secondary and tertiary care. This information will all be available on the case record form for the patient enrolled. The laboratory staff will also be stratified according to secondary or tertiary care.

To avoid bias any doctors identified on the delegation log for the UK Meningitis Study or NW studies will be ineligible.

Initial interview data produced from semi-structured interviews will be analyzed for emerging themes and further interview questions will be developed if necessary.

Laboratory staff

Focus groups will also be carried out with laboratory staff. One will be in a large teaching hospital and one in a smaller district general. Focus groups will be used in order to access the mixture of laboratory staff (e.g. microbiologists, virologists, biomedical scientists and managers) involved in testing CSF samples.

Analysis

Interviews will be audio recorded and uploaded on to a secure server at the University of Liverpool – password protected. Data will be transcribed by an experienced health services transcribing service. Data will only be seen by the research fellow, Dr Fiona McGill, her supervisor, Dr Paula Byrne, and the transcriber. Data will be anonymised and any references which may identify participants by location will be removed. Transcriptions will be checked for accuracy against the original recorded data. Transcribed data will be uploaded on to Atlas TI – computer software which is extensively used by qualitative researchers. The iterative approach will be used on the topic guides for the semi-structured interviews, this means that initial interviews will be analysed and discussed amongst the team, before subsequent interviews, in order to allow any developing or unexpected themes to be incorporated into subsequent versions of the topic guides. Data analysis will follow a grounded theory approach and use the constant comparative method.

Coding, the initial process in the analysis will begin with line-by-line coding on the first four interviews where a code or term(s) that best describes the data will be applied. Incident coding of each of the remaining interviews will then be completed to allow for a more in-depth analysis. During incident coding, each incident will be compared with other incidents in other interviews.

Codes generated will be linked directly to the data. Focused coding, where the codes are collapsed into categories and sub-categories, and finally, modified axial coding, a process of reassembling the data to give coherence to the developing theory.

6.9.2 Molecular studies to improve diagnostics in aseptic meningitis.

Background

The clinical differentiation between different causes of meningitis is difficult. A lumbar puncture is, therefore, necessary to provide cerebrospinal fluid (CSF) to determine the cause. It is not always easy to determine viral from bacterial meningitis without a lumbar puncture, therefore, antibiotics are often given to all suspected cases. As a result, positive cultures in cases of bacterial meningitis are declining. Consequently molecular tests, such as

the polymerase chain reaction (PCR), are now vital in the diagnosis for both viral and bacterial meningitis.

Even with using PCR a significant number of patients with meningitis never have a definitive cause found for their illness. Failure to obtain the correct microbiological diagnosis has been shown to lead to lengthened hospital stays and unnecessary antimicrobials and investigations.

Newer approaches to diagnosis are available

Multiplex PCR utilizes molecular methods to test for several pathogens at once. This means less sample being used, less consumables, reduced handling of the sample and quicker turnaround times. Multiplex PCR has been shown to be cost effective in some conditions. However, a concern with multiplex PCR is that sensitivity can be lost because not all primers work 100% effectively to detect all potential pathogens using a single PCR condition. Nevertheless there have been preliminary reports of comparable, and improved, sensitivity when multiplex has been compared with singleplex.

Multiplex PCR allows for the **rapid and accurate identification** of multiple pathogens at once.

Current laboratory practice in the molecular investigation of CSF is variable:

- In most NHS sites PCR for each potential pathogen is done as a singleplex or duplex reaction (i.e. only one or two pathogens at a time).
- Often the different PCRs are performed in different laboratories e.g. enterovirus PCR might be done at the local laboratory, the bacterial PCR sent to one laboratory and the remaining viral PCRs to another.
- Some laboratories will select the most appropriate investigations based on the initial CSF microscopy whilst others will only test for what is directly requested by the clinician.
- Usually the amount of CSF taken is very small, and with so many different tests in different locations, the sample has often all been used before investigations are completed.

All these permutations mean potential delay in the final diagnosis, or no definitive diagnosis at all. With increasing centralisation of diagnostic laboratories it is likely that more CSF samples will travel further to be tested. Therefore it will be even more important to define what best practice should be with regard to microbiological diagnosis in cases of meningitis. One solution to these problems is for all CSF samples from patients with meningitis to have the same broadrange multiplex PCR covering all common central nervous system (CNS) pathogens. This would make the most of the available sample (because less sample is used in a multiplex test than multiple individual tests), eliminate the sample travelling to several laboratories thus reducing potential false negatives associated with frequent freeze/thawing. It would also counteract the fact that the requesting physician does not always request all of the appropriate tests at the outset.

Methods

Leftover CSF samples will be tested for common CNS pathogens using new commercially available multiplex kits, and also by singleplex PCR for a comprehensive array of pathogens, to evaluate the sensitivity of these kits.

Other molecular methods will also be used on leftover samples to establish if there are any novel pathogens contributing to meningitis in the UK.

MassTag PCR is a form of multiplex PCR that uses primers with tags of different molecular weights to identify the product. The MassTag PCR allows a rapid and sensitive diagnostic platform that can screen up to 30 bacterial, viral and fungal agents.

High throughput sequencing can be used to identify novel pathogens unidentified from conventional PCR techniques. In the few years since the development of high throughput sequencing the costs have decreased drastically and the speed increased.

These methods will be utilised with collaborators in the US and the UK.

Statistical analysis

Confirmed clinical cases (i.e. CSF white cell count >4 cells/ml), expected to be about 60% of all suspected cases, will be analysed by routine conventional testing and by variants of PCR testing as described above.

Using routine conventional testing a proportion 0.6 of confirmed cases leads to successful pathogen detection (data from the Meningitis NorthWest study). The hypothesis states that multiplex PCR testing will increase the proportion of successful pathogen detections to 0.7. The primary analysis will apply McNemar's test to the matched pairs of binary outcomes (routine testing and multiplex PCR). In a secondary analysis, I will simultaneously compare the performances of all four testing methods (standard of care, singleplex and the 2 multiplex PCRs) using a generalized linear mixed model, specifically a logistic regression model with testing method as a fixed effect and patient as a random effect.

The table below shows the power of the primary analysis to detect an increase in the proportion of successful diagnoses from 0.6 to 0.7 when testing at the conventional 5% level of significance. Power is tabulated as a function of the number, N, of suspected cases and the standard deviation, SD, of the patient random effect.

	N				
SD	200	400	600	800	1000
0.0	0.33	0.62	0.8	0.9	0.95
0.2	0.34	0.61	0.79	0.89	0.95
0.4	0.32	0.6	0.78	0.89	0.94
0.6	0.31	0.59	0.75	0.88	0.94
0.8	0.31	0.57	0.75	0.86	0.93
1.0	0.29	0.55	0.73	0.84	0.91

Based on these results, a sample size of 600 suspected cases would be used so as to achieve a power of between 0.73 and 0.80 according to the value of SD, on which there is no prior information.

6.9.3 Immunology of aseptic meningitis

Over the last decade it has been discovered that autoimmune encephalitis is an important entity that accounts for some of the previously undiagnosed cases of encephalitis. It is feasible that some of the undiagnosed cases of meningitis are not caused by infections but immune phenomena. Therefore, samples that are already being taken as part of the UK Meningitis Study will be utilised to evaluate and describe the immunology of known causes of viral and bacterial meningitis and compared with the unknowns.

6.10 Gifting of samples

Consent will be obtained for all samples taken for genetic analysis to be gifted to the Liverpool Brain Infections Group, University of Liverpool and the rights to intellectual property will be relinquished by the patient and the NHS trust from whence they came.

7 STATISTICAL CONSIDERATION

7.1 Outcome Measures

7.1.1 Primary

Prevalence of Viral meningitis in the North West of England and the contribution of each virus to that.

7.1.2 Secondary

- a. Time to fever resolution
- b. Resolution of acute morbidity (using the TMS)
- c. Incidence of relapse and recurrence
- d. Change in Headache Impact Test over the study period
- e. Quality of Life Assessment (SF36)
- f. Neuropsychological Outcome (ABNAS)
- g. Economic Analyses (EQ5D)
- h. To determine the number of people with aseptic meningitis being offered an HIV test and the proportion of these that are positive.
- i. Pathogen Specific Outcomes
- j. Clinical Predictors of outcome or pathogen.

7.2 Sample Size

Based on previous retrospective epidemiological studies (Kupila et al and Michael et al) we expect to see the following number of cases.

58	No meningitis	Bacterial Meningitis	Aseptic meningitis	HSV-2 meningitis	VZV	Enterovirus
1066	682	160	223	38	18	58

This is based on Michael et al's study(36) finding 217 patients with suspected CNS infection over a 3 month period in 10 hospitals in the North West of England. 18 of these patients had aseptic meningitis, 13 had purulent meningitis and 55 just had meningism. I have, therefore, extrapolated that there were 86 patients with suspected meningitis (although this may be an underestimate.) Only 5 of the patients with aseptic meningitis had viral PCRs done and 1 of these (20%) was positive for HSV-2. Although this is clearly a small number it is similar to Kupila et al(5) who found 17% of their aseptic meningitis cases had HSV-2. They also found 26% with enterovirus and 8% with VZV.

I have extrapolated the numbers from Michael et al's study to calculate the expected numbers over a year and in 31 centres. I have calculated the expected prevalence of different viruses from the data in Kupila's study.

It is likely that this is an underestimate as it is based on retrospective data.

Using the HES data(3) there were 2741 finished consultant episodes of viral meningitis in England in 2009-2010. Based on the fact that the North West region has 13% of England's population (Census data) we could expect up to 356 cases of viral/aseptic meningitis in one year.

For this type of study approximately 50 patients are needed as a minimum. For comparisons between diagnostics groups (eg herpes meningitis versus bacterial meningitis), a minimum of 25 patients would be needed in each group to have 90% power to show a

difference of one standard deviation in the measure of interest, allowing for approximately 10% drop out. We are likely to have at least this number of patients with herpes meningitis, and probably many more.

7.3 Analysis Plan

Normally distributed data will be compared using Student's T test, and non-parametric tests, such as the Mann-Whitney U test, used for other data. Multiple logistic regression e.g. Cox regression, will be used to look for features predictive of particular pathogens. This will be adjusted for age and gender. Differences in median time to symptom resolution between groups will be analysed using two-sided actuarial (log-rank) methods, with a conventional 5% (type I error) significance level. The outcome analysis will also be adjusted for different research sites using multi-level modelling.

Assistance with analysis will be given by Dr Gina Pinchbeck, Senior Lecturer in Epidemiology.

8 Safety Considerations

8.1 Terms and Definitions

National Research Ethics Service (NRES) Definitions

An **Adverse Event (AE)** is defined as any untoward occurrence in a patient or research subject who is involved in a clinical research study and **which does not necessarily have a causal relationship** with study participation or procedures.

NRES defines a **Serious Adverse Event (SAE)** as an untoward occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

**'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.*

****Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

NRES defines related and unexpected SAEs as follows:

- **'related'** – that is, it resulted from administration of any of the research procedures;
- **'unexpected'** – that is, the type of event is not listed in the protocol as an expected occurrence.

NRES require that a SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is related and unexpected, is reported to the main Research Ethics Committee (REC).

8.2 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities

Moderate: interferes with routine activities

Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 9.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

8.3 Follow-up after Adverse Events

All adverse events should be followed up until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

8.4 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the BIUKCC in the first instance.

8.4.1 Non serious AEs

All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be sent to the BIUK coordinating centre.

8.4.2 SAEs

The BIUK coordinating centre will notify the main REC of all related and unexpected SAEs occurring during the study within 15 days. They will be reported on the SAE report form provided by the NRES on their website. This form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. Local investigators should report any SAEs as required locally.

8.5 Responsibilities – Investigator

The local investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study.

All SAEs must be reported immediately by the investigator to the BIUK coordinating centre on an AE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Subject ID
- A description of the event
- Date of onset
- Current status
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

- i. The AE form should be completed by a designated investigator, a physician named on the delegation log.
- ii. When submitting an SAE to the BIUK, study sites should also telephone the study manager/data manager on telephone number **0151 795 9606** to advise that an SAE report has been submitted.
- iii. Send the AE form by fax (within 24 hours or next working day) to the BIUK coordinating centre:

Fax Number: 0151 795 5528

- iv. The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
- v. In the case of a non-fatal SAE the subject must be followed-up until clinical recovery is or until the event has stabilised.

8.6 Responsibilities – BIUK Coordinating Centre

Staff at the BIUK coordinating centre will liaise with the Chief Investigator (or designated other) who will evaluate all SAEs received for seriousness, expectedness and causality. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The BIUK coordinating centre will also send an annual safety report containing a list of all SAEs to the MREC. Copies of the report will be sent to the Principal Investigator at all institutions participating in the trial.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

8.7 Safety Reports

Safety reports will be generated during the course of the study which allows for monitoring of SAE reporting rates across sites. The BIUK coordinating centre will send annual safety reports containing a list of all SAE's to MREC. Any inconsistencies noted at a given site may prompt additional training at sites, with the potential for the BIUK coordinating centre to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

9 ETHICAL CONSIDERATIONS

9.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

Ethical problems to be encountered in this study would include;

- Consenting of acutely ill patients. This problem can be countered by the fact that patients will be able to be recruited at any point during their acute admission and this can be either before or after the lumbar puncture +/- any treatment.
- We will be requesting extra blood and CSF samples for our genomics and proteomics work as well as storage for other future studies. This may provide anxiety to the patient who will be allayed by the patient information leaflet and reassurance that the sample will be pseudonymised and the samples will only be used for indications that they have consented to. Samples will be stored securely at the University of Liverpool.
- The use of questionnaires means that some data will have to be pseudonymised, as we will still need to access the participant's name and address. Reassurance will be given to the participant regarding confidentiality and no medical information will be divulged on the questionnaires. The completed questionnaire on return will have no identifying features.
- The study can include someone who lacks capacity (see section 9.1.1). Advice will be taken from a consultee (carer/family member) in accordance with GCP and the Mental Capacity Act (2005).
 - **Substantial Amendment 15 (August 2015) – no patient who lacks capacity will be recruited in sites in Scotland.**
- It is possible that participants may consider that they will get better/different treatment by either being in or not being in the study. All patients will be treated by their responsible physician and any treatment will not be influenced by the study. It will be emphasised that the study is observational and not interventional.
- There are also ethical issues with regard to requesting genital swabs from patients. These will be requested from those who have genital signs or symptoms but also from some asymptomatic patients. The reason for taking from asymptomatic patients is to assess if there is a relationship between asymptomatic genital shedding of HSV-2 and HSV-2 meningitis. In order to ascertain the importance of this a control group is also needed. The asymptomatic patients will be asked to take their own genital swabs which will lessen any embarrassment or distress and maintain dignity. If any of the swabs from the asymptomatic patients are positive for HSV they will be informed of this and advised to visit their local sexual health clinic. The relationship between HSV-2 meningitis and sexual health will be sensitively explained by the responsible clinician.
- Ethics of potential genetic analysis - the potential for identification of genetic variants could be associated with disease risk. While this information could possibly improve lives of individuals, providing information about low risk common variants that are not clinically relevant and have been identified using techniques that are not clinically validated may be harmful. To date, genetic research and analysis indicates that risk profiles generated by common, moderate and low risk genetic variants do not provide sufficient discrimination to warrant individualised prevention or treatment for complex diseases. The clinical utility of single, common, low-penetrance genes is therefore very limited. Given that the clinical implications of genetic profiles are unknown at the population and individual level and that these methods are being used for research purposes and have not been validated in the clinical setting, genetic data from the study **will not be disclosed to individual study participants.**

9.1.1 Patients lacking capacity

As patients who are admitted with meningitis, especially bacterial meningitis, may lack capacity due to acute illness it will be necessary to have processes to enrol these patients as well. Advice will be taken from a consultee. The Mental Capacity Act Code of Practice defines a consultee as someone who is involved in the patient's care, interested in their welfare and willing to help. It should not be a professional or paid care worker or anyone with a connection to the study. This will normally be a family member but not always. If the patient regains capacity they will be asked to consent or they may choose to withdraw from the study. Nothing will be done to the patient to which they appear to object.

Non Substantial Amendment (15) 12/08/2014.

Due to differences in Scottish Law sites in Scotland will NOT recruit any patients who do not have the capacity to consent for themselves.

9.2 Ethical Approval

The study protocol will receive the favourable opinion of a Multi-centre Research Ethics Committee (MREC) before commencing, but must also undergo site specific assessment (SSA).

A copy of local Research & Development (R&D) approval and of the PIS and consent form on local headed paper will be forwarded from each site before patients are entered into the study. Brain Infections UK should receive notification of positive SSA for each new centre via the MREC: usually this will be through the CI as they should be the main MREC applicant.

9.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. Informed consent is required for all patients participating in Brain Infections UK coordinated studies. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to patients by staff with experience in taking consent and who are familiar with the study. All potential participants will be given a patient information sheet (PIS). Upon reviewing the PIS, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the study may be obtained will be provided.

The patient should have the opportunity to discuss the study with their surrogates and think about it prior to agreeing to participate. A copy of the informed consent document will be given to the patient and/or consultee for their records.

Consent will be obtained for the participants name and address to be provided to the co-ordinating centre and a copy of the consent form, participant detail form and enrolment form will be kept there.

The patient or consultee may withdraw from the study at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

Amendment 10

Consent will be obtained for the patient's data (in an anonymised fashion) to be used in other relevant studies within the Brain Infections UK portfolio of studies. E.g. if a patient is enrolled to this study who later turn out to have Encephalitis, their data can be used in the analysis of the ENCEPH UK study (www.encephuk.org).

9.3.1 Deferred Consent

For optimal respect of a patient's autonomy informed written consent, before study participation is preferable. However, in the emergency setting (as suspected meningitis is a medical emergency) this is not always possible. In order to achieve the aims of the biomarkers of infection substudy it is essential that samples are taken concurrently with admission bloods and initial lumbar puncture (LP) (see section [6.8.3](#)). In order to obtain these crucial samples they may be taken (as long as there is no explicit refusal of consent) at the same time as the admission venepuncture/LP. Consent will be deferred until the patient is more stable in hospital. If written informed consent for use of these samples is **not** given the samples will be destroyed. The samples will not be processed or used until explicit informed consent from either the patient or consultee is given.

Deferred consent does not take the place of informed consent and if the patient is willing and able written, informed consent is still the preferred method.

9.4 Study Discontinuation

In the event that the study is discontinued all samples and data already received will be kept anonymised/pseudonymised and analysed where possible.

10 REGULATORY APPROVAL

Ethics approval will be granted from a Multi centre Research Ethics Committee. Clinical research governance approval is given through the sponsors, The Royal Liverpool and Broadgreen Universities Hospital Trust and The University of Liverpool.

11 STUDY MONITORING

Monitoring will be done centrally and will involve routine surveillance of site data with more detailed statistical testing if anomalies occur.

Day to day monitoring will be done by the data manager and will include such things as checking CRFs are complete, data collected are consistent with study protocol, no key data are missing and that data appear valid. These will be done when data are entered from the paper CRF to the electronic data base.

Centralised statistical techniques, built into the electronic database, will include missing data with discrepancy notes, range checks and rates of reporting between centres e.g. frequency of missing data can be compared between sites.

Monitoring of recruitment rates will be done by the SMG at their meetings.

If issues arise these will be reviewed by the SMG and site monitoring can be conducted to allow further training and review understanding of the protocol and study procedures.

11.1 Risk Assessment

A risk assessment has been carried out and determined the study to be low risk. This determines the level of monitoring needed.

11.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical study.

Each participating site should maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

Each participating site should identify any data to be recorded directly on the CRFs (i.e. no prior electronic or written record of the data), and to be considered to be source data.

11.3 Data Capture Methods

Paper CRFs will be used on site. These will then be faxed to the Brain Infections UK offices where the data will then be inputted into a password protected central web based database (OpenClinica™). This will be kept securely at the Brain Infections UK offices. The paper based copies will also be stored in locked filing cabinets at the Brain Infections UK offices. CRFs should be completed as soon as possible after enrolment and submitted within 1 working day of completion.

11.3.1 Case Reports Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above

it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRFs will be stored in the site file and the faxed copy will be stored at the Brain Infections UK offices.

All paper CRFs should be completed by personnel named on the delegation log as authorised to do so and faxed to the BIUK coordinating centre within 10 working days of enrolment.

19/03/2013 - If data is being directly entered into OpenClinica at site then a paper CRF does not need to be completed or forwarded to Brain Infections UK.

11.4 Monitoring at Brain Infections UK

Data sent to and stored at Brain Infections UK will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by fax or, where a secure fax machine is not available they may be sent by post or e-mail) for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialled (see section 12.3.1). The amended version should be returned to Brain Infections UK and the site's copy should also be amended. Brain Infections UK will send reminders for any overdue and missing data.

If there are frequent or recurring problems the site will be visited by a member of the research team.

11.5 Clinical Site Monitoring

11.5.1 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

11.5.2 Confidentiality

All personal information regarding study participants will be confidential. Personal identifiable information will be stored on a password protected database (OpenClinica™) which can only be accessed by BIUK staff.

Paper copies of these will be stored securely at site and centrally at the Brain Infections UK offices.

Informed consent will be obtained and data will be pseudonymised.

The questionnaires will have no patient identifiers, apart from the subject ID, on them.

The patient details, including addresses, will be kept securely at the Brain Infections UK offices. Electronic versions will be on OpenClinica™, a password protected database and the paper versions will be in locked cabinets, in a locked room.

All patient data will be identified by subject ID only. Patient specimens that are taken in addition to those taken in routine practice will be pseudonymised.

No patient will be identifiable in resulting publications and presentations.

All aspects of the study will comply with the Data Protection Act.

11.5.3 Quality Assurance and Quality Control of Data

Data will be evaluated for compliance with protocol when inputted into the central database.

The study will be conducted in accordance with the procedures identified in the protocol and it will be the responsibility of the SMG to monitor and assure protocol compliance.

11.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Study (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Study File, until the Brain Infections UK or Liverpool Brain Infections Group informs the investigator that the documents are no longer to be retained or for a maximum period of 15 years, whichever is sooner.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The Brain Infections UK and Liverpool Brain Infections Group undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

12 INDEMNITY

UK Meningitis Study is co-sponsored by The University of Liverpool and the Royal Liverpool and Broadgreen University Hospitals Trust and co-ordinated by Brain Infections UK, part of Liverpool Brain Infections Group, in the University of Liverpool. The University of Liverpool's professional indemnity and clinical trials insurance will apply as appropriate. However, in terms of liability, NHS hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical study, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgements made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

13 FINANCIAL ARRANGEMENTS

The main study is funded by the Meningitis Research Foundation. Some of the substudies (biomarkers of infection and DNA sampling) have been funded by means of flexibility and sustainability funding. Further funding will be sought for the other substudies.

Funding for substudies 6.9.1-6.9.3 (substantial amendment 12) has been granted from the National Institute for Health Research.

There will be no payments to patients or clinicians.

Thermometers will be provided for patients who are discharged before 3 weeks. Postage paid envelopes will be provided for patients to return the daily temperatures, TMS and questionnaires.

13.1.1 Substantial Amendment 17 (01/05/2015)

Following the decision to stop sending the TMS to patients on discharge, thermometers and postage paid envelopes will no longer be provided for this purpose.

14 STUDY COMMITTEES

14.1 Study Management Group (SMG)

The study management group will consist of Professor Tom Solomon (CI), Dr Fiona McGill (SM), Dr Michael Griffiths, Dr Benedict Michael, and Miss Hayley Jelleyman. The SMG will be responsible for the day-to-day running and management of the study and will meet at least 4 times a year.

14.2 Study Steering Committee (SSC)

The Study Steering Committee will consist of an independent chairperson (Dr A. Miller), members of the management group, co-applicants and a patient representative. The role of the SSC is to provide overall supervision for the study and provide advice through its independent Chairman. The ultimate decision for the continuation of the study lies with the SSC. As this study is low risk this will include protocol ratification and ensuring recruitment is being met. The SSC will meet 6-12 monthly.

14.3 Other contributors

The qualitative aspects of substantial amendment 12 will be supervised by Dr Paula Byrne, an established qualitative researcher at the Institute of psychology, health and society at the University of Liverpool.

15 PUBLICATION

The publication policy of Brain Infections UK will be followed. This will include a policy on the use of data and samples for derivative studies including authorship on such studies.

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Study Management Group.

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org/>) will be respected. The Study Management Group will form the basis of the Writing Committee and advise on the nature of publications. For main papers and presentations, names of members of the writing group shall be listed as authors in the masthead, with the addition of the phrase "on behalf of the Northern Meningitis Research Group." All co-applicants, collaborators, principal investigators and other relevant individuals, if not named authors, will be included in the authorship under the title of 'Northern Meningitis Research Group'.

The National Library of Medicine (NLM) indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.

The final report and publication will be published in accordance with the STROBE statement (strengthening the reporting of observational studies in epidemiology).

The members of the SSC will be listed with their affiliations in the acknowledgements of the main publication.

Regular updates regarding the study will be published on the Brain Infections UK website (www.braininfectionsuk.org). In addition, where consent has been obtained, regular e-mails will be sent to participants to inform them when the website has been updated. These e-mails will also be sent to all participating sites.

16 PROTOCOL AMENDMENTS

16.1 Version 1 (28/06/2011)

- Removal of section 6.2 on requests for autopsies following REC meeting.
- Adjustment of Patient Information Sheets/Consent forms to reflect this and to comply with requests from REC.

16.2 Version 2.1 (28/07/2011)

Addition of requirement to take an extra blood sample for serology/storage at enrolment for any patient consenting to have extra blood samples taken. See section 6.1.1

16.3 Version 3 (20/04/2012)

Additional serum sample.

16.4 Version 3.1 (14/05/2012)

Change to appendices in protocol to reflect changes made in AM02

16.5 Version 3.2 (13/06/2012)

Remote data entry

16.6 Version 4 (5/07/2012)

Addition of possibility of deferred consent to gain timely RNA sample collection.

16.7 Version 5 (17/09/2012)

Addition of healthy controls to receive follow up questionnaires

16.8 Version 5.1 (21/02/2013)

Addition of section on consent form to allow for anonymised data to be used in other studies within the Brain infections UK portfolio.

16.9 Version 5.2(19/03/2013)

Addition of extra sites, change of PISC to reflect amendment 10; addition in section 11.3.1 to allow for online data entry at site.

16.10 Version 6 (03/09/2013)

Prolongation and expansion of study following NIHR funding. Change of name to UK Meningitis Study. Addition of substudies 6.9.1-6.9.3. Addition of request to phone patients at 6 weeks and a year to chase up questionnaires/get answers to questionnaires over the phone.

16.11 Version 7 (06/05/2014)

Allows recruitment of participants who have contacted the Meningitis Research Foundation and expressed an interest to participate in the study to be involved in the qualitative arm of the study. The Meningitis Research Foundation will contact the study team, with the permission of the patient. The research team will then contact the patient and send a copy of the participant information sheet and consent form and if they are still keen to be involved, would arrange a mutually convenient time and place to carry out an interview. No clinical records will be accessed at any point

and only patients who approach via the Meningitis Research Foundation will be included.

16.12 Version 7.1 (19/08/2014)

Due to differences between arrangements required in compliance with the Mental Capacity Act (England and Wales) 2005 and the Adults with Incapacity (Scotland) Act 2000, the research team have decided not to recruit patients who lack capacity at NHS sites in Scotland.

16.13 Version 7.2 (25/11/2015)

Protocol is updated in line with amendments 16, 17, 18 and 19. The study is extended until 01 October 2016.

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17 APPENDICES

Appendix A: Patient Information Sheets and Consent Forms

A1) Patient Information Sheet (V10.1)

Meningitis UK study - Patient Information Sheet

We would like to invite you to take part in this study about meningitis. Before you decide we would like you to understand why the 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 study if you wish. Ask us if there is anything that is not clear. Part 1 tells you the purpose of the study and what will happen if you decide to take part. Part 2 will give more detailed information about the conduct of the study.

Part One

What is the purpose of the study?

The primary purpose of the study is to find out how much viral meningitis occurs in the UK and what the different causes of meningitis are.

Why am I being asked to take part?

You are being asked to take part because your doctor thought you might have had meningitis when you were admitted to hospital. (This may have now been either proven or not, either way, we would still like you to take part.)

Do I have to take part?

Taking part in the study is entirely voluntary. If you decide to take part you will be asked to fill in a consent form. If you do not wish to take part your medical care will carry on as normal. You may withdraw from the study at any point and do not need to give a reason.

What will happen if I take part?

Main Study

If you agree to take part, the study team will review your medical notes and the results of the tests that you will have or have had as part of your hospital admission.

We will also ask to keep any leftover spinal fluid if you have had a lumbar puncture (this would normally be stored or thrown away.)

Optional Sub studies

In addition there are some extra, optional parts to the study. If you consent to these we will ask for some extra blood +/- spinal fluid (only if you are having a lumbar puncture (or spinal tap) anyway for clinical reasons) that can be taken at the same time as your routine tests. For a few people we will request a further blood test in about 6 months time. You may be asked to take a genital swab (this is because herpes viruses, which cause some types of meningitis, can also occasionally be found in the genital area).

It is possible that when you were admitted to hospital the admitting doctors already took some samples for the extra blood/spinal fluid tests in order to get blood or spinal fluid that reflected your body when you were acutely unwell. It also reduces the amount of blood tests you will need. If this has happened a member of the research team will tell you and the

samples will have been stored and not tested in any way. If you decide not to consent to the study the samples will be destroyed.

You can be part of the main study and opt out of the optional parts.

We would also ask that if you are readmitted into hospital in the next year with similar symptoms that you or a relative/carer lets one of the study team know. This is so we can look at the rate of recurrence of meningitis.

Use of photographs/videos

Occasionally we may ask to take photographs/videos of study participants. Specific consent will be asked if this is the case, you do not have to agree. If photos/videos are taken they may be used in publications and/or for teaching and presentations. Again specific consent will be gained from you if this is going to be the case. Again you can agree to be part of the main study and decline to have photos/videos taken. If you agree to have photographs or videos taken they will be stored securely in locked offices at the University of Liverpool.

Will any genetic tests be done?

The optional sub studies will be looking at some genetic tests. If you agree to be part of these, the tests performed on the extra blood and spinal fluid samples (or leftovers if you have already had your lumbar puncture) will be looking at components of your genes that are released in response to your current illness. In addition we will look at the cells of your immune system and see how the two interact. The ultimate purpose of these tests will be to improve the diagnosis in meningitis for the future. We also ask for a sample of blood to look at your DNA – these samples will help us work out why some people get meningitis and others don't. **In all these tests there will be no results of any individual significance.** You can take part in the rest of the study but opt out of this section if you wish.

Do I have to agree to everything?

No, there are some parts of the study that are optional and you can discuss this with the person who gave you this information sheet.

What are the benefits of taking part?

The main benefits of taking part are for doctors and scientists to gain a better understanding of meningitis. This in turn, will hopefully help others who suffer from meningitis in the future.

What are the disadvantages in taking part?

The main disadvantage is that if you agree to take part in the optional studies you will have some extra blood tests and possible genital swabs. The care given to you in hospital and any treatment given will be exactly the same regardless of whether you are in the study or not.

Will my details be confidential?

Yes. We will follow good and legal practice and all information about you will be handled in confidence.

Part Two

What if I don't want to continue in the study?

You can leave the study at any point and don't need to give a reason. Unless you specifically say otherwise any information and samples already collected will still be used in the final analysis.

What if there is a problem?

If you have a complaint about how you have been dealt with, or any other problems, you can contact the study manager directly on fiona.mcgill@liv.ac.uk. If you prefer, you can contact another member of the research department on 0151 706 4603. You can contact the doctor who was looking after you at the hospital, or you can call the hospitals complaints department. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Liverpool but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my details be kept confidential?

Your consent form and contact details will be faxed to the study co-ordinating centre where the fax machine is kept in a locked room. All other study related information that leaves the hospital will have your name and address removed so that you cannot be recognised. All information which is collected about you during the course of the research kept strictly confidential. Occasionally an official from the research department in the university or the hospital may need access to your personal details. This is to ensure the research is being carried out properly and within good research practice.

Will my GP be informed?

Out of courtesy we will inform your GP that you are taking part in the study. We will not be informing the GP of any of your results. If you do not wish your GP to be informed then please let us know.

What will happen to any samples that I give?

Most of the samples we will be looking at will be part of your routine care. However, if you agree to be part of the optional studies the extra blood and spinal fluid samples will be processed and stored at the University of Liverpool. The samples will have your name and other identifiable information removed. Some of them may be sent, confidentially, to other centres if you agree. We may also request that any leftover blood/spinal fluid can be used in future research projects. We may request some of your other samples to be stored as well if you consent to it.

What will happen after the study?

The samples and information obtained will be kept securely in the university. If you consent to it we may contact you in the future regarding other studies we are running.

What will happen to my DNA?

If you agree to enter the sub studies we would ask that you consider ‘gifting’ us your DNA samples to allow for future research into infections. We will not use the DNA for any other purpose. We would also like to share the DNA, confidentially, with other researchers. The other researchers will not have information on where or who the DNA came from.

What will happen to the results of the study?

When the study is completed (it is expected to take around 2 years) the results will be published at scientific meetings and in scientific papers. If you wish to know the overall results of the study a report will be available on the website of the Meningitis Research Foundation. Or, if you prefer, you can contact the study team and they will be happy to give you the overall results. Individual results will NOT be available from the study team. If you consent to being contacted during the study we will send you e-mails informing you of any updates regarding the progress of the study, which will be published on our website.

Who is organising and funding the research?

The study is being run by the Liverpool Brain Infections Group, part of the University of Liverpool, and has been funded by the Meningitis Research Foundation.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by North Wales Research Ethics Committee - West.

Where can I find out more details?

Local investigator details

Name..... Tel
Number.....

Clinical Research Fellow

Dr Fiona McGill ***mennw@liv.ac.uk***

Tel Number: 0151 795 9606

www.braininfectionsuk.org

www.meningitis.org.uk

A2) UK Meningitis Study Consent Form (V.7)



UK Meningitis Study Consent Form

Name of Local Investigator:

Please complete 3 copies of this form. When completed give one to the participant to keep, one should be faxed to BrainInfections UK and then put in the site file and one should be kept in the participant's medical notes.

Participant to **initial** each box

1. I confirm that I have read and understand the information sheet dated..... for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
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 relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the NHS Trust, the University of Liverpool and other appropriate individuals e.g. members of the study team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I understand that my data (in an anonymised form) may be used in other relevant studies from the Liverpool Brain Infections Group.	
5. I agree to my name, address, phone number and e-mail address being given to and stored securely at the trial co-ordinating centre at the University of Liverpool (they will not be passed on to any third party).	
6. I agree to gift the remainder of any routinely taken sample (e.g. blood, spinal fluid, stool) to the University of Liverpool where it will be stored for use in future research. This may include the use of protein, DNA and RNA and may include sending samples to other institutions.	
7. I agree to take part in the above study.	

Optional

8. I agree to have extra samples of blood and CSF (where a lumbar puncture is being performed for routine clinical management) taken for genetic research purposes to improve the diagnosis of meningitis. These samples would also be gifted to the University.	
9. I agree to any sample that may have been taken already for research purposes being used for genetic research purposes to improve the diagnosis of meningitis. These samples would also be gifted to the University.	
10. I agree to being contacted in the future by members of the research team.	
11. I would like to receive regular updates by e-mail, regarding the progress of this study.	
12. I agree to any photographs or videos that are taken being used for teaching, education and publication (in scientific journals, books or internet).	

If you are readmitted to hospital following your discharge with similar symptoms please inform a member of the research team on 0151 795 9606

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

A3) Consultee Declaration Form (V8)**The UK Meningitis Study – Consultee Declaration Form**Introduction

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research. To help decide if he/she should join the study, we would like to ask you to act as a 'consultee' for them.

This involves considering what the wishes of your relative/friend would be if they were able to consent for themselves. **We are not asking you to give your own opinions or to consent for the patient.** We would ask your opinion on whether or not they would want to be involved. We will ask you to read the patient information sheet that would have been given to your relative/friend if they were able to decide for themselves. We will then ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part we will ask you to read and sign this consultee declaration. We will then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn. You can decide at any point during the study if you feel your friend/relative would no longer wish to be included. Nothing will be done to your friend/relative to which they appear to object.

If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking on the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

Name of Consultee	
Relation to patient	
Contact details for Consultee	
Address	
Phone Number	
E-mail	
Contact details for Participant	
Name	
Address	
Phone Number	
E-mail	
Name of Investigator:	

Consultee Please Initial Box

- 1) I.....have been consulted about’s participation in this research project. I have had the opportunity to ask questions about the study and understand what is involved.
- 2) In my opinion he/she would have no objection to taking part in the above study.
- 3) I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected.
- 4) I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from the University of Liverpool, regulatory authorities or the study team, where it is relevant to their taking part in this research.
- 5) I understand that personal data, including name and address of both myself and the patient, will be sent to and stored securely at the University of Liverpool (they will not be passed on to any third party).
- 6) **(optional)** I understand that if he/she does not object bloods will be taken for research purposes to improve the diagnosis of meningitis. This may include the use of RNA, DNA and protein. The samples will be anonymised before use and there will be no results of any individual significance for the patient.
- 7) I understand that any leftover spinal fluid (that would otherwise be thrown out) will be gifted to the University of Liverpool. These samples will also be anonymised.
- 8) I understand that if he/she regains capacity that they will have the option to either consent or withdraw themselves.

Consultee signature _____

Date ___/___/___

Investigator’s signature _____

Date ___/___/___

The following is what your friend/relative would have received if they were able to consent for themselves.

UK Meningitis Study - Patient Information Sheet

We would like to invite you to take part in this study about meningitis. Before you decide we would like you to understand why the 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 study if you wish. Ask us if there is anything that is not clear. Part 1 tells you the purpose of the study and what will happen if you decide to take part. Part 2 will give more detailed information about the conduct of the study.

Part 1

What is the purpose of the study?

The primary purpose of the study is to find out how much viral meningitis occurs in the UK and what the different causes of meningitis are.

Why am I being asked to take part?

You are being asked to take part because your doctor thought you might have had meningitis when you were admitted to hospital. (This may have now been either proven or not, either way, we would still like you to take part.)

Do I have to take part?

Taking part in the study is entirely voluntary. If you decide to take part you will be asked to fill in a consent form. If you do not wish to take part your medical care will carry on as normal. You may withdraw from the study at any point and do not need to give a reason.

What will happen if I take part?

Main Study

If you agree to take part, the study team will review your medical notes and the results of the tests that you will have or have had as part of your hospital admission.

We will also ask to keep any leftover spinal fluid if you have had a lumbar puncture (this would normally be stored or thrown away.)

Optional Sub studies

In addition there are some extra, optional parts to the study. If you consent to these we will ask for some extra blood +/- spinal fluid (only if you are having a lumbar puncture (or spinal tap) anyway for clinical reasons) that can be taken at the same time as your routine tests. For a few people we will request a further blood test in about 6 months time.

You may be asked to take a genital swab (this is because herpes viruses, which cause some types of meningitis, can also occasionally be found in the genital area).

It is possible that when you were admitted to hospital the admitting doctors already took some samples for the extra blood/spinal fluid tests in order to get blood or spinal fluid that reflected your body when you were acutely unwell. It also reduces the amount of blood tests you will need. If this has happened a member of the research team will tell you and the samples will have been stored and not tested in any way. If you decide not to consent to the study the samples will be destroyed.

You can be part of the main study and opt out of the optional parts.

We would also ask that if you are readmitted into hospital in the next year with similar symptoms that you or a relative/carer lets one of the study team know. This is so we can look at the rate of recurrence of meningitis.

Use of photographs/videos

Occasionally we may ask to take photographs/videos of study participants. Specific consent will be asked if this is the case, you do not have to agree. If photos/videos are taken they may be used in publications and/or for teaching and presentations. Again specific consent will be gained from you if this is going to be the case. Again you can agree to be part of the main study and decline to have photos/videos taken. If you agree to have photographs or videos taken they will be stored securely in locked offices at the University of Liverpool.

Will any genetic tests be done?

The optional sub studies will be looking at some genetic tests. If you agree to be part of these, the tests performed on the extra blood and spinal fluid samples (or leftovers if you have already had your lumbar puncture) will be looking at components of your genes that are released in response to your current illness. In addition we will look at the cells of your immune system and see how the two interact. The ultimate purpose of these tests will be to improve the diagnosis in meningitis for the future. We also ask for a sample of blood to look at your DNA – these samples will help us work out why some people get meningitis and others don't. **In all these tests there will be no results of any individual significance.** You can take part in the rest of the study but opt out of this section if you wish.

Do I have to agree to everything?

No, there are some parts of the study that are optional and you can discuss this with the person who gave you this information sheet.

What are the benefits of taking part?

The main benefits of taking part are for doctors and scientists to gain a better understanding of meningitis. This in turn, will hopefully help others who suffer from meningitis in the future.

What are the disadvantages in taking part?

The main disadvantage is that if you agree to take part in the optional studies you will have some extra blood tests and possible genital swabs. The care given to you in hospital and any treatment given will be exactly the same regardless of whether you are in the study or not.

Will my details be confidential?

Yes. We will follow good and legal practice and all information about you will be handled in confidence.

Part 2

What if I don't want to continue in the study?

You can leave the study at any point and don't need to give a reason. Unless you specifically say otherwise any information and samples already collected will still be used in the final analysis.

What if there is a problem?

If you have a complaint about how you have been dealt with, or any other problems, you can contact the study manager directly on fiona.mcgill@liv.ac.uk. If you prefer, you can contact another member of the research department on 0151 706 4603. You can contact the doctor who was looking after you at the hospital, or you can call the hospitals complaints department. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Liverpool but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my details be kept confidential?

Your consent form and contact details will be faxed to the study co-ordinating centre where the fax machine is kept in a locked room. All other study related information that leaves the hospital will have your name and address removed so that you cannot be recognised. All information which is collected about you during the course of the research kept strictly confidential. Occasionally an official from the research department in the university or the hospital may need access to your personal details. This is to ensure the research is being carried out properly and within good research practice.

Will my GP be informed?

Out of courtesy we will inform your GP that you are taking part in the study. We will not be informing the GP of any of your results. If you do not wish your GP to be informed then please let us know.

What will happen to any samples that I give?

Most of the samples we will be looking at will be part of your routine care. However, if you agree to be part of the optional studies the extra blood and spinal fluid samples will be processed and stored at the University of Liverpool. The samples will have your name and other identifiable information removed. Some of them may be sent, confidentially, to other centres if you agree. We may also request that any leftover blood/spinal fluid can be used in future research projects. We may request some of your other samples to be stored as well if you consent to it.

What will happen after the study?

The samples and information obtained will be kept securely in the university. If you consent to it we may contact you in the future regarding other studies we are running.

What will happen to my DNA?

If you agree to enter the sub studies we would ask that you consider 'gifting' us your DNA samples to allow for future research into infections. We will not use the DNA for any other purpose. We would also like to share the DNA, confidentially, with other researchers. The other researchers will not have information on where or who the DNA came from.

What will happen to the results of the study?

When the study is completed (it is expected to take around 2 years) the results will be published at scientific meetings and in scientific papers. If you wish to know the overall results of the study a report will be available on the website of the Meningitis Research Foundation. Or, if you prefer, you can contact the study team and they will be happy to give you the overall results. Individual results will NOT be available from the study team. If you consent to being contacted during the study we will send you e-mails informing you of any updates regarding the progress of the study, which will be published on our website.

Who is organising and funding the research?

The study is being run by the Liverpool Brain Infections Group, part of the University of Liverpool, and has been funded by the Meningitis Research Foundation.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by North Wales Research Ethics Committee - West.

Where can I find out more details?

Local investigator details

Name..... Tel
number.....

Clinical Research Fellow

Dr Fiona McGill *mennw@liv.ac.uk*
Tel number: 0151 795 9606

www.braininfectionsuk.org
www.meningitis.org.uk

Appendix B: Quality of Life Questionnaire**SF36**

We will be using the SF-36 questionnaire with expert advice from the department of health inequalities and the social determinants of health.

EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility	
I have no problems in walking about	<input type="checkbox"/>
I have some problems in walking about	<input type="checkbox"/>
I am confined to bed	<input type="checkbox"/>
Self-Care	
I have no problems with self-care	<input type="checkbox"/>
I have some problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
Usual Activities (e.g. work, study, housework, family or leisure activities)	
I have no problem with performing my usual activities	<input type="checkbox"/>
I have some problems with performing my usual activities	<input type="checkbox"/>
I am unable to perform my usual activities	<input type="checkbox"/>
Pain or Discomfort	
I have no pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
Anxiety/Depression	
I am not anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

Appendix C: A-B Neuropsychological assessment scale

For each item, if it is not a problem circle **0**; if it is a mild problem circle **1**; if it is a moderate problem circle **2**; and if it is a serious problem circle **3**. If a question is not relevant for you, no answer should be given

1	I am less enthusiastic about day to day activities	0 1 2 3
2	My mind does not work as fast as it should	0 1 2 3
3	I have difficulties remembering names of people	0 1 2 3
4	I have difficulties following a book or a film	0 1 2 3
5	I feel clumsy	0 1 2 3
6	I have problems finding the correct word	0 1 2 3
7	I am less capable of undertaking initiatives	0 1 2 3
8	My thinking has slowed down	0 1 2 3
9	I forget things, for example an appointment or where I put an object ...	0 1 2 3
10	I have difficulties concentrating on the things I am doing	0 1 2 3
11	I cannot use a pen or pencil accurately	0 1 2 3
12	I have problems understanding what I read	0 1 2 3
13	I tire easily and have little energy	0 1 2 3
14	It takes me longer to do day to day things	0 1 2 3
15	I forget things that people have said to me	0 1 2 3
16	I can't concentrate for more than a short period of time	0 1 2 3
17	I constantly bump against tables, doorposts, etc.	0 1 2 3
18	I feel worn out	0 1 2 3
19	It costs more time for me to get started	0 1 2 3
20	I get confused and forget what I was doing	0 1 2 3
21	I get distracted more easily	0 1 2 3
22	I sometimes stutter or am unable to find the correct words	0 1 2 3
23	I feel I react too slowly to things that are said to me	0 1 2 3
24	I cannot keep an activity going for long	0 1 2 3

Appendix D: Participating Sites

Participating Site	Local Collaborator /Principal Investigator at site
Royal Liverpool University Hospital Prescot Street Liverpool L7 8XP	Dr N Beeching Consultant Infectious Diseases E-mail: nicholas.beeching@rlbhut.nhs.uk
The Walton Centre NHS Foundation Trust Lower Lane Fazakerly L9 7LJ	Prof T Solomon Consultant Neurologist E-mail: tsolomon@liv.ac.uk
North Manchester Hospital Delaunays Road Crumpsall Manchester M8 5RB	Dr T Blanchard Consultant Infectious Diseases Physician E-mail: tom.blanchard@pat.nhs.uk
Manchester Royal Infirmary Oxford Road Manchester M13 9WL	Dr D McKee Consultant Neurologist E-mail: david.mckee@cmmc.nhs.uk
Countess of Chester Foundation NHS Trust Liverpool Road Chester CH2 1UL	Dr I Kustos Consultant Medical Microbiologist Email: ildiko.kustos@nhs.net
Wirral University Teaching Hospital NHS Foundation Trust Wirral University Teaching Hospital NHS Foundation Trust Clatterbridge Hospital Bebington Wirral CH63 4JY	Dr Kavya Mohandas Consultant microbiologist E-mail: kavya.mohandas@nhs.net
Aintree University Hospitals Trust University Hospital Aintree Longmoor Lane Liverpool L9 7AL	Dr Cecilia Jukka Consultant Medical Microbiologist E-mail: cecilia.jukka@aintree.nhs.uk
James Cook University Hospital Marton Road Middlesbrough TS4 3BW	Dr David Chadwick Consultant Infectious Diseases E-mail: davidr.chadwick@stees.nhs.uk
University Hospital of South Manchester Wythenshawe Hospital Southmoor Road Manchester M23 9LT	Dr Mark Roberts Consultant Neurologist E-mail: markrob@doctors.org.uk
Macclesfield District General Hospital Victoria Road Macclesfield Cheshire SK10 3BL	Dr Monty Silverdale Consultant Neurologist E-mail: monty.silverdale@srft.nhs.uk
Royal Oldham Hospital Rochdale Road Oldham OL1 2JH	Dr Magid El-Sayed Consultant Neurologist E-mail: magid.elsayed@srft.nhs.uk
Blackpool Victoria Hospital Whinney Heys Road Blackpool FY3 8NR	Dr Peter Flegg Consultant Physician in Infectious Diseases E-mail: dr.flegg@bfwhospitals.nhs.uk

UK Meningitis Study Protocol Version 7.2

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Royal Preston Hospital Sharoe Green Lane Fulwood Preston PR2 9HT	Dr David Orr Consultant Microbiologist E-mail: david.orr@lthtr.nhs.uk
CLOSED	
Royal Bolton Hospital Minerva Road Farnworth Bolton BL4 0JR	Dr Stefan Schumacher Consultant in Neurology E-mail: stefan.schumacher@srft.nhs.uk
CLOSED	
Royal Victoria Infirmary Newcastle Upon Tyne Queen Victoria Road Newcastle upon Tyne NE1 4LP	Dr Uli Schwaab Consultant in Infectious Diseases and Acute Medicine E-mail: uli.schwaab@nuth.nhs.uk
Fairfield Hospital Rochdale Old Road Bury BL9 7TD	Dr Chris Murphy Consultant neurologist E-mail: chris.murphy@srft.nhs.uk
CLOSED	
Whiston Hospital Warrington Road Prescot L35 5DR	Dr Rajiv Chandy Consultant gastroenterologist and general medicine E-mail: rajiv.chandy@sthkhealth.nhs.uk
Royal Blackburn Hospital Haslingden Road Blackburn BB2 3HH	Dr Iain Crossingham Consultant Acute Internal Medicine E-mail: iain.crossingham@elht.nhs.uk
CLOSED	
Southport and Formby District General Hospital Town Lane Kew Southport PR8 6PN	Dr Judith Bowley Consultant Microbiologist E-mail: judith.bowley@nhs.net
Salford Royal NHS Foundation Trust Stott Lane Salford M6 8HD	Dr Matthew Jones Consultant Neurologist E-mail: matthew.jones@srft.nhs.uk
Royal Albert Infirmary Wigan Lane Wigan WN1 2NN	Dr Camelia Faris Consultant Microbiologist E-mail: camelia.faris@wwl.nhs.uk
St James University Hospital Beckett Street Leeds LS9 7TF	Dr Jane Minton Consultant Infectious Diseases Physician E-mail: jane.minton@leedsth.nhs.uk
Bradford Royal Infirmary Duckworth Lane Bradford BD9 6RJ	Dr Philip Stanley Consultant in Infectious Diseases E-mail: philip.stanley@bthft.nhs.uk
CLOSED	
Warrington and Halton NHS Trust Lovely Lane Warrington WA5 1QG	Dr Karim Mahawish Consultant Physician E-mail: karim.mahawish@nhs.net
CLOSED	
Trafford Healthcare NHS Trust Moorside Road Davyhulme Manchester M41 5SL	Dr Ajith George Consultant in acute medicine E-mail: ajith.george@trafford.nhs.uk

UK Meningitis Study Protocol Version 7.2

25/11/2015

North Cumbria University Hospitals NHS Trust Newton Road Carlisle CA2 7HY	Dr Clive Graham Consultant Microbiologist E-mail: clive.graham@ncuh.nhs.uk
Mid Yorkshire NHS Foundation Trust Pinderfields Hospital Aberford Road Wakefield WF1 4DG	Dr Nural Amir Consultant Microbiologist E-mail: nural.amir@midyorks.nhs.uk
York Teaching Hospitals NHS Foundation Trust Wigginton Rd York YO31 8HE	Dr Neil Todd Consultant Microbiologist E-mail: neil.todd@york.nhs.uk
Heart of England NHS Foundation Trust Bordesley Green East Birmingham B9 5SS	Dr Ed Moran Consultant Infectious Diseases Physician E-mail: ed.moran@heartofengland.nhs.uk
Leicester Royal Infirmary Leicester LE1 5WW	Dr Martin Wiselka Consultant in Infectious Diseases E-mail: martin.wiselka@uhl-tr.nhs.uk
University Hospital of North Midlands Prince Road Stoke on trent ST4 7LN	Dr Antony Cadwgan Consultant Infectious Diseases E-mail: antony.cadwgan@uhns.nhs.uk
Dudley Group NHS Foundation Trust Russells Hall Hospital DY1 2HQ	Dr Hassan Paraiso Consultant Acute Medicine E-mail: hassan.paraiso@dgh.nhs.uk
Northern Devon Healthcare NHS Trust Raleigh Park Barnstaple EX31 4JB	Dr Alastair Watt Consultant Acute Medicine/Diabetes E-mail: alastairwatt1@nhs.net
Northumbria Healthcare NHS Foundation Trust Linnet Court, Cawledge Business Park Hawfinch Drive Alnwick, Northumberland NE66 2GD	Dr Simon Ellis Consultant in Acute Medicine and Infectious Diseases E-mail: simon.ellis@northumbria-healthcare.nhs.uk
The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust Gayton Road King's Lynn PE30 4ET	Dr Hartith Altemimi Consultant in Acute Medicine and Intensive Care Medicine E-mail: h.altemimi@uea.ac.uk
Royal Cornwall Hospital Truro TR1 3HD	Dr Sanjeev Gupta Consultant Microbiologist E-mail: sanjeev.gupta@cornwall.nhs.uk
Edinburgh Royal Infirmary 51 Little France Crescent, Edinburgh EH16 4SA	Dr Ann Lockman Consultant in Acute Medicine E-mail: ann.lockman@nhslothian.scot.nhs.uk
Aberdeen Royal Infirmary Foresterhill Rd, Aberdeen AB25 2ZN	Dr Sandy Mackenzie Consultant in Infectious Diseases E-mail: alexander.mackenzie@nhs.net
Kings College Hospital NHS Foundation Trust Denmark Hill, London SE5 9RS	Dr Phil Hopkins Consultant in Intensive Care Medicine, Anaesthesia and Trauma E-mail: p.hopkins@nhs.net
University Hospital Lewisham High St, Lewisham, London SE13 6LH	Dr Marthin Mostert Consultant Anaesthetist and Intensive Care Medicine E-mail: mmostert@nhs.net