NHS Research Ethics Committee NHS
APPLICATION FORM

This form should be completed by the chief investigator, after reading the guidance notes.
See glossary for clarification of different terms in the application form.

Short title and version number (maximum 70 characters – this will be inserted as header on all forms)**:**
EuroWilson

Name of NHS research committee to which application for ethical review is being made:
Trent MREC

Project reference number from above REC: 04/MRE04/65
Submission Date: 09/08/2004

PART A

A1. Title of Research

Full title: Wilson Disease: Creating a European Clinical Database and designing randomised controlled clinical trials.

Keywords: Wilson, Wilson's, clinical database

A2. Chief Investigator

Title: Professor

First Name/Initials: Stuart

Last Name: Tanner

Post: Professor of Child Health, University of Sheffield

Qualifications: BSc, MB, BS, MSc, FRCP(London & Glasgow) FRCPCH

Organisation: University of Sheffield

Address: Academic Unit of Child Health
Children's Hospital
Western Bank

Post Code: S10 2TH

E-mail: m.s.tanner@sheffield.ac.uk

Telephone: 0114 271 7303

Fax: 0114 275 5364

A copy of a current CV, maximum 2 pages of A4 for the chief investigator must be submitted with application

A3. Proposed Study Dates and Duration

Start Date: 01/01/2005
End Date: 31/05/2008
Duration: **Months** 3 **Years** 6

A4. Primary purpose of the research: *(Tick as appropriate)*

- ☐ Commercial Product development and/or licensing
- ☐ Publicity funded trial or scientific investigation
- ☐ Educational Qualification
- ☒ Establishing a Database/Data storage Facility
- ☐ Other

If other, give details:

A5. Tick the box if your research:

- ☐ Involves testing a medicinal product
- ☐ Involves testing a medicinal device
- ☐ Involves additional radiation above that for clinical care
- ☐ Involves using stored samples of human biological material (e.g. blood, tissue)
- ☒ Involves taking new samples of human biological material
- ☒ Involves only patient records or data with no other direct patient contact
- ☐ Involves prisoners or others in custodial care
- ☐ Involves adults with incapacity
- ☐ Has the primary aim of being educational (e.g. student research a project necessary for a postgraduate degree or diploma, other than MD or PhD)

A6. Do you consider that this research falls within the category where there is no local investigator?

◉ Yes ○ No

If yes please justify:

With reference to paragraphs 4.24- 4.28 of the SOPs:
4.24 There is minimal risk of physical or emotional harm as a result of the research procedures.
4.25 (a) There are no novel therapeutic interventions. (b) There are no novel clinical investigations. (c) No medical devices are involved. (d) There will be no clinical monitoring and assessment additional to current best practice
4.26 (a) There will be no qualitative assessments by local collaborators. (b) Local clinicians will be asked to supply information materials provided by the Chief Investigator and to administer the consent form. A member of the research team will be available to discuss any queries, by telephone, email or exceptionally by visit.
4.27 It is felt that this is an appropriate degree of responsibility to be assumed by local collaborators given the benign nature of the study.
4.28 The research procedures to be carried out by local collaborators are limited to administering the information materials and consent form as above, and : (a) routine investigations; (c) Collection of data or human tissue not in the context of a novel therapeutic intervention or clinical investigation.(d) Facilitating the recruitment of participants

Advice can be found in the guidance notes on this topic. Some studies do not require further consideration of site- specific issues by local research ethics committees, but will still require approval to proceed from the host organisation(s).

A7. What is the principal research question/objective? *(Must be in Language comprehensible to a lay person.)*

What is the incidence of Wilson's Disease in Europe, and what is the incidence of the major clinical sub-groups?

The objective of this Coordination Action is to set up a clinical database of newly presenting patients with Wilson's Disease in participating European countries. The total number presenting in 1 year, and the numbers presenting in the major diagnostic categories, will be used to plan a randomised controlled trial, or trials, of treatment in Wilson's Disease. Such trials would be the subject of a subsequent application.

A8. What are the secondary research objectives/questions? *(If applicable must be in Language comprehensible to a lay person.)*

1. Is a randomised clinical trial of treatment in Wilson's disease feasible?
2. What are the currently used treatments & what is the short-term outcome?
3. What is the genetic epidemiology and is a study of modifier genes indicated?

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance? *(Must be in Language comprehensible to a lay person.)*

Wilson's Disease is an inherited disorder in which failure to excrete copper from the liver into bile leads to retention of copper and hence damage to the liver, brain, kidney, and joints. Incidence estimates vary from 1/30,000 to 1/100,000. Presentation may be with liver disease, usually in children and young people; with neurological or psychiatric features, usually in teenagers or adults; or less commonly with abnormalities of the blood (haemolysis), kidneys, or joints. The liver disease may be of rapid onset, leading to liver failure for which liver transplantation is the only effective treatment, or it may be insidious leading to cirrhosis and its complications. The neurological disease has a slow onset, with abnormalities of speech, coordination and mood being early features, progessing to tremor, abnormalities of gait and movement, and severe disability.
The diagnosis is made on clinical, biochemical and mutational features. Drugs which remove copper from the liver such as penicillamine, trientine or BAL, or drugs which reduce copper absorption and storage such as zinc sulfate or acetate improve outcome but our knowledge about treatment is unsatisafsctory in the following respects:
1. Choice of drug, of dosage, and of monitoring recommendations is based on single-centre experience. A small survey of clinicians revealed wide differences in treatment choices and lack of certainty about optimum treatment. There is a lack of randomised controlled clinical trials (RCTs). A Cochrane style evaluation (Houwen, unpublished) of the current literature on Wilson Disease and treatment resulted in over 1000 hits. Over 500 articles were "expert" opinions in favour of either zinc treatment or the use of copper chelators. No randomized clinical trial could be found, and less than 20 articles described the results of a particular treatment in a series of patients.
2. On starting treatment there may be initial neurological deterioration; we do not know how to minimise that.
3. Whilst short-term results are good, long term outlook is uncertain.
4. It is possible to diagnose younger siblings before symptoms appear, but we do not know what is the safest and most effective treatment to start at that stage.

We know that the problem lies with failure of a particular copper-transporting protein in the liver. We know the responsible gene and that there are many different mutations. We do not understand why WD can cause such different clinical outcomes. To answer this, we need to consider genotype/phenotype relationships and the influence of modifier genes.

A10. Give a brief synopsis/summary of methods and overview of the planned research. This should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research. *(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what should happen to the research participant, how many times and in what order.)*

In 2002 the European Society of Paediatric Gastroenterology, Hepatology and Nutrition established a working group of paediatric hepatologists which was subsequently joined by representatives from the European Society for the Study of the Liver and the Movement Disorder Society. This has concluded that mounting a randomised controlled clinical trial (RCT) is not possible without data on the incidence, incidence of sub-types, current treatments, and short term outcomes. The working group became a Consortium which has secured funding from Framework 6 of the European LifeSciHealth programme to establish a European Clinical Database. Data from this will inform the process of setting up an RCT. Preliminary work has addressed diagnostic criteria, database items, choice of software, database host, and secure access. The aims of the project are to set up the database, collect and analyse 1 year's data, set up an RCT planning group and workshop, and to continue data collection and patient monitoring for 4 years.

The steps in this project, with anticipated timing in months from commencement, are:
1. Establish the administrative, management, review and assessment processes of the consortium 7
2. Prepare software to set up a clinical database to which data of patients may be submitted by a secure web-based protocol 7
3. Establish and train a network of participating clinicians, who will include paediatric hepatologists, adult hepatologists, and neurologists, situated in all European countries 7
4. Create a network between the laboratories undertaking molecular diagnosis of WD and set up quality assurance mechanisms 12
5. One year of data collection 19
6. Data analysis to determine the incidence of WD, and … 24
7. … the incidence of the clinical sub-types of WD, and . .24
8... the treatment regimes currently being used and their short-term effectiveness 24
9. In analysing this data, to determine whether there are groups of patients of sufficient size and homogeneity to mount an RCT or RCT 36
10. Continue patient accrual to the database, and monitoring of existing patients, providing a long-term data resource. 48
11. Prepare a proposal for an RCT or RCTs 48

As part of the routine diagnostic assessment of a patient with Wilson's disease, a blood sample is sent to a molecular diagnostic laboratory. Permission will be requested from participants for those samples to be retained for 3 purposes, namely
1. Re-testing with improved technology as it becomes available
2. Exchange of anonymised samples for a quality assurance scheme between laboratories
3. Use of anonymised samples, linked to anonymised clinical details, in a possible future study of genes modifing the clinical features and severity of Wilson's disease

A15. What is the expected total duration of participation in the study for each participant?

2 hours to receive information about the project and give consent.
Data storage for up to 3.5 years as a part of this study, but permission will be sought f...Cont'd on Additional Pages.

A16. What are the potential adverse affects, risks or hazards for research participants either from giving or withholding medications, medical devices, ionising radiation, or other interventions(including non clinical)?

NONE.
Participants' clinical assessment, investigation and management will not differ from current best practice.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to life-style for research participants?

None

A18. What is the potential for benefit for research participants?

1. A uniformly high standard of assessment of Wilson's disease will be encouraged in all participating centres, by the use of a data entry form. This may lead to better evaluation of patients.
2. The project web-site www.eurowilson.com will be an information resource, and will provide links to other sources of support such as the WD patient associations which exist in most participating countries
3. Quality assurance procedures will improve the rigour of laboratory diagnosis.
4. There will be increased profile of the disease.
5. Participants may feel satisfaction that they are contributing to improvements for later patients, possibly including younger siblings

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience for researchers themselves? *(if any)*

Time consumed by taking part

A20. How will potential research participants in the study be(i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

i) All patients diagnosed with Wilson's Disease in the study period will be eligible for inclusion. We will rely upon clinician awareness of the project. There are 3 relevant groups of clinicians:
I Paediatric hepatologists: Contacts are made with
- the 3 supraregional paediatric hepatology centresa at Birmingham, Kings and Leeds
- the British Society of Paediatric Gastroenterology, Hepatology and Nutrition
- the Royal College of Paediatrics and Child Health
- the Children's Liver Disease Foundation
II Adult hepatologists, who will be circulated through the British Association for the Study of the Liver
III Adult neurologists, who are circulated each month by the British Neurological Surveillance Unit. The Director of the BNSU has agreed to Wilson's disease being one of the 10 topics on the notification card for an initially 1 year period. Contact will also be made with the Movement Disorder Society
.Other mechanisms will be
-Patient societies will be informed of the study.
- A web-site will explain the project and give information on Wilson's Disease.

ii) Approach and recruitment may be made at any time after diagnosis. Ideally, data entry should occur at the time of clinical assessment. The data entry proforma should serve as an aide to clinical data recording, and may be printed off to be included in the patient's clinical record. However the information to be entered into the database should all have been collected in the routine assessment of the patient. Situations where data entry may be delayed after diagnosis include
- patients who present with acute liver disease requiring assessment for transplantation, where sensitivity must be shown in giving carers additional decisions whilst they are coming to terms with a life-threatening situation
- clinicians who belatedly become aware of the project
The patient or carer will be approached by a member of his/her clinical team, informed of the project, supplied with informative literature and the web-site address.

iii) The patient or carer will be given at least 24 hours to decide whether to participate in the study. Permission will be requested for the following discrete processes:
- inclusion of anonymised information in the database
- retention of DNA in the diagnostic molecular laboratory for re-analysis by improved techniques
- use of anonymised DNA sample for quality assurance or for modifier gene analysis

A21. Will research participants be recruited via advertisement?
○ Yes ◉ No

Give details:

Enclose a copy of the advertisement/radio script/website/video for a television (with a version number and date).

A22. What are the principal inclusion criteria? *(Please justify)*

A diagnosis of Wilson's Disease

A Validation Group will confirm the diagnosis in each case submitted to the database

A23. What are the principal exclusion criteria? *(Please justify)*

The diagnosis is not confirmed.

A Validation Committee will consider all cases. They will use existing algorithms and scoring systems to reach a decision where possible. We anticipate that there will remain a diagnostically uncertain group. For example it can initially be difficult to distinguish Wilson's disease from autoimmune hepatitis. Quantitating this group is important in RCT planning.

A24. Will the participants be from any of the following groups? *(Tick as appropriate)*

- [x] Children under 16
- [ ] Adults with learning disabilities
- [x] Adults who are unconcious or very severly ill
- [ ] Adults who have a terminal illness
- [ ] Adults in emergency situations
- [ ] Adults with mental illness(particuarly if detained under Mental Health Legislation)
- [ ] Adults suffering from dementia
- [ ] Prisoners
- [ ] Young Offenders
- [ ] Adults in scotland who are unable to consent for themselves
- [ ] Healthy volunteers
- [ ] Those who could be considered to have a particuarly dependant relationship with the invetigator, e.g. those in care homes, medical students
- [ ] Other vunerable groups

Justify their inclusion:

1. Children under 16 are expected to comprise 30-50% of the participants
2. The category of "adults who are unconscious or severely ill" includes 2 rare circumstances:
(a) an adult who develops fulminant hepatic failure (more usually a paediatric problem)
(b) Impairment of cognitive function to the extent that a patient cannot give informed consent. This is rare because the principal neurological problems of WD are motor. ...Cont'd on Additional Pages.

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

○ Yes ◉ No ○ Not Known

Give details and justify their inclusion:

A26.Will informed consent be obtained from the research participants?

◉ Yes ○ No

Give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe the arrangements to be made for obtaining consent from a legal representative.

If consent is not to be obtained, please explain why not.

Written information will be supplied describing the disease, the project and the items for which consent is being sought. This information will be in the patient's own language, written for an average reading age of 12 years. It will refer to the project website.

For children, information will be provided in an age-appropriate way. Since the majority of children with Wilson's disease will be > 8 years, Gillick competence will be assumed. Web material in cartoon form has been created (www. eurowilson. com). It will be emphasised that participation involves no extra hospital visits, blood tests, scans or biopsies.

For adults who are severely ill or who have cognitive impairment, permission will also be sought from the appropriate caring family member.

An age-appropriate consent form will be given to the patient or family by a member of the clinical mangement team. In the event that the patient has no queries, or only simple queries easily addressed by the clinician, then a signature will be obtained. If further discussion is requested, a member of the research team will be requested to make contact by telephone, letter, email, or visit. An interval of at least 24 hours between giving information and requesting consent will be stipulated. It will be made clear that neither consent nor with-holding of consent influence treatment, and that consent to some rather than all components is acceptable. For example, a patient may consent to clinical but not genetic data being made available. It will be made clear that consent may be withdrawn at any time

...Cont'd on Additional Pages.

Copies of the written information and all other explanatory material should accompany this application.

A27. Will a signed record of consent be obtained?

◉ Yes ○ No

Attach a copy of the consent form to be used, with a version number and date.

If answer is no, please justify:

A28. How long will the participant have to decide whether to take part in the research?

At least 24 hours

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English? *(E.g. translations, use of interpreters etc.)*

This is a European study, in which material will be produced in English, French, Spanish, German and Italian. Information on www.eurowilson.com has been translated into French, German and Italian, and will be translated into further European languages.

In the UK, materials will also be translated into Hindi and Urdu

Professional translators will be employed

Child-friendly materials will be produced. Please see an example in the leaflet "Wilson's disease for younger people" attached.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The web-site will have a news page. Patient associations, professional societies and participating centres will receive regular reports.

A31. Does this study have, or require, approval of PIAG (Patient Information Advisory Group) or other bodies with a similar remit? *(see Guidance notes)*

○ Yes ◉ No

Give details:

A32. Will the research participant's General Practitioner be informed that they are taking part in the study?

◉ Yes ○ No

Enclose a copy of the information sheet /letter for the GP with a version no. and date

Will permission be sought from the research participants to inform their GP before this is done?

◉ Yes ○ No

Explain why not:

It should be made clear in the patient information sheet that the research participant's GP will be informed.

A33. Will individual research participants receive any *payments* for taking part in this research?

○ Yes ◉ No

Indicate how much and on what basis this has been decided:

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives* or *benefits* for taking part in this research?

○ Yes ◉ No

Indicate how much and on what basis this has been decided:

A35. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for <u>negligent</u> harm?

For participants in the UK indemnity will be provided by the University of Sheffield

Participants in other European countries will be covered by corresponding arrangements in their own country

Please forward copies of the relevant documents

A36. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by or on behalf of, participants for <u>non-negligent</u> harm?

For participants in the UK indemnity will be provided by the University of Sheffield

Participants in other European countries will be covered by corresponding arrangements in their own country

Please forward copies of the relevant documents

A37. How is it intended the result of the study will be reported and disseminated? *(Tick as appropriate)*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] Written feedback to research participants
- [ ] Presentation to participants or relative community groups
- [ ] Other/none e.g. Cochrane Review, University Library

If other/none of the above, give details and justify:

A38. How will the results of research be made available to research participants and communities from which they are drawn?

Web-site

Peer-reviewed journal

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- [ ] Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- [x] Electronic Transfer by magnetic or optical media, email, or computer networks
- [ ] Sharing of data with other organizations
- [ ] Export of data outside the European Union
- [ ] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual Files including X-Rays
  - [ ] NHS computers
  - [ ] Home or other computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop Computer

Further details:

Data will be entered by secure web-base protocol to a server at HC Forum, Grenoble, an academic unit based within the University of Grenoble.

A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used, and at what stage:

In a centre expected to see a number of cases, such as the 3 supraregional paediatric liver centres, a participating clinician will sign on to the database using a personal smart card in a card reader attached to a computer with web access. They will receive a patient number from the database. A note of the patient's name and the database patient number will be retained in a secure location by the entering clinician. Data will then be entered without any patient identifier other than this number. The data will be stored in the server of HC Forum, and will not be stored on any personal or institutional computer of the entering clinician. It will be possible for the entering clinician to make a print-out of the completed data entry proforma to serve as a record in the patient's clinical notes, but this will not carry the database number.

...Cont'd on Additional Pages.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

Data will be held by HC Forum, an academic unit based within the University of Grenoble. The process of data entry includes validation steps which include prompts for missing data and questioning of unlikely values. Anonymised cases are initially entered into a secure private domain, and then offered to the Wilson's disease consortium. At that stage, they are reviewed by a Validation Committee, which will review acccuracy of diagnosis.

A data anlysis group will be convened. Its chair and consortium membership are identified.

A42. Who will have control of, and act as the custodian for, the data generated by the study?

Ultimate responsibility lies with the Coordinator of the Consortium, who is the applicant.

The data custodian will be Dr Olivier Cohen, Director of HC Forum, and a data manger to be appointed.

A43. Who will have access to the data generated by the study?

The data analysis group, the RCT planning group, and the Consortium.

A44. For how long will data from the study be stored? 3 Years 6 Months

Give details of where they will be stored who will have access and of the custodial arrangements for the data:

Project funding is for 4 years, of which the first 6 months, beginning 1 June 2004, is for preparatory work. We recognise that this cohort of patients is potentially a long-term data resource, but that retention of data will require additional funding. Therefore permission will be sought both for 3.5 year and for indefinite storage, the latter contingent upon (a) funding and (b) an explicit purpsoe being stated upon the project web-site.
Data will be stored at HC Forum, Grenoble. The data analysis group, the RCT planning group and the consortium will have access. The Director of HC Forum, and a data manager appointed for the purpose, will have custody. In th...

Cont'd on Additional Pages.

A45. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi-centre research group
- [ ] Internal review (e.g. involving colleagues, academic supervisor)
- [ ] None external to the investigator
- [ ] Other, e.g. methodological guidelines

If other, give details:

If you are not in possession of any referees or other scientific critique reports relevant to your proposed study, justify and describe the review process and outcome. If review has been undertaken but not seen by the researcher, Give the details of the body who has undertaken the review:

A copy of the referee's report is attached

A copy of any referees comments or other scientific critique reports relevant to the proposed research must be enclosed with the application form.

A46. Has similar research on this topic been done before?

○ Yes ◉ No

Why should it be replaced?

A47. Have all existing sources of evidence, especially systematic reviews, been fully considered?

◉ Yes ○ No

Please give details of search strategy used:

A Cochrane style evaluation (Houwen, unpublished) of the current literature on Wilson Disease and treatment resulted in over 1000 hits. Papers were graded according to the US Agency for Healthcare Policy and Research Definition. Over 500 articles were "expert" opinions in favour of either zinc treatment or the use of copper chelators. No randomized clinical trial could be found, and less than 20 articles described the results of a particular treatment in a series of patients. In only one article, describing 58 patients, both treatment options (zinc and D-penicillamine) were evaluated in a non-randomized way. As no strict end points wer...Cont'd on Additional Pages.

A48. What is the primary outcome measure for the study?

Data on incidence to inform the construction of an randomised controlled clinical trial protocol

A49. What are the secondary outcome measures? *(If any)*

Deliverables and outcomes are set out in the Annexe as attached

A50. How many participants will be recruited? How many of these participants will be in a control group?

Since the objective is to determine the number of new cases (participants) this is not known, but is estimated to be 272-748

...Cont'd on Additional Pages.

A51. Has the size of the study been informed by a formal statistical power calculation?

○ Yes ◉ No

Indicate the basis upon which this was done, giving sufficient information to allow the replication of the calculation:

It has been informed by current estimates of prevalence

A52. Has a statistician given an opinion about the statistical aspects of the research?

Give the name and contact details: ○ Yes ◉ No

Give a brief summary of advice offered, and attach a copy of the comments if available:

Enclose a copy of comments. If the comments are not available then please enclose a summary of the opinion

A53. Describe the statistical methods and/or other relevant methodological approaches (e.g. for qualitative research) to be used in the analysis of the results. Give details of the methods of randomization process to be used if applicable:

1. The primary result will be a count of total number of new cases presenting
2. Diagnostic categories will be refined. Some, such as fulminant hepatic failure are well-defined. Others, such as "chronic liver disease" may need sub-division with regard to histology. This will be a function of the data analysis group.
3. This group will also review data with respect to
 a) geographical spread
 b) genetic epidemiology
 c) current treatment
 d) short-term outcome
 e) variations in practice
3. Homogeneity within diagnostic categories will be tested
4. Numbers of patients presenting in each category will be quantitated
5. The RCT planning group will have co-opted statistical expertise ab initio. It will receive data from the first year's anlysis and consider feasibility of power calculations for RCTs

A54. Where will the research take place? *(Tick as appropriate)*

- [x] UK
- [x] Other States in the European Union
- [ ] Other States in the European Economic Area
- [ ] Other

Give details:

Please see Workplan in attached Annexe

A55. Has this or a similar application been previously rejected by a research ethics committee in the U.K. the European Union or in the European Economic Area?

○ Yes ◉ No

Name of research ethics committee or regulatory authority:

Decisions and date taken:

Research ethics committee reference number:

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?

Include the type of organisation by ticking the box and give approximate numbers if known.

Number or organisations

- [x] Acute teaching NHS Trusts
- [x] Acute NHS Trusts
- [ ] NHS Community and/or Primary Care Trusts
- [ ] NHS Trusts providing mental healthcare
- [ ] NHS Care trusts
- [ ] Social Care Organisations
- [ ] Prisons
- [ ] Independent hospitals
- [ ] Educational establishment
- [ ] Independent research units
- [ ] Other (Give Details)

It is expected that most of the paediatric cases will be known to the 3 supraregional liver centres, namely Kings College Hospital; Birmingham Children's Hospital; Leeds Teaching Trust. Adult cases may arise in any Trust; it is overwhelmingly likely that all will be seen in an acute Trust by an appropriate specialist. However it is not possible to state the total number of Trusts in which patients will arise.

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

Please see section 6.1 of the workplan. Each submitted case will be examined by a Validation Committee. The conduct of the research will be monitored by an Oversight Committee. Audit reports will be produced at 18, 36 and 48 months after starting the project. Data will be monitored by the Analysis Group.

Will a data monitoring committee be convened? ◉ Yes ○ No

What are the criteria for electively stopping the trial or other research prematurely?

1. Failure to achieve data accrual from substantial areas of Europe
2. The heterogeneity of patients implies that an RCT will not be possible.

Details of membership of the data monitoring committee, their standard operating procedures and summaries of reports of interim analyses to the data monitoring committee must be forwarded to the NHS research committee approving the study.

A58. Has funding for the research been secured? ◉ Yes ○ No

Give details of funding organisation(s) and amount secured and duration:

i

Organisation: Sixth Programme Framework of EC LifeSciHealth
Address: European Commission
DG Research - RTD-F2
SDME 8/38 Brussels
Postcode: B-1049 Brus
UK Contact: Mrs Gill Wells

Telephone: 0032-2-2950940 Fax: 0032-2-2955365
Email: Gill.Wells@sheffield.ac.uk, catherine.berens@cec.eu.int

Amount: £ 532164 Duration: 48 Months

ii

Organisation:
Address:
Postcode:
UK Contact:

Telephone: Fax:
Email:

Amount: £ Duration: Months

iii

Organisation:
Address:
Postcode:
UK Contact:

Telephone: Fax:
Email:

Amount: £ Duration: Months

If No, what arrangements are being made to cover any costs of the research? If no external funding is being sought, please say

A59. Has the funder of the research agreed to act as sponsor as set out in the research Governance Framework?
○ Yes ◉ No ○ Not Known

Has the employer of the chief investigator agreed to act as sponsor of the research?
◉ Yes ○ No ○ Not Known

Give details of the organisation who will act as the sponsor of the research:

Organisation: Sheffield Children's NHS Trust
Address: Western Bank
Sheffield
Postcode: S10 2TH
UK Contact: Tracy Elliott, Research Manager

Telephone: +44 114 226 7904 Fax: +44 114 275 5364
Email: tracy.elliott@sch.nhs.uk

A copy of documentation indicating that the organisation has accepted the role of sponsor should be enclosed if the sponsor is not the main funder or chief investigator's employer.

A60. Has any responsibility for the research been delegated to a subcontractor?

○ Yes ◉ No

Give details including:
Name of research contract organisation/site management, and summary of delegated responsibility

A61. Will individual *researchers* receive any personal payment over and above normal salary for taking part in this research?

○ Yes ◉ No

Indicate how much and on what basis this has been decided:

A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?

○ Yes ◉ No

Indicate how much and on what basis this has been decided:

A63. Will the host organiseation or the researchers department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

○ Yes ◉ No

Give details:

A64. Does the chief investigator or any other key investigator/collaborator have any direct personal involvement (e.g. financial, share-holding, personal relationship etc.) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

Give details:

A65. Other relevant reference numbers if known (give details and version numbers as appropriate):

Applicant's/organisation's own reference number, e.g. R&D (if available):
Sponsor's/protocol number: SCH/04/027
Funder's reference number: 503430
International Standard Randomized Controlled trial Number (ISRCTN):
European Clinical Trials Database (EUDRACT):

Project website: www.eurowilson.com

A66. Other key investigators/collaborators *(all grant co-applicants should be listed)*

i
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If further collaborators are required, please enter at end of session or attach a further sheet.

A67. If the research involved a specific intervention (e.g. a drug, medical device, dietary manipulation, life-style change etc), what arrangements are being made for continued provision of this for the participant (if appropriate) once the research has finished?

Not applicable

PART A: SUMMARY OF ETHICAL ISSUES

A68. What do you consider to be the main ethical issues or problems that may arise with the proposed study, and what steps will be taken to address these?

Please see section 9 of the Workplan

1. Some of the patients will be children. This is addressed by providing information in a child friendly way, and information for parents. No procedures or visits will be necessary additional to those indicated on clinical grounds
2. Some patients will be very sick, such as those with acute liver failure. Addressed by delaying request for consent until the acute situation has resolved. Information does not have to be submitted immediately
3. A minority of patients with neurological disease may have cognitive impairment. Addressed by seeking permission from a competent family member
4. Concerns about confidentiality of data addressed by putting secure systems in place for anonymisation, data transfer and storage.
5. Different processes for obtaining consent may apply in different European countries. Addressed by making this MREC form the model for other participants

A69. Do you need to add further information about certain questions in part A?
This question is not applicable for the online version of Corec form.

PART B: Section5 - Use of newly obtained Human Biological Materials

1.What samples will be collected and or analysed by whom will they be collected?

The diagnosis of Wilson's disease now includes mutation testing, which is carried out in a small number of laboratories across Europe. Sheffield is the UK reference centre. The results of mutation analysis will be included in the anonymised data collected about all participating patients. Permission is sought to :
a) use surplus DNA for a quality assurance scheme to be set up between participating laboratories
b) retain DNA for future evaluation of new diagnostic techniques
c) retain DNA for a future possible study of modifier genes

2. Are samples taken solely for research purposes (or are they a bi-product of those taken primarily for clinical purposes i.e. surplus to clinical requirements)?

No sample will be taken purely for research purposes; they will be surplus to clinical requirements

3. How will samples be labeled/identified?

Indicate if samples can be considered to be "identified", "coded", "de-identified", "anonymised" or "anonymous", and at what stage identifiers are removed. (See guidance notes for definitions.)

Samples sent for diagnostic purposes will be identified.

Samples used for technology development and for quality asurance will be de-identified

Samples used for modifier gene studies will be de-identified, and data linked to anonymised data about clinical presentation and course

4. Give details of where the sample(s) will be stored, for how long, who will have access and of the custodial arrangements.

In the UK, samples will be analysed and stored in the North Trent Molecular Genetics Laboratory CPA), under the direction of Dr Ann Dalton

5. Will the research participant retain any rights to the sample(s)?

○ *Yes* ◉ *No*

Give details; if the sample is a gift, this must be clear in the information sheet. What will happen to the samples if a participant withdraws from the study?

If a participant withdraws from the study, his or her sample will be retained in the laboratory for the purpose of future clinical care. Examples of this would be the need to check mutations again with newer methods, if a question of genetic counselling arose. It will not be used for quality asssurance or further research

6. Is it known how the samples will be used in the future?

◉ *Yes* ○ *No*

Give details and indicate if consent will be obtained for the future use of samples:

Previous paragraphs describe the use of these samples for (a) diagnosis; (b) technology improvement; (c) quality assurance; (d) a possible future study of modifier genes. If any other research project related to Wilson's disease for which these samples might be needed is considered, then a further consent will be sought.

7. Does the research involve the analysis or use of genetic material from human biological materials?

◉ *Yes* ○ *No*

8. Would it be possible to link the results of any genetic analysis back to individuals?

◉ *Yes* ○ *No*

9. Is it intended to link the results of any genetic analysis back to individuals?

◉ *Yes* ○ *No*

Give details of what support or counseling service will be available to individuals:

For clinical purposes, genetic analysis will be linked to individuals.
For quality assurance or research on modifier genes, there will be no linkage to individuals

PART B: Section 7 - Declaration

- The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by the ethical principals underlying the Declaration of Helsinki, and good practice Guidelines on the proper conduct of research.
- If the research is approved I undertake to adhere to the study protocol without unagreed deviation and to comply with any conditions set out in the letter sent by the NHS Research Ethics Committee notifying me of this.
- I undertake to inform the NHS Research Ethics committee of any changes in the protocol, and to submit annual reports setting out the progress of the research.
- I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patent or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.
- I understand that research records data may be subject to inspection for audit purposes if required in future.
- I understand that personal data about me as a researcher in this application will be held by the Research Ethics Committee and its operational managers, and that this will be managed according to the principals established in the Data Protection Act.

Signature of the Chief Investigator: _

Date:

Print Name: Malcolm Stuart Tanner

1.Do you need to add further information about certain questions in part B?

This question is not applicable for the online version of Corec form.

ENSURE THAT YOU COMPLETE AND SIGN THE FORM AND ENCLOSE ANY RELEVANT ADDITIONAL DOCUMENTS.

Additional Information to Part's A, B & C

Answer from Question A6 Cont'd...

Answer from Question A15 Cont'd...

or long term storage conditional upon funding being secured to continue to provide a secure storage facility.

Answer from Question A24 Cont'd...

Answer from Question A26 Cont'd...

Answer from Question A40 Cont'd...

Adult neurologists reporting a case to the BNSU will be contacted by the a member of the chief investigator's team. Date of birth and gender will be requested, and a patient identifier number will be obtained from Grenoble. This number will be used to identify data sent by mail from the clinician to the chief investigator, who will enter this data onto the database. Similar arrangements will be made for cases reported to the chief investigator by adult hepatologists.

Answer from Question A44 Cont'd...

e event that HC Forum ceases to be able to offer this storage the Consortium will seek an Amendment to the approval recommending either destruction or alternative secure storage.

Answer from Question A47 Cont'd...

e defined no firm conclusions could be drawn.

Answer from Question A50 Cont'd...

No control group is included.