ELUCIDATE

ELF to Uncover Cirrhosis as an Indication for Diagnosis and Action for Treatable Events

Investigation of the effectiveness and cost effectiveness of the Enhanced Liver Fibrosis test in detecting cirrhosis to facilitate early management of portal hypertension and detection of hepatocellular cancer

Part of the NIHR Applied Programme Grant RP-PG-0707-10101 Evaluating the benefits for patients and the NHS of new and existing biological fluid biomarkers in liver and renal disease

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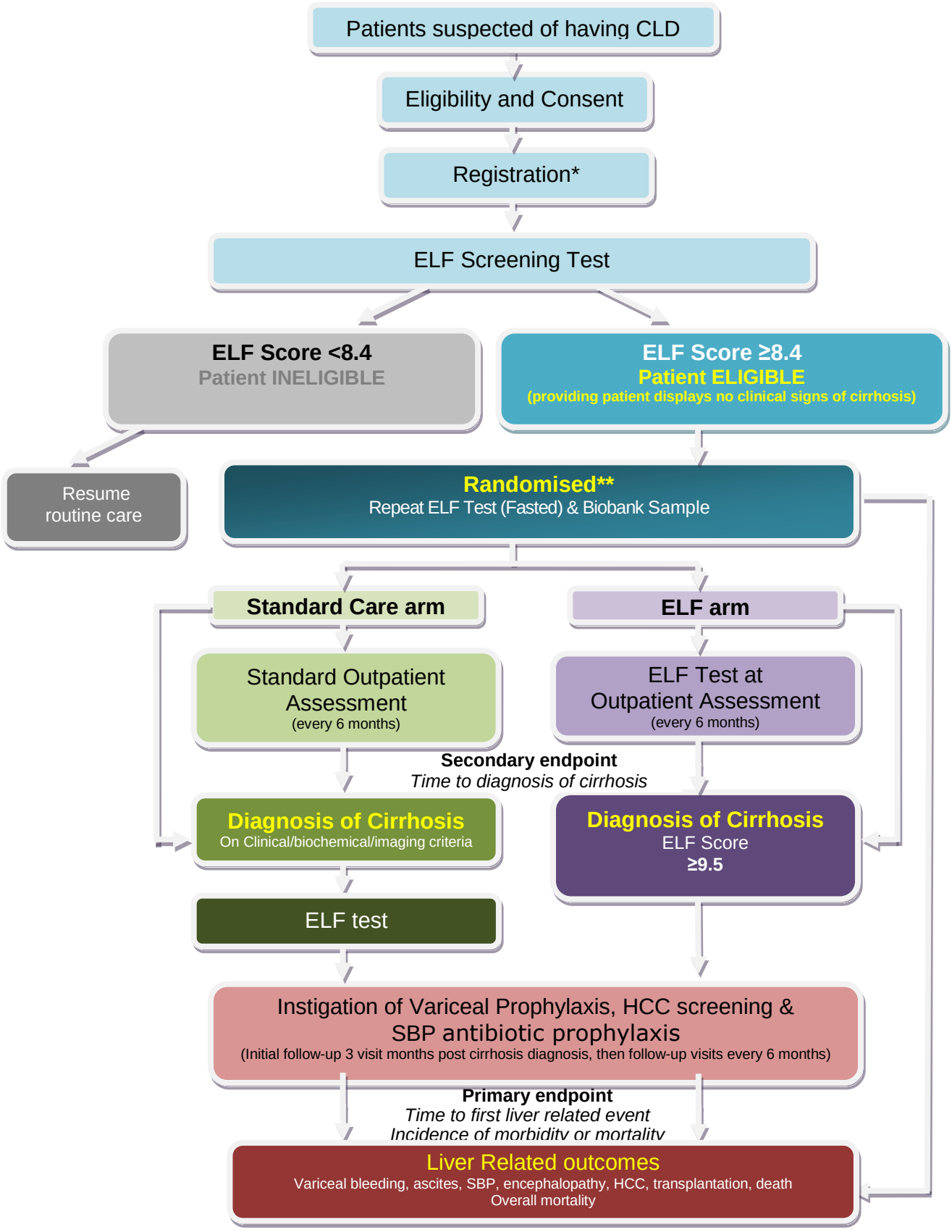
3 FLOW DIAGRAM



*Registration line due to close 28/02/2013
**Randomisation line due to close 30/04/2013

4 BACKGROUND

4.1 CHRONIC LIVER DISEASE EPIDEMIOLOGY

Chronic Liver Disease (CLD) is now the fifth most common cause of death in men in the UK aged 35-54[1-3]. The leading causes of CLD in the UK are Alcoholic Liver Disease (ALD), Non-Alcoholic Fatty Liver Disease (NAFLD), and Chronic Hepatitis C (CHC). These main aetiological agents cause liver inflammation that triggers a repair response in the liver that results in fibrosis that may progress if the insult persists. Fibrosis develops over many years and is asymptomatic until the complications of end-stage fibrosis or cirrhosis become manifest with jaundice, portal hypertension, and liver failure. Once cirrhosis has developed hepatocellular cancer arises at approximately 5% per annum[4,5].

4.2 MORBIDITY AND MORTALITY FROM CIRRHOSIS

The morbidity from cirrhosis results in a considerable healthcare and financial burden including inability to work, variceal bleeding, recurrent ascites, hepatic encephalopathy, and liver cancer. While liver transplantation can extend life expectancy, a limited supply of organs means that the identification of suitable recipients and optimal timing of transplantation are essential.

The major treatable complications of cirrhosis are portal hypertension (incidence approximately 8% per annum) and hepatocellular cancer (incidence approximately 5% per annum)[6]. Evidence shows that early detection of varices and treatment with prophylactic use of beta blockers to reduce portal hypertension or band ligation reduces morbidity and increases survival[7]. Similarly early detection of ascites and treatment has been shown to reduce the morbidity associated with bacterial peritonitis from 17% to 2%[8]. Well respected guidelines now advocate endoscopic surveillance for varices and prophylactic intervention on the basis of strong evidence of patient benefit in terms of morbidity and mortality and health-economic justification[9].

The case for surveillance and early detection of hepatocellular cancer in patients with cirrhosis has been evaluated in several observational studies and randomised controlled trials[10,11]. Surveillance of cirrhotic patients for hepatocellular cancer has been shown to identify smaller tumours at a point where potentially curative therapies can be offered. As a result, international guidelines advocate surveillance for hepatocellular cancer recommending a combination of biannual ultrasound scanning and alphafetoprotein measurement (AFP) [12,13.]

4.3 PORTAL HYPERTENSION

Early detection of cirrhosis and instigation of prophylactic treatment of portal hypertension with beta blockers[7] or, for medium or large varices, variceal band ligation[14-16] has been shown to reduce morbidity and mortality. However, many cases of cirrhosis are not identified until they present with variceal bleeding which is associated with a mortality of 25%[17-19]. Earlier detection of cirrhosis and instigation of prophylaxis would translate into improved survival and less cost to the health service.

4.3.1 Hepatocellular cancer

Retrospective analyses have identified criteria associated with better outcomes for tumour resection and liver transplantation in patients with hepatocellular cancer (HCC). These include the presence of a single lesion less than 3 cm in diameter or no more than 3 tumours with none measuring greater than 1 cm in diameter[13,20]. These guidelines have been extended to include evidence of slow growth in tumour size[21]. However, many hepatocellular cancers are identified at a time when the tumour has grown larger than 5 cm, or when there are more than three tumours measuring three or more cm, often ruling out successful transplantation[22]. In these situations, when transplantation or curative resection is contraindicated treatment is directed at increasing length of survival rather than cure.

Currently many patients are diagnosed after the growth of their tumours has ruled them out for curative resection or transplantation. More effective methods for detecting cirrhosis in a broad high risk population will permit earlier instigation of tumour surveillance. This in turn will result in earlier detection and greater proportion of patients being cured through resection or transplantation, translating into greater health gain and cost-effectiveness.

4.4 DETECTION OF CIRRHOSIS

In the vast majority of cases, liver fibrosis is asymptomatic and cirrhosis develops insidiously so that opportunities for disease modification or cure are missed.

4.4.1 Symptoms

Cirrhotic patients are often asymptomatic and those that are unwell may present with non-specific symptoms such as fatigue, poor concentration, and itching[23], making the accurate diagnosis of early cirrhosis difficult.

4.4.2 Simple Blood Tests

Standard biochemical tests of liver function such as aminotransferases (AST, ALT, GGT) are frequently abnormal in patients with CLD, thus they are not specific for advanced fibrosis or cirrhosis. In addition they may be normal in 25% of patients with cirrhosis and thus are also not sensitive[24]. These tests are neither sufficiently sensitive nor specific for use in screening for cirrhosis.

4.4.3 Liver biopsy and Histology

The severity of liver fibrosis has traditionally been assessed histologically by the reference standard, liver biopsy. Several scoring systems have been used to accurately quantify the degree and severity of liver fibrosis. The Ishak fibrosis scoring system with seven ordinal stages (Ishak F0-F6) has been shown to be sensitive at showing liver fibrosis severity and its subsequent progression [25]. A numerically increasing Ishak fibrosis stage is representative of increasing fibrosis. Ishak stages F3 and F4 are diagnostic of moderate and moderate to severe fibrosis with Ishak stages F5 and F6 diagnostic of severe fibrosis and cirrhosis respectively.

However, while the liver biopsy has long been regarded as the reference standard method for assessing liver fibrosis, recently increasing awareness of the errors associated with liver biopsies have drawn attention to its failings. It is now recognised that liver biopsy is hazardous[26], inaccurate, subject to sampling error[27] and variation in interpretation[28]. These failings of liver biopsy have led to an increasing interest in the identification of alternative non-invasive tests for liver fibrosis.

4.4.4 Imaging

Imaging has a major role in the detection and assessment of liver fibrosis. However, all imaging modalities including ultrasound, elastography, cross-section imaging with X-rays or magnetic resonance require access to technology and skilled operators; all are subject to operator error and time-consuming. Furthermore the accuracy of elastography has recently been questioned in the context of inflammatory liver disease[29,30].

4.4.5 Serum tests

Blood tests for fibrosis and cirrhosis are highly attractive because they have the potential to be automated, highly accurate, reproducible (with a low coefficient of variation), and repeatable at short intervals. Serum markers of liver fibrosis can be divided into those that are 'indirect' that measure liver function, and those that are 'direct', measuring constituents of liver matrix and enzymes involved in fibrogenesis and fibrolysis. Indirect measures such as aminotransferases, clotting factors, bilirubin, and platelets are subject to the influence of inflammation, drug effects, and other comorbidity[31].

The accuracy of 'direct' markers of fibrosis theoretically may be affected by other fibrotic disorders but this has not been a major problem encountered in clinical evaluation. Studies have demonstrated that single markers are less accurate then panels of markers in the detection of liver fibrosis[32]. One such panel of direct markers is the Enhanced Liver Fibrosis (ELF) test[33].

4.4.6 ELF

The Enhanced Liver Fibrosis (ELF) test is a CE marked (EU Regulatory Approved) test for liver fibrosis that has been developed over a decade in a cohort of over 1,000 patients and subsequently validated in thousands more. The test has been shown to accurately reflect the severity of liver fibrosis in a wide range of chronic liver diseases, at all stages of liver fibrosis.

The test can detect mild and moderate degrees of fibrosis accurately although performance is best in the detection of advanced fibrosis and cirrhosis; in patients with Chronic Hepatitis C area under the curve (AUC) receiver operating characteristic curves (ROCs) of 0.85 for 0-3 vs. 4-6 and 0.87 for 0-4 vs. 5-6 Ishak stages respectively, and in patients with NAFLD, AUC ROCs of 0.90 and 0.82 for severe fibrosis and moderate fibrosis[34,35]. Analysis of the risk of liver-related complications in a cohort of 500 patients with CLD followed over a period of 7 years revealed that an increase of 1 unit in the ELF score correlated with a doubling of the risk of liver-related events[36].

Analysis of data from studies of ELF shows that ELF correlates with severity of liver fibrosis as determined by liver biopsy and fibroelastography. The long-term follow-up of patients enrolled in the original ELF study revealed that ELF scores at baseline predict the incidence of liver related events as well as mortality[35]. The ELF scores of patients whose liver biopsies have been classified using widely accepted Ishak fibrosis staging system suggest the categories in Table 1.

Table 1. ELF scores and fibrosis staging.

Fibrosis stage (Ishak)	ELF Range[35]
Normal/Mild (F0-F2)	<8.37
Moderate (F3)	8.37-8.73
Moderate/Severe (F4)	8.74-9.12
Severe (F5)	9.13-9.49
Cirrhosis (F6)	≥9.5

However this categorisation undervalues the performance of serum markers by converting linear variables into categorical ordinal variables.

4.5 ELUCIDATE IN THE CONTEXT OF THE NIHR PROGRAMME GRANT

This trial is a part of the National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-RG-0707-10101) – Evaluating the benefits for patients and the NHS of new and existing biological fluid biomarkers in liver and renal disease, which aims to develop a stringent approach to protein biomarker evaluation. This trial will determine whether use of the ELF test will significantly alter the diagnostic timing and subsequent management of cirrhosis of the liver in order to reduce serious complications and improve outcomes for patients and service provision.

5 AIMS AND OBJECTIVES

5.1 AIMS

This trial aims to answer the following questions -

Does the use of serum markers of liver fibrosis:

a) permit earlier detection of liver cirrhosis in patients with Chronic Liver Disease (CLD) to allow earlier interventions?
b) affect the process of care, through a) increased use of beta-blockers/band ligation of varices to prevent haemorrhage/HCC; b) increased use of endoscopy and ultrasound/AFP's to detect HCC at a surgically curable stage; and c) effective early treatment to normalise Liver Function Tests (LFT's) in patients with Hepatitis B and Hepatitis C.
c) result in patient benefit through improved survival and reduced liver-related morbidity and mortality?
d) improve the cost-effectiveness of the management of end-stage liver disease?

5.2 OBJECTIVES

We propose to:

a) Evaluate the performance of the ELF test in the early detection of cirrhosis
b) Evaluate the impact of the early detection of cirrhosis using ELF on the ability to implement effective prophylaxis for varices, ascites, and encephalopathy aimed at preventing haemorrhage and facilitating earlier detection of HCC while it is still treatable, and to evaluate the later clinical impact of such prophylaxis if it can be delivered successfully. Similarly for early treatment to normalise LFTs in patients with Hepatitis B and Hepatitis C.
c) Undertake an economic evaluation of the ELF test in the early detection of cirrhosis and ergo in the initiation of measures to reduce the incidence of severe complications following cirrhosis.

6 DESIGN

A randomised controlled trial of screening for cirrhosis using the ELF test in patients with chronic liver disease and pre-cirrhotic moderate to severe fibrosis as classified by clinical, laboratory, or histological evidence, due to viral hepatitis B or C (HBV/HCV), non-alcoholic liver disease, alcoholic liver disease, Primary Biliary Cirrhosis (PBC), Primary Sclerosing Cholangitis (PSC), autoimmune hepatitis (AIH), haemochromatosis, or combinations of these diseases.

6.1 REGISTRATION

PLEASE NOTE THAT THE REGISTRATION LINE IS DUE TO CLOSE 28/02/2013

PATIENTS MUST NOT BE APPROACHED FOR TRIAL ENTRY AFTER THIS DATE.

IF YOU HAVE APPROACHED PATIENTS PRIOR TO 28/02/2013 WHO ARE UNABLE TO CONSENT UNTIL AFTER THIS DATE, PLEASE CONTACT CTRU TO DISCUSS.

Patients suspected of being at high risk for CLD will be considered for eligibility for registration and invited to provide written, informed consent. If they consent, they will be registered and will provide a serum sample for an ELF test. Patient data will also be collected and recorded (see section 14.1). The ELF test will be analysed and the result of the ELF test will be made available to the investigator normally within 1 week.

Samples can only be used to determine eligibility for randomisation if they have been kept at room temperature for no longer than 2 days between being taken and arriving at iQUR. If shipping delays are anticipated (eg at a weekend), store the serum sample in the fridge and ship when delivery within 2 days is possible. Further guidance related to this can be found in the Sample Processing SSOP. If a sample has been kept at room temperature for

more than 2 days from the time it was taken, then a repeat sample will be required.

Only patients with an ELF score of ≥ 8.4 (denoting at least moderate fibrosis, Table 1) will be eligible for randomisation. Results will be fed back to the investigator as <8.4 not eligible for randomisation or ≥, 8.4 and eligible for randomisation.

At this stage patients will also be invited to participate in the optional translational research biobank research. For this research, a single additional serum sample is required. Whilst patients will consent to the biobank research at the registration visit, this sample will be taken at the randomisation visit i.e. not at the registration visit (please see section 12.5).

6.2 RANDOMISATION

PLEASE NOTE THAT THE RANDOMISATION LINE IS DUE TO CLOSE 30/04/2013

RANDOMISATIONS MUST BE PERFORMED BY THIS DATE. IF THIS IS NOT POSSIBLE, PLEASE DISCUSS SPECIFIC CASES WITH CTRU.

The randomisation visit should occur as soon as possible following receipt of the test results from the registration visit and preferably within 6 weeks of the registration visit, but up to 12 weeks is permissible. However, if there is likely to be a delay in excess of 6 weeks please contact the CTRU to discuss.

If more than 12 weeks has passed since registration, a repeat ELF test should be taken to ensure that the patient remains eligible for the trial, and has not progressed to cirrhosis. The patient should then be randomised within the timeframes above for the closure of the randomisation line.

Patients with a registration ELF score of ≥ 8.4 will return to clinic for their randomisation visit when it will be explained that their ELF test has demonstrated they are above the threshold for randomisation. They will be asked to confirm whether or not they are still happy to continue participating in the trial and willing to be randomised. Patients will also be assessed to ensure their liver disease has not progressed to clinically evident cirrhosis in the interval from their registration visit.

Should the patient be judged at this visit to still be pre-cirrhotic, proceed with 24 hour telephone randomisation whilst patient is in clinic completing the Randomisation Visit Patient Questionnaires.

Should the patient be judged to have developed clinical signs/symptoms of cirrhosis they are no longer regarded as eligible for the trial. Please DO NOT proceed with randomisation. The patient should begin management for cirrhosis according to local practice.

Patients with an ELF score of <8.4 will also have no further study participation and will resume normal care. However, all patients who consent to the trial (whether randomised or not) will be flagged with the NHS Information Centre for longer term morbidity and mortality data from the Medical Research Information Service and Hospital Episode Statistics (please see section 6.3) These patients may be contacted by telephone to explain and discuss the reasons why they are ineligible for the study. A written explanation may also be provided (please see Investigator Site File for 'ELUCIDATE Letter for Ineligible Patients').

Eligible participants will be randomised on a 1:1 ratio to the intervention (standard follow-up screening for cirrhosis plus an ELF test) or non-intervention arm (standard follow-up screening for cirrhosis) of the trial using an automated 24-hour telephone randomisation system provided by the Clinical Trials Research Unit (CTRU). If the patient is randomised to 'follow-up screening for cirrhosis with ELF test' and the ELF score indicates they are cirrhotic, the randomisation system will also notify the caller so 'management' of cirrhosis can begin. All participants will have further data collected and recorded (see section 14.2). Those patients who consented for the optional trial translational research biobank will provide a serum sample for the biobank at the randomisation visit.

6.3 FOLLOW-UP

From the date of randomisation, patients will undergo follow-up assessments every 6 months until 30 months post-randomisation, unless they are diagnosed as cirrhotic. Where patients are diagnosed as cirrhotic within 30 months post-randomisation, an initial follow-up assessment will take place at 3 months after diagnosis, and subsequent visits for the purposes of data collection will take place at 6-monthly intervals. . All patients who consent to the trial (whether randomised or not) will be flagged with the NHS Information Centre for longer term morbidity and mortality data from the Medical Research Information Service and Hospital Episode Statistics (see section 11).

7 ELIGIBILITY

7.1 ELIGIBILITY FOR REGISTRATION

7.1.1 Inclusion criteria

- Patients with chronic liver disease who have not been diagnosed as having cirrhosis.

This may be due to any aetiology including (this list is not exhaustive):

- virus-serological and nucleic acid evidence of chronic Hepatitis C, chronic Hepatitis B
- fat: ultrasound evidence of fatty liver disease
- alcohol: history of excessive alcohol consumption
- autoimmune hepatitis (SMA, ANA, LKMA antibodies and raised immunoglobins)
- Primary Biliary Cirrhosis (AMA, M2 antibodies)

- Primary Sclerosing Cholangitis (ERCP or MRCP evidence of beading of biliary tree)
- Haemochromatosis- HFE genotype HDCY, DDCC or HHYY or mutation negative with liver biopsy evidence of iron overload

- Aged ≥ 18 years old and < 75 years of age
- Give their written, informed consent to participate
- Likelihood of ability to comply with the follow-up schedule
- Life expectancy > 6 months

7.1.2 Exclusion criteria

- unable to provide consent
- Imaging, histological or laboratory diagnosis of cirrhosis (other than ELF) /portal hypertension as evidenced by any one of the following:
  - Imaging evidence of portal hypertension (splenomegally, varices or ascites)
  - Liver biopsy diagnostic of cirrhosis (Ishak F6 or equivalent)
  - Thrombocytopaenia (platelets < 100 10^9/L)
  - Hypoalbuminaemia (albumin < LLN)

- Acute Liver Injury or Acute Liver failure (hepatic dysfunction <6 months in duration)
- An ongoing or previous episode of hepatic decompensation (acute on chronic liver failure) including:
  - encephalopathy, variceal bleeding, ascites, jaundice or liver synthetic dysfunction

- An Established diagnosis of hepatocellular cancer or elevated alpha feto-protein without investigation to exclude hepatocellular cancer

- Patient being treated with heparin (ELF test cannot be performed).

- Previously screened and found ineligible for the ELUCIDATE Trial

Note that
- HIV co-infection is NOT an exclusion criterion.
- The solitary finding of a coarse appearing liver on imaging is not an exclusion criterion.

7.2 ELIGIBILITY FOR RANDOMISATION

7.2.1 Inclusion criteria

- ELF score ≥ 8.4.

7.2.2 Exclusion criteria

- ELF score < 8.4

- Clinical, histological or laboratory diagnosis of cirrhosis (please see section 7.1.2)

8 RECRUITMENT AND CONSENT

8.1 RECRUITMENT

PLEASE NOTE THAT THE REGISTRATION LINE IS DUE TO CLOSE 28/02/2013

PATIENTS MUST NOT BE APPROACHED FOR TRIAL ENTRY AFTER THIS DATE.

IF YOU HAVE APPROACHED PATIENTS PRIOR TO 28/02/2013 WHO ARE UNABLE TO CONSENT UNTIL AFTER THIS DATE, PLEASE CONTACT CTRU TO DISCUSS.

PLEASE NOTE THAT THE RANDOMISATION LINE IS DUE TO CLOSE 30/04/2013.

RANDOMISATIONS MUST BE PERFORMED BY THIS DATE. IF THIS IS NOT POSSIBLE, PLEASE DISCUSS SPECIFIC CASES WITH CTRU.

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The trial aimed to randomise 1000 patients. It is anticipated that, at the close of recruitment, approximately 700 patients will have been randomised..

8.1.1 Trial Sites

Subjects will be enrolled from liver clinics in secondary care through the National Institute for Health Research Clinical Research Network (NIHR CRN) Comprehensive Clinical Research Networks (CCRNs) supported by the British Liver Disease Clinical Study Group. Patients will be recruited from clinics and services run by participating hepatology centres including satellite and outreach clinics.

Research centres will be required to have obtained local ethical and management approvals and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

8.1.2 Patient Recruitment

Nurses will review their caseload for potentially eligible participants. Subjects fulfilling eligibility criteria (section 7.1.1) will be invited to participate in the study. Wherever possible, eligible patients will be sent a trial information summary to consider prior to their next clinic appointment (e.g. include with appointment reminder letter). The Patient Information Summary will include an overview of clinical research, and an introduction to the rationale, design, and personal implications of the trial. The patients will have the opportunity to discuss the trial with their family and other healthcare practitioners before they are asked whether they would be willing to take part in the trial.

At the patient's next clinic visit, the patient will be provided with the full Patient Information Leaflet for the trial and further verbal details of the trial, and will be given the opportunity to discuss the trial with the Nurse or attending clinical/medical staff. The Patient Information Leaflet contains detailed information about the rationale, design, and personal implications of the trial. Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent to registration, subsequent randomisation (if eligible at that time), and long-term follow-up via routine data sources of the NHS Information Centre (see Section 11) regardless of whether the patient is randomised or not.

Should the patient require more time to consider participating in the trial, they are free to do so and if they subsequently assent, eligibility and consent can be undertaken at a later clinic visit. The participant is free to withdraw at any time without reason and without it affecting their care, and this is made clear in the Patient Information Leaflet.

8.2 INFORMED CONSENT

By consenting to participate in this trial, all patients agree to:

- Be registered to the ELUCIDATE trial (see section 9.3)
- Provide a blood sample for ELF testing (see section 10.1)
- Be registered with standard patient registers for morbidity and mortality relating to the trial endpoints (e.g. Hospital Episode Statistics and Medical Research Information Service of the NHS Information Centre) regardless of their ELF test result (see section 11)
- Be randomised if the ELF result shows the patient to be eligible (i.e. ELF score ≥ 8.4, see section 10.1) and
- Provide a sample for the Leeds NIHR Biomarker Biobank (this part is optional; the patient can participate in ELUCIDATE without consenting to providing a biobank sample, see section 12.5)

In order to investigate patient understandings of clinical biomarkers, experiences of testing, acceptability, perceived utility, and motivations for testing, in-depth semi-structured interviews will be undertaken in a small selection of patients. This qualitative research will form a separate protocol and patients will consent to this separately.

Informed consent will be undertaken by a member of the attending healthcare team who has received Good Clinical Practice (GCP) training and is approved by the Principal Investigator as permitted to take informed consent. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be kept in the patient's notes. The consent form must be signed by a member of the attending healthcare team who has been authorised to do so according to the study Authorised Personnel Log. The original consent form will be retained in the Investigator Site File; a copy of the consent form

will be given to the patient, a second copy filed in the patient's healthcare records (as per local practice), and a third copy returned to the CTRU.

The consent process will cover both the registration and randomisation aspects of the trial.

9 SCREENING & REGISTRATION

9.1 SCREENING

Participating research sites will be required to complete a log of all patients screened for eligibility for the duration of recruitment. Anonymised information will be collected including:

- age
- gender
- ethnicity
- whether the patient is registered or not registered

9.2 NON-REGISTRATION

Screened patients who are not registered either because they are ineligible or because they decline participation will also have the following information recorded:

- the reason not eligible for study participation OR
- the reason eligible but declined

This anonymised information will be returned on a monthly basis to the Clinical Trials Research Unit (CTRU).

9.3 REGISTRATION

PLEASE NOTE THAT THE REGISTRATION LINE IS DUE TO CLOSE 28/02/2013

PATIENTS MUST NOT BE APPROACHED FOR TRIAL ENTRY AFTER THIS DATE.

IF YOU HAVE APPROACHED PATIENTS PRIOR TO 28/02/2013 WHO ARE UNABLE TO CONSENT UNTIL AFTER THIS DATE, PLEASE CONTACT CTRU TO DISCUSS.

Screened patients who are both eligible for trial participation and provide written informed consent will be registered. Informed consent must be obtained prior to registration. Following confirmation of eligibility and written informed consent patients will be registered into the study by an authorised member of staff at the trial research site. Patients will be required to have a blood sample(s) taken at the registration visit (see section 10).

Registration will be performed centrally using the CTRU automated 24-hour telephone registration system. Authorisation codes and PINs, provided by the CTRU, will be required to access the registration system.

The following information will be required at registration:

- Unique authorisation and PIN code
- Name of trial research site and site code
- Name of person registering patient
- Patient initials
- Patient date of birth
- Confirmation of eligibility
- Confirmation of written informed consent
- Confirmation of collection and despatch of blood sample(s)
- Confirmation of fasting status
- Confirmation of registration visit health questionnaire completion (EQ-5D™* and SF-12v2™†)

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†SF-12V2™ Health Survey © 2000 by QualityMetric Incorporated – All rights reserved. SF-12V2™ is a trademark of QualityMetric Incorporated.

Direct line for registration +44 (0)113 343 3699

The CTRU will then issue you with an individual patient trial number. This number should be used on all trial documentation and clinical samples.

Investigators must ensure that all local baseline investigations aiming to confirm eligibility are performed prior to registration and randomisation (see section 12.1-12.2).

10 REGISTRATION BLOOD TESTS

Following consent a blood sample should be collected at the registration visit in order to perform the ELF test. This will determine whether the patient fulfils the final eligibility criterion (ELF score ≥ 8.4) and can be randomised. Serum samples will be required for the following:

- Sample for local assessments as required for baseline assessment (see section 14.1, Table 2)
- Sample for ELF test to be processed and sent for central analysis (see section 10.1)

Investigations in this trial combine both local and central assessment. Addresses for the central laboratory investigation (ELF test) can be found on the inside of the back cover. The central investigations are of key importance to eligibility and screening, and collection of biological samples for these investigations is compulsory. It is important that adequate serum samples are obtained, processed, and sent to the stated destinations as per the Site Specific Operations Document.

Samples can only be used to determine eligibility for randomisation if they have been at room temperature for no more than 2 days between being taken and arriving at iQUR. If shipping delays are anticipated (eg at a weekend), store the serum sample in the fridge and ship when delivery within 2 days is possible. Further guidance related to this can be found in the Sample Processing SSOP. If a sample has been kept at room temperature for more than 2 days from the time it was taken, then a repeat sample will be required..

Patients will be asked for their consent to participate in the translational research at registration into this trial, and biological samples will be collected from consenting patients to be stored for future use in the translational research protocol, subject to ethical approval. Additional translational research investigations will form a separate, optional research protocol.

10.1 ELF TESTING

ELF testing is required at registration. Patients should be requested to refrain from eating a large meal in the 2 hours prior to providing this sample. This stipulation should be applied to all ELF blood samples throughout the ELUCIDATE trial unless explicitly stated (i.e. randomisation visit where patients are requested to arrive for their visit in a fasted state). Once the ELF sample has been collected, processed, and sent to the central laboratory as detailed in the Site Specific Operations Document, it should take approximately 1 week to obtain the result of the ELF test. In order to ensure equipoise, patients will be informed only of whether the patient's ELF score means they are eligible for randomisation (≥ 8.4) or not (< 8.4). Knowledge of ELF scores may cause patients or clinicians to modify their behaviour and this could influence disease progression and result in confounding so that patients in the ELF arm of the trial progressed more slowly than those in the routine group for reasons other than the trial intervention.

Following on from randomisation to the ELF arm, the research staff at site will also be informed as to whether the patient's ELF score indicates 6 monthly follow up (between 8.4 and 9.49), or indicates that the patient should start immediate management for cirrhosis (≥9.5) (see section 13).

10.1.1 ELF result < 8.4

If the ELF result is less than 8.4, the patient is not eligible for randomisation, and the non-randomisation log should be completed (see section 12.1).

10.1.2 ELF result ≥ 8.4

If the ELF result is greater than 8.4 the patient should be randomised into the trial provided they are still otherwise eligible (see section 7.1). At randomisation, if the patient has been randomised to screening with ELF testing, clinicians will be informed if the patient's ELF score is 9.5 or greater, in which case they should start immediate management for cirrhosis (see section 13).

10.1.3 Quality assurance of ELF result

Anonymised samples that are surplus to the central laboratory, following ELF testing, will be used for Quality Assurance testing in designated NHS laboratories.

11 FLAGGING WITH ROUTINE DATA SOURCES

All patients who have consented and have been registered to the trial will be registered with routine NHS data sources (e.g. Hospital Episode Statistics). This will allow for collection of endpoint data in all patients, including those patients who are not randomised into the trial as their ELF scores were below 8.4.

12 RANDOMISATION

12.1 NON-RANDOMISATION

12.1.1 Non-participating patients

Participating sites will be required to complete a log of all patients who are registered to the trial but are not subsequently randomised, either because they are ineligible or because they decline further participation. Anonymised information will be collected including:

- age
- gender
- ethnicity
- date screened
- the reason not eligible for study participation OR
- eligible but declined and reason for this OR
- other reason for non-registration

This information will be collected on a monthly basis by the CTRU.

12.2 RANDOMISATION

PLEASE NOTE THAT THE RANDOMISATION LINE IS DUE TO CLOSE 30/04/2013.

RANDOMISATIONS MUST BE PERFORMED BY THIS DATE. IF THIS IS NOT POSSIBLE, PLEASE DISCUSS SPECIFIC CASES WITH CTRU.

Following receipt of the results of the registration ELF test, patients who fulfil the eligibility criteria for randomisation (section 7.2) will be randomised on a 1:1 basis to ‘screening for cirrhosis with ELF’ or ‘screening for cirrhosis with standard care’. Patients who are above the threshold for randomisation should be seen following receipt of the results of the registration blood tests (including ELF testing) as soon as possible and preferably within 6 weeks of the registration visit, but up to 12 weeks is permissible. However, if there is likely to be a delay in excess of 6 weeks please contact the CTRU to discuss.

Patients should also be asked to arrive fasted for this visit to allow for Glucose ± HOMA-IR testing. For trial purposes, a patient is considered fasted if they have gone without food either overnight or for more than 4 hours. During this fasted period, however, the consumption of water is allowed.

A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following characteristics (details of these stratification factors will be required for randomisation):

- Centre
- Age (≥ 18 to < 40, ≥ 40 to < 65 and ≥ 65 to < 75)
- Gender (Male, Female)
- Baseline ELF score:
  (≥ 8.4 to < 9.5, ≥ 9.5 to < 11.5 ≥ 11.5 to < 12.5 and ≥ 12.5)
- History of high alcohol consumption (at any time), defined as > 6 units*/day for 12 months or more for males and > 4 units/day for 12 months or more for females (Yes, No)
- Current alcohol consumption per day (Males: 0 units (teetotal), < 3 units (light), 3-6 units (moderate), > 6 units (high); Females: 0 (teetotal), < 2 units (light), 2-4 units (moderate), > 4 units (high))
- Type of CLD (ALD, Viral, Unknown/Other, NAFLD)

*one unit is defined as 10 grams of alcohol

Randomisation will be performed centrally using the CTRU automated 24 hour telephone registration system. Authorisation codes and PINs, provided by the CTRU, will be required to access the registration system.

The following information will be required at randomisation:

- Unique authorisation and PIN code
- Name of person randomising patient
- Patient trial number (from registration)
- Confirmation of continued eligibility
- Patient's date of birth
- Patient's gender
- Patient's baseline ELF score (information will be input by CTRU)
- Patient's alcohol consumption (past and current)
- Type of CLD
- Confirmation of randomisation visit health questionnaires completion (EQ-5D™, SF-12v2™, and Health Usage Questionnaire)

Direct line for randomisation +44 (0)113 343 3699

The randomisation system will allocate the patient's trial number and randomisation result: routine clinical monitoring or routine clinical monitoring plus ELF monitoring. Where patients are randomised to routine clinical monitoring plus ELF monitoring the randomisation system will also instruct

whether the ELF score indicates the patient should commence the management and treatment of cirrhosis.

12.3 SCREENING FOR CIRRHOSIS WITH ELF

Subjects in the intervention arm will have their ELF score measured every 6 months. If the ELF score is ≥ 9.5 the patient will be deemed to have cirrhosis. These patients should be contacted as soon as possible and recalled in to clinic to commence cirrhosis management. (Please see section 13)

Patients in the ELF arm will also be screened for cirrhosis using standard clinical means. If the patient is deemed to be cirrhotic on clinical criteria (by examination, on the basis of laboratory tests (other than ELF) or through imaging), the patient will have been deemed to have cirrhosis and cirrhosis management will commence.

12.4 SCREENING FOR CIRRHOSIS WITH STANDARD CARE

Subjects in the standard care arm will be seen every 6 months. If the patient is deemed to be cirrhotic on clinical criteria (by examination, on the basis of laboratory tests (other than ELF) or through imaging), the patient will have been deemed to have cirrhosis and cirrhosis management will commence.

12.5 BIOBANK SAMPLE

For all randomised patients who consent to take part in the translational research aspect of the trial, a serum sample will be obtained, processed, stored, and sent to the central repository as detailed in the Site Specific Operations Document. Note no DNA sampling will be done on the biobanked samples from this trial.

Additional translational research investigations will form a separate, optional research protocol.

13 PROTOCOL FOR MANAGEMENT OF PATIENTS DIAGNOSED WITH CIRRHOSIS

The aim of the ELUCIDATE trial is to evaluate the effect of early instigation of prophylactic and therapeutic strategies for the management of complications of cirrhosis of the liver. Susceptible patients are randomised to be screened for cirrhosis using the ELF test or to routine care.

All patients diagnosed as cirrhotic either by ELF or clinical means should attend an initial post-cirrhotic follow up visit, at 3 months after the diagnosis of cirrhosis. All subsequent follow-up visits for the purposes of data collection should take place every 6 months.

Once cirrhosis is diagnosed it is important that all patients at a site are managed according to standardised protocols that are documented and used for all patients enrolled at a given centre. It is recognised that different centres may choose to use their established protocols and this is permitted in ELUCIDATE provided that these local protocols are documented and adhered

to for all study participants and include as a minimum the investigations listed below.

Management of cirrhosis should as a minimum include:

- Ultrasound scanning (see sections 13.1.3 and 14.4 for details and timings)
- Oesophagogastroduodenoscopys (OGD) ,(see sections 13.1.1 and 14.4 for details and timing),
- Measurement of AFP levels (see section 13.1.3 and 14.4 for details and timing).

Should a study site not have established protocols, or if the study site prefers to use protocols recommended by the ELUCIDATE team, the following recommendations are based on appraisal of national and international guidelines. Wherever possible all trial sites should adhere to the protocols for the management of varices, ascites, and HCC as described below.

13.1.1 Portal Hypertension

All patients with diagnosis of cirrhosis should have an oesophagogastroduodenoscopy (OGD) as screening for varices within 3 months of diagnosis as defined by an ELF score ≥ 9.5 or by clinical criteria, unless they have had an OGD in the last 18 months prior to the diagnosis of cirrhosis.

Timing of initial oesophagogastroduodenoscopy (OGD) following a diagnosis of cirrhosis:

- If the patient underwent OGD within 18 months prior to being diagnosed as cirrhotic, the next OGD should be performed **within 18 months of the previous OGD** unless clinically indicated sooner.
- If the patient did not have an OGD within 18 months prior to being diagnosed as cirrhotic, they should undergo OGD screening for oesophageal varices **within 3 months** of diagnosis of cirrhosis.

Timing of subsequent OGDs after a diagnosis of cirrhosis:

- If the previous OGD did not identify oesophageal varices, subsequent OGDs should be repeated **every 18 months from the previous OGD.**.
- If small oesophageal varices at OGD are identified, OGDs should be repeated **every 6 months** to look for variceal progression.
- For large oesophageal varices currently being treated, the timing of subsequent OGDs can be dictated by local guidance.

<u>Primary prophylaxis for oesophageal varices</u>

- moderate or large oesophageal varices should be banded as primary prophylaxis
- banding should be repeated until the varices are obliterated with banding at weekly visits
- alternatively patients can be treated with non-cardioselective beta-blockers

Secondary prophylaxis for oesophageal varices

- bleeding oesophageal varices should be obliterated with banding at weekly visits
- in addition to band ligation, patients should be considered for treatment with beta-blockers unless contraindicated

13.1.2 Prophylaxis of Spontaneous Bacterial Peritonitis

All patients with ascites should be prescribed Norfloxacin 400mg *od* unless contraindicated. Norfloxacin can be substituted with an alternative antibiotic as per agreed local protocol.

13.1.3 For Hepatocellular Cancer (HCC)

All patients diagnosed with cirrhosis should have alpha-fetoprotein (AFP) measured and an ultrasound scan (USS) performed as detailed below, for HCC screening.

Timing of initial scan following a diagnosis of cirrhosis:

- If the patient underwent an USS within 6 months prior to being diagnosed as cirrhotic, the next USS should be performed **within 6 months of the previous scan** unless clinically indicated sooner.
- If the patient did not have an USS within 6 months prior to being diagnosed as cirrhotic, they should undergo USS as screening for HCC **within** 3 monthsof diagnosis of cirrhosis.

Timing of subsequent scans after a diagnosis of cirrhosis:

- If the previous USS did not identify any lesions and the patient's AFP level remains stable, subsequent scans should be repeated **every 6 months from the timing of the previous scan**.

Timing of initial AFP test following a diagnosis of cirrhosis:

- If the patient had an AFP test within 6 months prior to being diagnosed as cirrhotic, the next AFP measurement should be performed **within 6 months of the previous test** unless clinically indicated sooner.
- If the patient did not have an AFP test within 6 months prior to being diagnosed as cirrhotic, they should undergo an AFP test **within 3 months** of diagnosis of cirrhosis.

Timing of subsequent AFP tests after a diagnosis of cirrhosis:

- The AFP test should be repeated **every 6 months from the previous test**.

Any space occupying lesions, equivocal USS or rising AFP in the absence of a lesion on ultrasound should be followed by triple phase CT and/or MRI scans.

Suspected HCC should be managed according to local, national, and international guidelines and the management should be documented in the patient's CRFs.

Patients should be considered for liver transplantation if they have:

- a solitary lesion measuring less than 5 cm in diameter or
- 3 lesions measuring less than 3 cm in diameter
- no evidence of extrahepatic manifestations,
- no evidence of vascular invasion.

All other patients should be considered for therapeutic interventions as per local protocols.

14 ASSESSMENTS & DATA COLLECTION

Trial data will be recorded by research staff on Case Report Forms (CRFs) and submitted to the CTRU at the address given in the Investigator Site File. Details on the schedule of CRFs, data to be collected, and guidance on the completion of CRFs will be given to individual sites when approval to participate in the trial is obtained.

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File) which will be provided by CTRU, and keep copies of all completed CRFs for the trial.

A tabulated summary of all local and central assessments is provided in Tables 2-5.

ELUCIDATE is a pragmatic trial enrolling patients with known chronic liver disease who will undergo a number of tests as part of their routine care. It is important that the results of these routine tests are recorded on the CRFs. In addition, patients will be asked to provide blood samples for non-invasive assessment of liver fibrosis (ELF tests) that are additional to routine care, form part of the protocol and are fully funded by the research grant.

Addresses to which the samples should be sent and procedures are provided in the Site Specific Operations Document and the inside of the back cover.

Where applicable (e.g. copies of laboratory reports), *it is the responsibility of staff at research sites to obliterate all personal identifiable data on any hospital reports, letters, etc. prior to sending to the CTRU*. Such records should only include trial number, initials, and date of birth to identify the patient.

REGISTRATION VISIT

Table 2 details information to be recorded at registration. The baseline data must have been collected in the month prior to registration or at the registration visit as follows (note ELF test must be performed at the registration visit):

- Physical examination
- Demographics
- Medical history (including details of concomitant disease)
- ELF test
- Health questionnaires (EQ-5D™ and SF-12v2™)* – patients to self-complete at the visit

Table 2. Assessments to be performed at Registration.
X = compulsory.

Assessment	Registration
History	X
Exam	X
EQ-5D™/SF12v2™	X
ELF	X

14.1 RANDOMISATION VISIT

Table 3 details randomisation visit assessments. The randomisation visit should occur as soon as possible following receipt of the test results from the registration visit (including ELF testing) and preferably within 6 weeks after the registration visit, but up to 12 weeks is permissible. However, if there is likely to be a delay in excess of 6 weeks please contact the CTRU to discuss. Patients should be asked to arrive fasted for their randomisation visit – it is important that patients are not told their randomisation result until after they have completed the questionnaires. At this visit the patients will have another ELF sample taken and will repeat the health questionnaires. It should be noted that the results of this ELF test do not contribute to a patient's eligibility and are not considered as part of the randomisation process.

Table 3. Assessments to be performed at Randomisation.
W = only to be taken from patients who have consented to take part in the optional Leeds NIHR Biomarker Biobank, **X** = compulsory, **Y** = test result required but any test result irrespective of date of test is acceptable (please record date), **Z** = none of these tests are required as part of the ELUCIDATE protocol but if tests are performed as part of routine care please record findings and date of test (in the case of USS, CT or MRI please record information obtained at any point between the 12 months preceding registration and the randomisation visit). Note that none of the tests labelled Z need to be performed as part of the ELUCIDATE protocol.

Assessment	Randomisation
Physical exam/history	X
GP letter	X
Biobank Sample	W
EQ-5D™/SF12v2™ and Health Usage Questionnaire	X
ELF	X
LFTs	X
FBC	X
INR	X
Glucose	X
HOMA-IR	Z
AIP/Igs	Y
HBV/HCV Serology/treatment	Y
HIV treatment	Y
Ferritin/Fe Sat	Y
HFE	Z
AFP	X
USS	Z
CT	Z
MRI	Z
Liver biopsy	Z
OGD	Z
Fibroscan	Z

14.2 POST-RANDOMISATION FOLLOW-UP ASSESSMENTS

Patients will be followed up at 6-monthly intervals post-randomisation for 30 months (five follow-up visits; Table 4, over page). Variation of plus or minus one month around the visit due date is permitted. See section 14.3 for the follow-up schedule after a diagnosis of cirrhosis.

14.2.1 Follow-up assessments

At each follow up visit all patients will undergo:

- Physical examination (weight, vital signs)
- Medical history (including details of concomitant disease and medication)
- Blood tests (simple LFTs, Platelets, Albumin, and clotting)

- Health questionnaires (EQ-5D™ SF-12v2™ and Health Usage Questionnaire)- patients to self complete at visit

14.2.2 Follow-up ELF testing for patients randomised to ELF test arm

Patients randomised to the follow-up arm with ELF testing will also undergo blood sample collection at each follow-up visit. The sample will be forwarded to the central laboratory for analysis.

As with all samples (except those taken at randomisation) patients should be requested to refrain from eating a large meal in the 2 hours prior to providing the sample. (please see section 10.1).

Table 4. Assessments to be performed at Follow-up prior to diagnosis of cirrhosis.
X = compulsory, **Z** = none of these tests are required as part of the ELUCIDATE protocol but if tests are performed as part of routine care please record findings and date of test, **E** = only for patients randomised to monitoring with ELF. Note that should the patient be diagnosed as cirrhotic within the monitoring period (by ELF or clinical means), they should move to the follow-up schedule described in section 14.4 and Table 5 (every 3 months rather than every 6 months).

Assessment	Month				
	6	12	18	24	30
History	X	X	X	X	X
Exam	X	X	X	X	X
EQ-5D™/SF12v2™and Health Usage Questionnaire	X	X	X	X	X
ELF	E	E	E	E	E
LFTs	X	X	X	X	X
FBC	X	X	X	X	X
INR	X	X	X	X	X
AFP	Z	Z	Z	Z	Z
USS	Z	Z	Z	Z	Z
CT	Z	Z	Z	Z	Z
MRI	Z	Z	Z	Z	Z
Liver biopsy	Z	Z	Z	Z	Z
OGD	Z	Z	Z	Z	Z
Fibroscan	Z	Z	Z	Z	Z
HBV/HCV Serology/treatment	**Z**	**Z**	**Z**	**Z**	**Z**
HIV treatment	**Z**	**Z**	**Z**	**Z**	**Z**

14.3 FOLLOW-UP FOR PATIENTS AFTER DIAGNOSIS OF CIRRHOSIS

Following ELF or clinical diagnosis of cirrhosis, an authorised member of the research team at site should complete a Cirrhosis CRF and ensure that this is forwarded by fax to the CTRU within 7 days of diagnosis.

Subsequent to diagnosis, patients should attend an initial follow-up assessment at 3 months post diagnosis. All subsequent follow-up visits

should take place every 6 months. , Assessments to be performed are listed in Table 5 (over page). As per the pre-cirrhosis follow up visits a variation of plus or minus one month around the visit due date is permitted.

It is important to note that an individual patient may experience multiple episodes of liver related complications such as bacterial peritonitis, variceal haemorrhage or encephalopathy. Following on from a liver related complication, follow-up should continue on a 6-monthly schedule. If however, patients undergo liver transplantation, further 6 monthly follow-up will cease.

Table 5. Assessments to be performed at Follow-up for patients diagnosed with cirrhosis.

X = compulsory, **Z** = none of these tests are required as part of the ELUCIDATE protocol but if tests are performed as part of routine care please record findings and date of test. **R** = following *confirmed* clinical diagnosis of cirrhosis (according to clinical/biochemical/imaging criteria) patients randomised to the Routine Clinical Monitoring only arm should also have a single ELF test performed as soon after clinical diagnosis is confirmed and has been recorded in patient's notes. Patients should be requested to refrain from eating a large meal in the 2 hours prior to providing the sample. (Please see section 10.1).

Assessment	Months from diagnosis of cirrhosis					
	0	3	9	15	21	27
History	X	X	X	X	X	X
Exam	X	X	X	X	X	X
ELF	R					
EQ-5D™/SF12v2™ and Health Usage Questionnaire	X	X	X	X	X	X
LFTs	X	X	X	X	X	X
FBC	X	X	X	X	X	X
INR	X	X	X	X	X	X
Glucose	X					
HOMA-IR	Z					
Liver biopsy	Z	Z	Z	Z	Z	Z
Fibroscan	Z		Z		Z	
AFP, USS, CT, MRI, OGD	SEE SECTION 14.3.1					

14.3.1 Compulsory scheduled assessments for the management of liver related complications.

OGD Timing

Timing of initial oesophagogastroduodenoscopy (OGD) following a diagnosis of cirrhosis:

- If the patient underwent OGD within 18 months prior to being diagnosed as cirrhotic, the next OGD should be performed **within 18 months of the previous OGD** unless clinically indicated sooner.
- If the patient did not have an OGD within 18 months prior to being diagnosed as cirrhotic, they should undergo OGD screening for oesophageal varices **within 3 months** of diagnosis of cirrhosis.

Timing of subsequent OGDs after a diagnosis of cirrhosis:

- If the previous OGD did not identify oesophageal varices, subsequent OGDs should be repeated **every 18 months from the previous OGD.**.
- If small oesophageal varices at OGD are identified, OGDs should be repeated **every 6 months** to look for variceal progression.
- For large oesophageal varices currently being treated, the timing of subsequent OGDs can be dictated by local guidance.

Ultrasound scans/CT scan and AFP timing

Timing of initial scan following a diagnosis of cirrhosis:

- If the patient underwent an USS within 6 months prior to being diagnosed as cirrhotic, the next USS should be performed **within 6 months of the previous scan** unless clinically indicated sooner.
- If the patient did not have an USS within 6 months prior to being diagnosed as cirrhotic, they should undergo USS as screening for HCC **within 3 months** of diagnosis of cirrhosis.

Timing of subsequent scans after a diagnosis of cirrhosis:

- If the previous USS did not identify any lesions and the patient's AFP level remains stable, subsequent scans should be repeated **every 6 months from the timing of the previous scan**.

Timing of initial AFP test following a diagnosis of cirrhosis:

- If the patient had an AFP test within 6 months prior to being diagnosed as cirrhotic, the next AFP measurement should be performed **within 6 months of the previous test** unless clinically indicated sooner.
- If the patient did not have an AFP test within 6 months prior to being diagnosed as cirrhotic, they should undergo an AFP test **within 3 months** of diagnosis of cirrhosis.

Timing of subsequent AFP tests after a diagnosis of cirrhosis:

- The AFP test should be repeated **every 6 months from the previous test**.

14.4 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date the last participant's last data item is collected..

14.5 CESSATION OF FOLLOW-UP

Cessation of follow-up should only occur under the following circumstances:

- Patient has completed the final follow-up visit at 30 months post-randomisation
- Patient undergoes liver transplantation
- Patient has an episode of severe encephalopathy of (Westhaven criteria 3-4) or otherwise loses capacity to consent
- Patient dies
- Patient withdraws from trial

14.6 PREGNANCIES

All pregnancies and suspected pregnancies must be reported immediately to the CTRU Trial Manager/Coordinator. If pregnancy is confirmed, patients should continue follow-up assessment if possible, however, no trial-specific interventions (i.e. ELF testing) should be performed.

14.7 QUALITATIVE SUB-STUDY

Patient understandings of clinical biomarkers and experiences of testing, their acceptability to the patients, their perceived utility and patient experiences and motivations for testing are important factors of translation of biomarkers into clinical practices. As such, qualitative research will be performed in a small sample of participants in this study, consisting of in-depth semi-structured interviews which will last on average of an hour. This qualitative work will form a separate protocol and will obtain separate ethical approval to the main trial.

15 SERIOUS ADVERSE EVENTS PROCEDURES

15.1 GENERAL DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this trial intervention and can include;

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

In addition the following criteria may be used in order to collect protocol-defined reportable adverse events which do not meet the criteria for serious (below):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

A Serious Adverse Event (SAE) is defined in general as “any untoward medical occurrence or effect that:

- results in death,
- is life-threatening*,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- consists of a congenital anomaly or birth defect,
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

*the term life-threatening 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 was more severe.

A SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is Related and Unexpected will be reported to the main Research Ethics Committee (REC). The National Research Ethics Service (NRES) defines Related and Unexpected SAEs (RUSAEs) as follows:

- *Related*: that is, it resulted from administration of any research procedures; and
- *Unexpected*: that is, the type of event is not listed in the protocol as an expected occurrence.

15.2 STUDY DEFINITIONS

15.2.1 Expected AE/SAEs – Not Reportable

This is a trial investigating ELF as a monitoring tool in a patient population with high levels of morbidity and co-morbid diseases and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected.

For the purposes of this trial, adverse events related to the underlying disease under study or treatment for disease under study will be collected and recorded in the CRFs and followed as appropriate. These adverse events may include (but does not represent an exhaustive list):

- Varices with or without bleeding
- Ascites
- Spontaneous Bacterial Peritonitis
- Encephalopathy
- Liver cancer
- Alcohol injection of liver tumour
- Embolisation of liver tumour
- Chemo-embolisation of liver tumour
- Radiofrequency ablation of liver tumour
- Transplantation
- Cirrhosis
- Venepuncture injury (in ELF monitoring arm)

- Oesophogastroduodenoscopy complications (ruptured varices, perforated oesophagus)
- Complications of treatment for portal hypertension (requiring intervention including bradycardia, cardiac arrest, collapse related to beta blocker treatment)
- Complications of management of HCC (imaging adverse events e.g. contract reaction)

In recognition of this, events fulfilling the definition of an adverse event or serious adverse events will not be reportable in this study unless they are classified as 'related' to trial procedures.

15.2.2 Related and Unexpected SAEs – Expedited Reporting

All Related and Unexpected SAEs occurring from the date of consent up to 30 months post randomisation must be recorded on the Related & Unexpected Serious Adverse Event Form and faxed to the CTRU within 24 hours of the trial team becoming aware of the event. The original form should also be posted to the CTRU in real time and a copy retained on site.

For each study Related & Unexpected SAE the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected

Any follow-up information should be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All Related & Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor and the main REC by the CTRU on behalf of the Chief Investigator within 15 days.

15.3 RESPONSIBILITIES

15.3.1 Principal Investigator/Authorised Individual at local site

1) Checking for SAEs when patients attend for treatment/follow-up
2) Judgement in assessing:
    - Seriousness
    - Causality
    - Expectedness
3) To ensure all Related & Unexpected SAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow-up information as soon as available
4) To report Related & Unexpected SAEs to local committees in line with local arrangements.

15.3.2 Chief Investigator

1) Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment
2) Undertake SAE review
3) Review all events assessed as Related & Unexpected in the opinion of the local investigator. In the event of disagreement between the local assessment and the Chief Investigator or Co-Chief Investigators, local assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the main REC.
4) Review annual/periodic safety reports as required.

15.3.3 CTRU

1) Expedited reporting of Related & Unexpected SAEs to the main REC and Sponsor within required timelines
2) Preparing annual safety reports to the main REC and periodic safety reports to the Project Team.
3) Notifying Investigators of Related & Unexpected SAEs which compromise patient safety.

15.3.4 Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

15.3.5 Data Monitoring and Ethics Committee (DMEC)

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

16 ECONOMIC EVALUATION

16.1 WITHIN-TRIAL ECONOMIC EVALUATION

The economic evaluation will compare the observed costs and outcomes of the cohort of patients randomised to ELF guided detection and management with those of a cohort of patients randomised to standard care. The perspective of the analysis will be that of the NHS and Personal Social Services.

The primary outcome measure for the within trial economic evaluation is the Quality Adjusted Life Years. Quality of Life weights will be calculated using the EQ-5D™ algorithm[37]. Life years lived will be obtained from the mortality data collected within the clinical trial at the end of 30 months follow-up.

The primary analysis will consider all direct NHS and Social Care costs incurred by patients randomised to ELF guided detection and management or standard care. Health and social care resource utilisation will be identified using a simple questionnaire completed by the study participants at randomisation and follow-up visits.

Costs and outcomes will be discounted at 3.5% per annum. All costs will be indexed to the trial start year (2009) using the NHS Pay and Prices Index.

The primary result of the economic evaluation will be the incremental cost effectiveness ratio of ELF guided detection and management vs. standard care (ICER). This will be calculated as the difference in the mean cost of the interventions divided by the difference in the mean outcomes.

Parameter uncertainty will be examined using a non-parametric bootstrap simulation[38].

Results of the probabilistic sensitivity analysis will be presented as the expected incremental cost effectiveness ratio; a scatter plot on the cost effectiveness plane and as a cost effectiveness acceptability curve (CEAC). The Expected Net Benefit of ELF guided detection and management will be calculated for a range of values of lambda, including £5,000, £15,000, £20,000 and £30,000; reflecting the work of Martin and colleagues[39].

16.2 SECONDARY WITHIN-TRIAL ECONOMIC EVALUATION

The secondary within-trial economic evaluation will substitute SF-12v2™ quality of life weights for the EQ-5D™ quality of life weights used in the primary analysis. In all other regards the secondary within-trial economic evaluation will be identical to the primary within-trial economic evaluation.

16.3 LONG TERM ECONOMIC EVALUATION

The clinical trial outcome and resource utilisation data will be used to update the parameters of the pre-existing life time horizon cost effectiveness model. The model will then be used to calculate the expected incremental cost effectiveness ratio ELF guided detection and management, using a lifetime horizon.

Perspective and discounting will be consistent with the methods of primary within trial analysis.

Parameter uncertainty will be examined using Monte Carlo simulation. Results of the probabilistic sensitivity analysis (PSA) will be presented as the expected incremental cost effectiveness ratio; a scatter plot on the cost effectiveness plane and as a cost effectiveness acceptability curve (CEAC). The Expected Net Benefit of ELF guided detection and management will be calculated for a range of values of lambda, including £5,000, £15,000, £20,000 and £30,000; reflecting the work of Martin and colleagues[39].

16.4 RESPONSIBILITIES

The management and quality assurance of the health related quality of life and resource utilisation data will be the responsibility of the CTRU.

Implementation of the planned economic analyses will be the responsibility of the Lead Health Economics investigator, Professor Christopher McCabe, of the Academic Unit of Health Economics, University of Leeds.

17 ENDPOINTS

17.1 PRIMARY ENDPOINT

- Time from randomisation to occurrence of first severe complication

Severe complications are defined by:

1. Variceal haemorrhage confirmed by one of the following:
   a) visualisation through endoscopy
   b) imaging
   c) post-mortem

2. Spontaneous bacterial peritonitis:
   Ascites confirmed by:
   a) Imaging and/or
   b) aspiration
   and infection confirmed by:
   a) microscopy and/or
   b) culture

3. Hepatocellular cancer (HCC) beyond the Milan criteria*.[40, 41]
   N.B. For the purposes of the trial cases of HCC falling within the Milan criteria are not regarded as endpoints as they are regarded as treatable.

4. Encephalopathy - grade 3 or 4 defined using the Westhaven criteria (Appendix 1) [42].

5. Liver-related mortality. Any of the following:

   a) Any mention of liver disease in part one of the death certificate
   b) death due to hepatocellular cancer (HCC)
   c) death due to liver failure
   d) death due to bleeding from portal hypertension
   e) death due to hepato-renal syndrome
   f) death due to sepsis occurring as a result of chronic liver disease
   g) death due to spontaneous bacterial peritonitis
   h) death due to encephalopathy

17.2 SECONDARY ENDPOINTS

- Time from diagnosis of cirrhosis (by ELF or clinical means) to incidence of first severe complication

* Milan criteria: One lesion less than 5cm, up to 3 lesions smaller than 3cm, no extrahepatic manifestations, no vascular invasion.

- Time from randomisation to diagnosis of cirrhosis by ELF or clinical means (to allow instigation of prophylaxis and screening)

- Process outcomes, namely:
  - treatment with beta-blockers/band ligation (BB/BL) of varices
  - use of endoscopy and ultrasound/AFP tests
  - treatment to normalise LFTs in patients with Hepatitis B and Hepatitis C.

- Detection and timing of complications following cirrhosis, including:
  - Detection of small varices
  - Detection of large varices
  - Incidence of treatable hepatocellular cancer (HCC)

- All causes of mortality

- Specific liver-related morbidity

- Economic evaluation of the ELF test in the early detection of cirrhosis and as such in the initiation of measures to reduce the incidence of severe complications following cirrhosis.

- Quality of Life (QoL)

- Proportion of non-randomised patients (ELF < 8.4) who go on to develop cirrhosis (diagnosed by clinical means) within the follow-up period.

17.3 STUDY DEFINITIONS

- Small varices are defined as varices that flatten with insufflations or minimally protrude into the oesophageal lumen[42]

- Large varices are defined as varices that protrude into the oesophageal lumen and touch each other (presence or confluence), or that fill at least 50% of the oesophageal lumen[42].

- Hepatocellular cancer classifications will follow standard guidelines[21,40]

18 STATISTICAL CONSIDERATIONS

18.1 SAMPLE SIZE

The RCT is testing the hypothesis that if we monitor patients with chronic liver disease using the ELF score, we will detect liver cirrhosis earlier, and as a result there will be fewer severe complications as well as improvements in other important patient outcomes. We are therefore aiming to show that the incidence of severe complications following cirrhosis is less in the ELF arm.

It was anticipated that the trial would recruit over 24 months with an additional 30 months follow up, and with an additional 39 months long-term follow-up for the primary endpoint of time from randomisation to incidence of first severe complication (taking us to 5 years after the end of the programme grant). Previous studies[43] have led us to anticipate that in the standard arm, at 36 months, in patients with an ELF ≥ 9.5, we will observe severe complications of the order of 3% variceal bleeds, 10% liver decompensation, 1.5% requirement for liver transplantation, 7.5% liver related mortality giving a 22% incidence of potentially preventable undesirable clinical endpoints at 36 months in these patients.

Previous data[9] has illustrated that approximately 20% of patients will have varices suitable for therapy. Such therapy has a large effect on the progression of these varices (for instance a reduction from 37% progressing to 11%); on the risk of bleeding from these varices (reduced from 30% to 14% in patients with medium to large varices); and on mortality at 36 months (reduced from 7% to 2% over 24 months[9]). Based on this prior data we hypothesise that we could reduce the incidence of the undesirable clinical endpoints of cirrhosis by 40% in the ELF arm.

Eighty out of the first 225 (37%) patients have presented with an ELF >9.49. We are aiming to recruit 500 patients per arm, so we would expect 185 control arm patients to have an ELF >9.49. With a 22% incidence rate of severe complications at 36 months, 24 months of recruitment and 30 months of follow up the expected number of events in these 185 patients can be calculated, using the method described by Collett[44] for sample size estimates based on exponential survival distributions (more details of which can be seen in the SAP). This produces an estimate of 46.4 events in these 185 control arm patients. We would also expect approximately 10% of the remaining 315 control arm patients to progress to cirrhosis on clinical grounds and to subsequently have a similar probability of then developing severe complications. This adds another 5.1 estimated events from this group, giving a total of approximately 52 estimated events in the control arm. We expect to reduce this number by 40% in the ELF arm, giving a total number of estimated events in this arm of 31. The median survival times, assuming negative exponential survival distributions, that would produce these numbers of events for the control and ELF arms with 24 months of recruitment and 30 months of follow up are 22.5 and 39.1 years, respectively. These figures can be used to calculate the power to detect such an effect size, which, with a type I error rate of 5%, gives a figure of 70%. However, if follow-up is continued until five years beyond the end of the programme grant, i.e. 69 months of follow-up rather than 30, the power to detect this effect size increases to just over 90%.

To calculate the power, with these 1000 patients, to detect a difference in the secondary endpoint of numbers of patients encountering severe complications subsequent to being detected with cirrhosis, we also need to estimate the numbers of patients developing cirrhosis in the two arms. We expect approximately 10% of the 315 patients with an ELF score between 8.4 and

9.49 to develop cirrhosis during the 24 months of recruitment and 36 months of follow-up, which when added to the 185 patients who present with cirrhosis in this arm through having an ELF >9.49 gives a total of 216 patients developing cirrhosis in the ELF arm. In the control arm we expect 185 patients to have an ELF >9.49 and we expect approximately 46 of these to develop severe complications after 24 months of recruitment and 36 months of follow-up and therefore be diagnosed as cirrhotic at that point. We expect a further one third of these 185 patients to be diagnosed as cirrhotic on clinical grounds which adds another 62 patients. In addition we estimate that approximately 10% of the 315 patients with an ELF score between 8.4 and 9.49 will progress to cirrhosis on clinical grounds. This gives a total of 139 patients developing cirrhosis in the control arm. Therefore we are expecting approximately 31/216 patients encountering severe complications in the ELF arm subsequent to development of cirrhosis compared with approximately 52/139 in the control arm, after 24 months of recruitment and 36 months of follow-up. With a type I error rate of 5% we would have >99% power to detect this difference in this secondary endpoint.

The trial as its original size was thus well powered (at least 90% for the primary endpoint from randomisation with an additional 5 years of follow-up) to show that this ELF monitoring policy will be of real clinical benefit.

Following the recommendation by the funding body to close the trial to recruitment, it is anticipated that by the time the resulting protocol amendment is approved and implemented, approximately 700 patients will have been randomised. Based on this, and with follow-up continuing until July 2014, the trial will have adequate statistical power to report on changes in the process of the care which are critical to the prevention of gastro intestinal haemorrhage and Hepatocellular Carcinoma (HCC) in patients with chronic liver disease who are monitored using the ELF test.

The first process of care would be the use of beta-blockers/band ligation (BB/BL) of varices to prevent haemorrhage. The ELUCIDATE trial will not report the major liver events and survival within the period of the Programme. However, recruitment as planned will be sufficient for these analyses if the patients are followed for a further five years and additional funding is being sought to complete this work.

Power calculations are based on our hepatology estimates of the identification of large varices in cirrhotic patients and the expected identification of cirrhotic patients in the ELF and control arms. Once identified as cirrhotic, approximately 10% of patients are predicted to be treated with beta-blockers/band ligation (BB/BL) of varices.

In the ELF arm, current estimates suggest 40% of patients will be diagnosed with cirrhosis initially, and 10% diagnosed during follow up to July 2014. Therefore in this total of 50% of patients, we would predict the use of BB/BL in 1 in 10, i.e. 5% of the total. In the control arm, conservatively we predict the clinical diagnosis of cirrhosis to be made in under 10% of the patients by July 2014: therefore 1% of the total would receive BB/BL. Based on the

assumption of 700 patients randomised at the end of the recruitment period and follow up until July 2014, power is 86%. We will have approximately 40% power for this endpoint at the interim analysis in summer 2013. Similarly with the additional follow up until July 2014, we will have good power to show changes in the frequency of endoscopy and ultrasound/AFP's to detect HCC at a surgically curable stage and also to detect changes in Liver Function Tests (LFT's) in patients with Hepatitis B and Hepatitis C. The power to detect changes in the frequency of endoscopy and ultrasound/AFP's should be very good (>90%) at the interim analysis in summer 2013, and the power to detect changes in LFTs should be of the order of 60% for Hepatitis B patients and 90% for Hepatitis C patients.

As previously mentioned we will also have enough patients to have good statistical power (approximately 80%) after five years further follow up for the detection of changes in the primary endpoints of the existing trial which are major liver events and survival. These endpoints will only be delivered with long follow up of five years. This will capture major liver events and long term consequences of ELF testing, survival and health economics.

The detailed information collected within the Programme and the impact of ELF on the process of care will provide detailed information that will be essential in the interpretation of the long follow up and the impact of ELF testing on major liver events and survival.

18.2 PLANNED RECRUITMENT RATE

We aimed to randomise up to 1000 patients within 24 months of recruitment. The power for the primary endpoint of time to occurrence of liver related outcomes from randomisation is sufficiently great that we will still be very well powered even if there is a substantial drop out rate of as high as 15%-20%. The recruitment target is approximately 42 patients per month. In order to randomise 1000 patients into the trial, it is estimated from previous research[36] that approximately 2160 patients will have to be registered to undergo screening with the ELF test (to have 1000 patients meet the randomisation inclusion criteria of ELF ≥ 8.4).

Following the recommendation by the funding body to close the trial to recruitment, it is anticipated that by the time the resulting protocol amendment is approved and implemented, approximately 700 patients will have been randomised.

19 STATISTICAL ANALYSIS

The statistical analysis plan is the responsibility of the CTRU Study Statistician. The analysis plan outlined in this section is detailed further in the statistical analysis plan and will be reviewed before the final analysis is undertaken. The analysis plan will be written in accordance with current CTRU Standard Operating Procedures (SOPs) and will be finalised and agreed by the following people: the Study Statistician, the Supervising Statistician, the Chief Investigator, the CTRU Principal Investigator, and the

Senior Trial Coordinator. Any changes to the finalised analysis plan, and reasons for the changes, will be well documented.

19.1 FREQUENCY OF ANALYSIS

Interim reports will be presented to the Data Monitoring and Ethics Committee (DMEC) in strict confidence at approximately yearly intervals or as soon as sufficient data have been accrued to make them meaningful. A single formal interim analysis is planned on the primary endpoint at a time when approximately half the number of expected events will have occurred, estimated to be approximately summer 2013, roughly 27 months after the start of recruitment to version 5.0 of the protocol. This interim analysis will include the new process outcomes, where we anticipate we will have sufficient information for an informative analysis at this time. The DMEC, in the light of the interim reports and of any advice or evidence they wish to request, will if necessary report to the Trial Steering Committee (TSC) if there are concerns regarding the safety or efficacy of either of the study treatment policies.

Apart from the interim analysis to the DMEC in summer 2013, no other formal analyses are planned until 6 months prior to the end of the revised 6 years of the Programme Grant, in July 2014, close to 3 years of recruitment and follow-up. Analyses after the 6 year timescale of the Programme Grant will be considered by the TSC at a later stage, and include the final analysis of time from randomisation to incidence of first severe complication at the end of the additional 5 years of follow up.

19.2 STATISTICAL ANALYSIS POPULATIONS

All analyses will be conducted on the intention-to-treat (ITT) population and carried out at a 2-sided 5% level of significance. The ITT population is defined as all patients randomised to treatment regardless of non-compliance, loss to follow-up, or death.

The secondary endpoint analysis, incidence of cirrhosis in non-randomised patients, will be conducted on follow-up data from those patients who registered and consented to the trial, but who were not randomised due to having an ELF score of < 8.4 (see section 6.3).

Attempts will be made to retrieve missing data via a thorough data cleaning process.

19.2.1 Primary endpoint analysis

Incidence and timing of severe complications of cirrhosis will be calculated from the date of randomisation to the occurrence of the first event (severe complication). Cirrhosis is diagnosed either by, having an ELF score ≥ **9.5** in the ELF arm or in the control arm, via standard methods. An ‘event’ encompasses variceal haemorrhages, spontaneous bacterial peritonitis, unresectable hepatocellular cancer, encephalopathy (grade 3 or 4) and liver

related mortality. Cox regression analysis, adjusting for the minimisation factors (see section 12.2), will be used to compare the differences between the control and ELF arm. Overall survival curves will be calculated using the Kaplan-Meier method, hazard ratios and corresponding 95% confidence intervals will be presented.

19.2.2 Secondary endpoint analysis

Incidence and timing of severe complications of cirrhosis from the date of diagnosis of cirrhosis (in clinic, date of clinic visit or blood sample) will be analysed using Cox regression analysis, adjusting for the minimisation factors (see section 12.2), and will be used to compare the differences between the control and ELF arm. Overall survival curves will be calculated using the Kaplan-Meier method, hazard ratios and corresponding 95% confidence intervals will be presented.

Timing to diagnosis of cirrhosis will be calculated from date of randomisation to the date the patient is diagnosed as having cirrhosis (in clinic) either by, in the ELF arm, having an ELF score ≥ 9.5 or in the control arm, via standard methods. Cox regression analysis, adjusting for the minimisation factors (see section 12.2), will be used to compare the differences between the survival curves, which will be calculated using the Kaplan-Meier method. Hazard ratios and corresponding 95% confidence intervals will be presented.

Detection and timing of complications of cirrhosis will be calculated from the date of diagnosis of cirrhosis, to the detection of the first event. An ‘event’ in this instance encompasses small and large varices, treatable HCC and inoperable HCC. Cox regression analysis, adjusting for the minimisation factors, will be used to compare the differences between the survival curves. Overall survival curves will be calculated using the Kaplan-Meier method, hazard ratios and corresponding 95% confidence intervals will be presented.

Details of all causes of mortality will be collected and documented, specifically including the number of deaths and whether or not they are suspected to be related to any treatments/trial procedures. All liver-related mortalities will be summarised separately.

Details of the economic evaluation of the ELF test are given in Section 16.

For Quality of Life (QoL), we will look at the difference in expected quality-adjusted survival to final follow-up using the Cox proportional hazards model. We will examine the impact of missing data using a Multiple Imputation method.

The proportion of non-randomised patients (where ELF < 8.4 indicating minimal/mild liver fibrosis) who go on to develop cirrhosis during the follow-up period will be summarised in order to assess false-negative rates (see section 6.3).

20 DATA MONITORING

20.1 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will review the safety and ethics of the study. Detailed unblinded reports will be prepared by the CTRU for the DMEC at approximately 6-12 month intervals. The formal interim analysis on the primary endpoint and on the process of care outcomes will be reported to the DMEC in summer 2013, approximately 27 months after the start of recruitment.

The DMEC will be provided with detailed unblinded reports containing the following information:
- Rates of occurrence of SAEs (see section 14)

20.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of the consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG) if necessary.

20.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the Trial Steering Committee (TSC) and, where applicable, to individual NHS Trusts.

21 QUALITY ASSURANCE & ETHICAL CONSIDERATIONS

21.1 QUALITY ASSURANCE

The study will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, the NHS Research Governance Framework and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 and through adherence to CTRU Standard Operating Procedures (SOPs).

21.2 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the Declaration of Helsinki (recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964) in its latest form. Informed consent will be obtained from the patients

prior to registration/randomisation into the study. The right of a patient to refuse participation without giving reason must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (REC) and the appropriate Site Specific Assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms, and all other relevant study documentation.

22 CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from patients to record personal details including name, date of birth, postcode, NHS number and/or hospital number
- appropriate storage, restricted access, and disposal arrangements for patient personal and clinical details
- consent from patients for access to their healthcare records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from patients for the data collected for the trial to be used to evaluate safety and develop new research
- patient name, address, and telephone number will be collected when a patient is randomised into the trial but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth
- where central monitoring of source documents by the CTRU (or copies of source documents) is required (such as scans or local blood tests), the patient's name must be obliterated by site before sending
- where anonymisation of the documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to the CTRU

If a patient withdraws consent from further trial participation and/or further collection of data their samples will remain on file and will be included in the final study analysis.

22.1 ARCHIVING

At the end of the study, data will be securely archived at the CTRU for a minimum of 10 years. Site files will be archived by the participating NHS Trusts for 10 years and arrangements for confidential destruction will then be made.

23 STATEMENT OF INDEMNITY

The trial is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the trial. The NHS

has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

As this is a clinician-led study, there are no arrangements for no-fault compensation.

24 STUDY ORGANISATIONAL STRUCTURE

24.1 RESPONSIBILITIES

Chief Investigator - as defined by the NHS Research Governance Framework, is responsible for the design, management, and reporting of the study.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the study in accordance with the NHS Research Governance Framework and CTRU SOPs.

24.2 OPERATIONAL STRUCTURE

Co-Chief Investigators – The co-Chief Investigators are involved in the design, conduct, coordination, and management of the trial.

Trial Management Group (TMG) – The TMG, comprising the Chief Investigator, CTRU team, other key external members of staff involved in the trial and a nursing representative will be assigned to responsibility for the clinical set-up, ongoing management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for: protocol completion; Case Report Form (CRF) development; obtaining approval from the main Research Ethics Committee (REC) and supporting applications for Site Specific Assessments; completing cost estimates and project initiation; nominating members and facilitating the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC); reporting of Related & Unexpected Serious Adverse Events (RUSAEs); monitoring of screening, recruitment, adherence to protocol and follow-up procedures; auditing consent procedures, data collection, trial end-point validation, and database development.

Clinical Trials Research Unit (CTRU) – The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs including: registration/randomisation design and service; database development and provision; protocol development; CRF design; trial design; monitoring schedule; and statistical analysis for the trial. In addition, the CTRU will support main REC, Site Specific Assessment, and R&D submissions and clinical set-up, ongoing management including training, monitoring reports, and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, organising committee meetings, and all statistical analyses.

Trial Steering Committee (TSC) – The TSC, with an Independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety, and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

ELUCIDATE Clinical Team – The Clinical Research Fellow and Trial Co-ordinator will support the CTRU in site set-up and coordination including: liaising with site research staff and updating them on trial processes; organisation of training for site research staff, ensuring sites are able to comply with the study protocol; conducting site visits and source data verification; liaising with sites and central laboratories to ensure timely and appropriate collection and safe processing of biological samples; assisting with development and maintenance of trial documentation; and liaising with TMG, TSC, and DMEC and attending meetings as appropriate.

24.3 FUNDING

This study is funded as part of a National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-PG-0707-10101): *Evaluating the benefits for patients and the NHS of new and existing biological fluid biomarkers in liver and renal disease*.

25 PUBLICATION POLICY

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published

and that all these conditions must be met (www.icmje.org).

In light of this, relevant members of the Project Team will be named as authors in any publication. In addition, all collaborators will be acknowledged as contributors for the main study publication, giving details of roles in planning, conducting, and reporting the study.

To maintain the scientific integrity of the study, data will not be released prior to the first publication, either for study publication or oral presentation purposes, without the permission of the Chief Investigator. In addition,

individual collaborators must not publish data concerning their patients which is directly relevant to the questions posed in the study.

26 REFERENCES

1 Department of Health. On the State of the Public Health. Annual Report of the Chief Medical Officer. 2001. London. Department of Health.

2 Leon DA & McCambridge J. Liver cirrhosis mortality rates in Britain, 1950 to 2002. Lancet 2006; 367(9511):645.

3 Griffiths C, Rooney C & Brock A. Leading causes of death in England and Wales – how should we group causes? Health Statistics Quarterly 2005; 28:6-17.

4 Morgan TR, Mandayam S & Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S87-S96.

5 Bialecki ES & Bisceglie AM. Clinical presentation and natural course of hepatocellular carcinoma. European Journal of Gastroenterology & Hepatology 2005; 17(5):485-489.

6 D'Amico G, Pagliaro L & Bosch J. The treatment of portal hypertension. A meta-analytic review. Hepatology 1995; 22(1):332-354.

7 D'Amico G, Pagliaro L & Bosch J. Pharmacological treatment of portal hypertension: an evidence based approach. Seminars in Liver Disease 1999; 19(4):475-505.

8 Grangie, J-D, Roulot D, Pelletier G, Pariente E-A, Denis J, Ink O, Blanc P, Richardet JP, Vinel JP, Delisle F, Fischer D, Flahault A & Amiot X. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patient with ascites: a double-blind randomized trial. Journal of Hepatology 1998; 29(3):430-436.

9 Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, and the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, the Practice Parameters Committee of the American College of Gastroenterology. Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. Hepatology 2007; 46(3):922-938.

10 Zhang BH, Yang BH & Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. Journal of Cancer Research and Clinical Oncology 2004; 130(7):417-422.

11 Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC & Zhu YR. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. Journal of Medical Screening. 2003; 10(4):204-209.

12 Parikh S & Hyman D. Hepatocellular cancer: a guide for the internist. The American Journal of Medicine 2007; 120(3):194-202.

13 Ryder S. British Society of Gastroenterology guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003;52(Suppl III):iii1–iii8

14 Lo GH, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, Cheng JS & Lai KH. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. Gastrointestinal Endoscopy 2004; 59(3):333-338.

15 Schepke M, Kleber G, Nurnberg D, Willert J, Koch L, Veltzke-Schlieker W Hellerbrand C, Kuth, J, Schanz S, Kahl S, Fleig WE & Sauerbruch T. Ligation versus propanalol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology 2004; 40(1):65-72.

16 Lay CS, Tsai YT, Lee FY, Lai YL, Yu CJ, Chen CB & Peng CY. Journal of Gastroenterology and Hepatology 2006; 21(2):413-419.

17 Gines P, Quintero E & Arroyo V. Compensated cirrhosis: natural history and prognosis. Hepatology 1987; 7(1):122-128.

18 Orrego H, Israel Y, Blake JE & Medline A. Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. Hepatology 1983; 3(6):896-905.

19 Schlichting P, Christensen E, Andersen PK, Fauerholdt L, Juhl E, Poulsen H & Tygstrup N. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology 1983; 3(6):889-895.

20 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A & Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. New England Journal of Medicine 1996; 334(11):693-699.

21 Regalia E, Coppa J, Pulvirenti A, Romito R, Schiavo M, Burgoa L & Mazzaferro V. Liver transplantation for small hepatocellular carcinoma in cirrhosis: analysis of our experience. Transplantation Proceedings 2001; 33(1-2):1442-1444.

22 Llovet JM & Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. Journal of Hepatology 2008; 48(Suppl 1):S20-S37.

23 Kaplowitz N (1992). Liver and Biliary Diseases. Lippincott Williams and Wilkins, London.

24 Sanai FM, Benmousa A, Al-Hussaini H, Ashraf S, Alhafi O, Abdo AA, Alameri HF, Akbar HO & Bzezi KI. Is serum alanine transaminase level a reliable marker of histological disease in chronic hepatitis C infection? Liver International 2008; 28(7):1011-1018.

25 Goodman Z. Grading and staging systems for inflammation and fibrosis in chronic liver diseases, Journal of Hepatology 47 (2007) 598–607.

26 Cadranell JF, Rufat P & Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Associations of the Liver (AFEF). Hepatology 2000; 32(3):477-481.

27 Bedossa P, Dargere D & Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003; 38(6):1449-1457.

28 The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology 1994; 20(1):15-20.

29 Arena U, Vizzutti F, Gorti G, Ambu S, Stasi C, Bresci S, Moscarella S, Boddi V, Petrarca A, Laffi G, Marra F & Pinzani M. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008; 47(2):380-384.

30 Sagir A, Erhardt A, Schmitt M & Haussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008; 47(2):592-595.

31 Afdhal N & Nunes D. American Journal of Gastroenterology 2004; 99(6):1160-74

32 Parkes J, Guha IN, Roderick P, Rosenberg WM. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. Journal of Hepatology 2006; 44(3):462-474.

33 Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, Hubscher S, Roskams T, Pinzani M & Arthur M. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004; 127(6):1704-1713.

34 Parkes J, Bialek S, Bell B, Terrault, NA, Zaman A, Sofair AN, Manos MM, Guha IN, Cross R, Harris S, Roderick PJ & Rosenberg WM. European Liver fibrosis markers accurately distinguish fibrosis severity in a cohort of patients with Chronic Hepatitis C; an external validation study. Hepatology 44(Suppl 1): Abstract - The Liver Meeting: 57th Annual Meeting of the American Association for the Study of Liver Diseases 2006.

35 Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, Burt AD, Ryder SD, Aithal GP, Day CP & Rosenberg WM. Noninvasive markers of fibrosis in non-alcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple marker. Hepatology 2008; 47(2):455-460.

36 Parkes J, Roderick P, Harris S, Day C, Mutimer D, Collier J, Lombard M, Alexander G, Ramage J, Dusheiko G, Wheatley M, Gough C Burt A, Rosenberg W. Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. Gut 2010;59:1245e1251

37 Dolan P. Modeling valuations for EuroQol health states. Medical Care 1997; 35(11):1095–1108

38 Fenwick E, Claxton K & Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001; 10(8):779–787.

39 Martin S, Rice N & Smith PC. Does health care spending improve health outcomes? Evidence from English programme budgeting data. Journal of Health Economics 2008; 27(4):826-842

40 Ryder S, on behalf of the HCC management in the UK (HUG) writing committee. UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults. Gut *in press*. http://www.mccn.nhs.uk/userfiles/documents/04a%20HCC%20guidelines%20accepted%20version%20march%2009.pdf (accessed 24/11/09).

41. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl. J Med 1996;334:693-699.

42. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei A (2002). "Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998". Hepatology 35 (3): 716–.

43 Parkes J. Non invasive biomarkers in chronic liver disease. PhD thesis – submitted 26 February 2008. University of Southampton.

44 Collett D. (1994). Modelling Survival Data in Medical Research. Chapman and Hall, London.

45 Freedman LS. Tables of numbers of patients required in clinical trials using the logrank test. Statistics in Medicine 1982; 1(2):121-129.

27 GLOSSARY OF TERMS

AE	Adverse event
AFP	Alpha feto-protein
AIH	Autoimmune Hepatitis
AIP/Igs	Autoimmune profile/immunoglobulins
ALD	Alcoholic liver disease
ALT	Alanine transaminase
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibodies
AST	Aspartate transaminase
AUC	Area under curve
CCRN	Comprehensive Clinical Research Network
CEAC	Cost effectiveness acceptability curve
CHC	Chronic Hepatitis C
CLD	Chronic Liver Disease
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computed tomography
CTRU	Clinical Trials Research Unit (University of Leeds)
DDCC	H63D homozygotes
DMEC	Data Management and Ethics Committee
DNA	Deoxyribonucleic acid
ELF	Enhanced Liver Fibrosis
EQ-5D™	Health state questionnaire © 2009 EuroQol Group
ERCP	Endoscopic retrograde cholangiopancreatography
FBC	Full blood count
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HDCY	Compound heterozygotes for C282Y and H63D
HFE	Hemochromatosis gene
HHYY	C282Y homozygotes
HOMA-IR	Homeostatic model assessment – insulin resistance
ICER	Incremental cost effectiveness ratio
INR	International normalized ratio (prothrombin time)
ITT	Intention to treat
LFT	Liver Function Test
LKMA	anti-liver kidney microsome antibody
LLN	Lower limit of normal
M2	Variant of AMA
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
NHS	National Health Service
NIHR	National Institute for Health Research
OGD	Oesophagogastroduodenoscopy
PBC	Primary biliary cirrhosis
PSA	Probabilistic sensitivity analysis
PSC	Primary sclerosing cholangitis

QoL	Quality of Life
REC	Research Ethics Committee
ROC	Receiver operating characteristic
RUSAE	Related & unexpected serious adverse event
SAE	Serious adverse event
SF-12v2™	Health survey © 2000 by QualityMetric Incorporated
SMA	Smooth muscle antibodies
SOP	Standard Operating Procedure
SST	Serum Separator Tube
TMG	Trial Management Group
TSC	Trial Steering Committee
USS	Ultrasound scan

28 APPENDIX 1

WEST HAVEN CRITERIA FOR SEMIQUANTATIVE GRADING OF MENTAL STATE

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behaviour
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

29 APPENDIX 2

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