Full Title: Management of Patients with Chronic Liver Disease admitted to Hospital as an Emergency: Data Linkage Study.

Short Title: Link MAP-CLD

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CONTENTS

KEY WORDS

Liver Disease, Data Linkage, Critical Care, Transplantation.

LIST OF ABBREVIATIONS

AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
CLD	Chronic Liver Disease
CRF	Case Report Form
DMC	Data Monitoring Committee
EA	Emergency Admission
GAfREC	Governance Arrangement for NHS Research Ethics
GCP	Good Clinical Practice
HES APC	Hospital Episode Statistics Admitted Patient Care
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
ICU	Intensive Care Unit
ICNARC	Intensive Care National Audit and Research Centre
IG	Information Governance
LSHTM	London School of Hygiene and Tropical Medicine
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY SUMMARY

STUDY OVERVIEW	
Full title	Management of Patients with Chronic Liver Disease (CLD) admitted to Hospital as an Emergency.
Objectives	• To evaluate the impact of different patterns of service organisation, provision and delivery in the English NHS on patient care and outcomes. • To identify processes of care that may be used to address the existing marked inequalities in health, improve patient experience, engagement with healthcare and survival.
Type of trial	Mixed methods project: this application and protocol relates to quantitative data linkage work package.
Trial design and methods	This quantitative component will use linked national datasets in combination with a detailed characterisation of general and specialist liver and critical care service provision and practice to study determinants of received care and clinical outcomes of CLD patients after a first emergency admission (EA), in the study period between 1 April 2009 and 31 March 2022 in the English NHS.
Health condition(s) or problem(s) studied	Emergency hospital admissions of people with CLD.
Target sample size	Data on approximately 100K subjects
Trial duration per participant:	Not applicable.
Main inclusion/exclusion criteria:	All adult patients with CLD with a first emergency hospital admission in the study period from 1 April 2009 to 31 March 2022 according to HES-APC data and classified according to ICD-10 diagnostic codes. Data from people who have chosen the National Data Opt-Out will be excluded from the study cohort.
Statistical methodology and analysis:	Multiple methods to be utilised: please see statistics plan in section 9.
STUDY TIMELINES	
Study Duration/length	2 years
Expected Start Date	01/09/2022
End of Study definition and anticipated date	Completion of planned analyses and submission of final report. 01/09/2024
Key Study milestones	Funding already awarded. REC approval 1/09/2022
STORAGE of SAMPLES (if applicable)	
Human tissue samples	Not applicable
Data collected / Storage	Only existing data will be used in this part of the study. All data analysed will be de-identified at source. All storage and analysis of the de-identified dataset will be at the London School of Hygiene and Tropical Medicine (LSHTM).

1 INTRODUCTION

Liver disease is a serious and increasing health problem in the UK. However, people with liver disease often do not know that they are affected until they need to be admitted to hospital as an emergency. These people are often very ill, and a quarter of them die within two months of coming into hospital. The care they get when they are in hospital, and after being discharged, varies greatly across the country. This variation in care has major effects on how long they survive. Survival of those who live in the most deprived areas is half that of those who live in the most well-off ones. We want to understand how and why the place where people live and the care that is available to them affect the way they are treated and their survival. We also want to see how variation in outpatient care after discharge makes a difference. Through this research we hope to understand what clinical practices have the best results and how we can guarantee that they are delivered across the country.

To do this research, we will gather very detailed information about the arrangements for care given to people with liver disease in each hospital in England and then use the health information routinely recorded when people are treated in these hospitals. Information from different parts of the NHS will be 'linked' together into a single database so we can analyse the complete course of people's illness. Data analysed by the research team will have names and all other identifying information removed. We will analyse data from more than 100,000 people with liver disease who had emergency admissions to NHS hospitals in England over more than a decade.

2 BACKGROUND AND RATIONALE

The increasing prevalence of liver disease in the UK, the resulting increase in morbidity and mortality, and the regional variation in survival has been extensively reviewed in reports of the Lancet Commission on Liver Disease in the UK and the Atlas of Variation in Risk Factors for Liver Disease in England (1,2). Below we summarise these reports as well as evidence from an extended review of the literature that was carried out to support this application. This review highlighted serious questions about the current provision and delivery of care for patients with CLD, especially in patients who were admitted to hospital as an emergency.

Mortality rates from CLD in the UK have increased 400% since 1970, and in people younger than 65 years have risen almost five-fold (1,2). Most patients die in working age and CLD is now the third biggest cause of premature mortality. In 2018, liver disease was the leading cause of death for those age 35-49 years. However, the prevalence of liver disease and its outcome is not uniform across the UK. Studies in England have shown wide variation: premature mortality varies 7.7-fold and hospital admissions 8.5-fold by Clinical Commissioning Group (CCG). This variation is closely linked to the level of socio-economic deprivation. People with CLD who live in the most deprived areas of England die nearly 10 years earlier and have a mortality rate that is twice as high compared to those who live in the most affluent ones (1,2).

CLD has a wide range of different aetiologies. People with CLD, particularly if it is alcohol-related, often first come to medical attention with an unplanned emergency admission (EA) to hospital when their disease is already advanced. Over a quarter of these patients die within 60 days of their first EA (3,4). Re-admissions are common and associated with a worse prognosis, and nearly 70% of patients who survive a first EA will die within 5 years (3).

Provision of specialist care for people with CLD admitted as emergencies shows wide variation across the UK with major imbalances between service provision and local disease burden (5). A study of CLD patients admitted to hospital between 2004 and 2012 in England and Wales suggested that early input

of liver specialists – hepatologists or gastroenterologists – may improve patient care and is associated with a reduction in early mortality by more than 20% (3). However, more recent evidence indicates that specialist care is still lacking, with very few districts general hospitals having dedicated hepatology services, and very limited provision for out-of-hours or weekend care (6).

An evidence-based care bundle ('BASL Care Bundle') has been developed for the early care of patients with CLD after being admitted as an emergency. An evaluation in seven hospitals in North West England shows that the care bundle's introduction may be associated with reduced mortality in "outlier hospitals", but it has not been evaluated elsewhere (7,8).

People with CLD are often severely ill when first admitted and up to a third may require transfer to a high-dependency unit (HDU) or ICU for "critical care" support. However, there is variation in ICU admission rates and not all receive the critical care that they may benefit from, particularly if their CLD is alcohol-related (9,10). A National Confidential Enquiry into Patient Outcome and Death (NCEPOD) review of deaths in patients with alcohol-related CLD identified systematic stigma and linked mortalities (9). Appropriate escalation of care with ICU admission often did not occur, even if indicated, and when a patient had been admitted, treatment was often inappropriately limited or withdrawn. Nihilism is not justified as ICU survival for CLD in England has shown progressive improvement (11).

After hospital discharge, continued input from liver specialists is also important. Research from outside the UK suggests that prompt, coordinated specialist outpatient review is associated with lower readmission rates, healthcare costs and improved survival (12-15). In the UK, care and support for outpatients with CLD are poorly characterised but appear very variable. For example, in people whose CLD is severe, referral to liver transplant (LT) centres by local specialists for possible LT is key but there is a more than 5-fold difference in the rates of LT between CCGs – a difference that does not correlate with local prevalence of CLD (2).

Evidence explaining why this research is needed now

Since 2014, the Reports of the Lancet Commission into Liver Disease in the UK have raised concerns about the increasing mortality from CLD, particularly after an EA, drawing attention to the marked regional variation in survival and of the limited and unequal provision of the specialist care.

There is a need to re-configure the currently limited UK services so that they deliver care associated with the best possible outcomes in a consistent way across the country. UK-based initiatives to address these shortfalls have been proposed but to date their adoption has been patchy and their large-scale and long-term effects are unknown. These initiatives include the care bundle developed by the British Association for the Study of the Liver (BASL) and NICE Pathways as well as the recent recommendation for regional liver centres linked to a hub-and-spoke network of surrounding district general hospitals (16). Wider initiatives to re-configure clinical services for maximum benefit for this often disadvantaged patient group – particularly in relation to outpatient care – have not been tested in the NHS.

It is currently difficult to establish which processes of care improve patient outcomes because data on different aspects of care are collected in different datasets or data are simply unavailable. Linking national datasets at patient level – and supplementing this with key novel information on the configuration of services – will provide for the first time a rich source of detailed clinical information

about the about 9,000 people with CLD having a first EA each year. By mapping processes and outcomes of patients over time, across hospitals and between clinical networks, we have a unique opportunity to disentangle the factors related to the organisation and delivery of liver services, derived from our mapping of existing health service characteristics, and those related to particular processes of care derived from the analysis of national linked datasets as detailed in this protocol, that have the greatest impact on patient outcomes.

There is also an urgent need to investigate the currently poorly characterised stigma that confronts many people with CLD once admitted to hospital and the difficulties of engagement with healthcare that result. In a separate work package of the same research project, ethnographic observations of liver care services and interviews with CLD patients will inform how liver service can be designed best to meet CLD patients' needs, so that they can benefit from timely escalation of care or referral for liver transplantation. The findings of the social science work package (which will be the subject of a separate protocol) will inform this quantitative work package Our proposed research project provides an opportunity to develop a systematic approach to re-configure liver services available in the NHS, specifically confronting the stigma and disadvantage experienced by many CLD patients, in order to strengthen their engagement with healthcare.

3 OBJECTIVES

3.1 Primary Objective

The overall aim is to identify which characteristics of treatments and services for acutely ill people with CLD impact on care processes and outcomes.

The project will investigate:

1. Time trends in acute secondary care use for patients with CLD and their outcomes.
2. Regional variation in acute secondary care use for patients with CLD and their outcomes.
3. The impact of regional clinical networks on referral and transfer patterns.
4. The impact of regional, hospital and patient characteristics on critical care use of CLD patients who had a first EA.
5. The impact of regional, hospital and patient characteristics on use of liver transplantation after a first emergency hospital admission in patients with CLD.
6. The impact of coordinated specialist outpatient review after discharge on readmissions, referral for transplantation, and mortality.

Our analyses will also seek to assess the impact of the Covid-19 pandemic on all these aspects of care.

4 STUDY DESIGN

Work Package 1: Mapping Health Service Characteristics.

Information on the characteristics of English acute NHS hospital trusts, including staffing and configuration of gastroenterology and hepatology service provision will be collated from multiple

existing sources. These sources will be supplemented by hospital trust-level data collected through direct contact with individual hospital trusts. This organisational survey will be the source of information on health service characteristics at provider, clinical network and regional levels.

Existing sources of hospital trust-level information:

1. **National Confidential Enquiry into Patient Outcome and Death (NCEPOD) Alcohol-related Disease Survey.**

This survey is currently ongoing, and its submission is mandatory for all Acute hospital trusts in the United Kingdom as part of the NHS Quality Accounts. Data from the survey is expected to be complete in the spring of 2022. It follows up the 2013 NCEPOD report "Measuring the Units" on the care of patients with alcohol-related CLD liver disease with focus on key areas of current service provision and practice relevant to the acute care of patients with CLD from all causes.

Details of hospital trust-level service configuration includes whether a specialist or non-specialist team is delivering care to patients admitted with decompensated cirrhosis of all aetiologies, the presence and availability of a specialist Alcohol Care Team, participation in liver clinical networks and the relationship with a specific liver transplant unit. Details of hospital trust practices includes utilisation of the BASL Care Bundle of early evidence-based interventions and the 24/7 availability of on-site endoscopic treatment for variceal bleeding. A subjective assessment of difficulties encountered in the admission to ICU of patients with decompensated alcohol-related liver disease is also provided.

2. **Royal College of Physicians Consultant Census (RPCCC).**

This national annual census has been undertaken by the Royal College of Physicians (RCP) since 2004 with data now available for the 2018/19 census. It is anticipated that data from the 2020/21 census will be available in early 2022. Census returns are supplemented via an information exchange with the General Medical Council with near complete coverage of the UK consultant workforce. It provides hospital trust-level detail on the number and speciality of consultant staff in post, their clinical workload, and how these have changed over time.

3. **Improving Quality in Liver Services (IQILS) accreditation standards evidence.**

Improving Quality in Liver Services (IQILS) is a programme run by the RCP and supported by professional bodies and patient groups. Established in 2017, participating hospital trusts seek accreditation by demonstrating achievement of specific organisational and clinical standards for the care of patients with liver disease.
As such, each hospital trust provides evidence of the detail of the current configuration of liver disease services and of the clinical performance against key performance standards, developed by BASL and NICE. To date 56 hospital trusts have achieved accreditation and by 2022 it is anticipated that this number will have risen to approximately 100.

4. **Intensive Care National Audit and Research Centre unit-level information**

The Intensive Care National Audit and Research Centre (ICNARC) maintains a high-quality database containing unit-level information including type of unit and number of beds, derived bed occupancy and measures of case mix.

5. **British Association for the Study of Liver Disease (BASL) national audit.**

In 2018 and 2019, BASL undertook a detailed survey of the configuration and provision of hepatology services in acute NHS hospital trusts. Responses were received from 126 hospital trusts and detail

medical and nursing staffing arrangements, in-hours and out-of-hours specialist service and procedure provision (including endoscopy and transjugular intrahepatic portosystemic shunt), and participation in clinical network arrangements for urgent referrals, emergency transfers and liver transplantation. Clinical networks are well characterised, and hospital trusts are classified into network participants and non-participants, referral sites, regional centres, and transplantation centres.

6. **NHS England Datasets**

Other relevant hospital trust-level characteristics to be included from NHS England datasets will be the relevant hospital size in beds, bed occupancy and transplant centre status.

Time period considerations

Up-to-date organisational characteristics of bed numbers, occupancy and transplant status will be available throughout the study period but characteristics from some data sources will need to be updated through direct contact with NHS hospital trusts.

Work Package 2: Understanding Determinants of Variation in Practice and Outcomes after Emergency Hospital Admission.

The study will use linked existing electronic patient-level healthcare data to map the full "patient journey" of patients with CLD. The patient journey will start from the first emergency hospital admission and we will examine determinants of Intensive Care Unit (ICU) admission, length of stay, inter-hospital transfer for specialist care or liver transplantation and in-hospital and longer term mortality.

We will use three existing national datasets linked at patient-level:

- Hospital Episodes Statistics (HES) data (inpatient, outpatient data, A&E attendances and ONS mortality data)
- Intensive Care National Audit and Research Centre Case Mix Programme (ICNARC-CMP) database
- UK Transplant Registry maintained by NHS Blood and Transplant

The research team analysing the data will not have access to patient identifiers. Please see the Data Flow Diagram attached as appendix 2.

We will include all adult patients with CLD disease who were admitted with a first emergency hospital admission in the study period from 1 April 2009 to 31 March 2022 according to HES-APC data, with an expected cohort size of about 100,000 CLD patients. Patients will be considered to have CLD according to ICD-10 diagnostic codes.

Explicit coding schemes will be developed. We will create coding schemes that describe the clinical characteristics of the patients, including the nature and severity of the CLD, their comorbidities, and their adversity-related health issues. Coding schemes will also be developed to capture critical care admissions, predominantly based on data items available through linkage with ICNARC data but enhanced by also including information available in HES records of hospital admission and adult critical care episodes. In addition, we will derive measures that capture specific patterns of secondary care use in the year immediately after the first emergency admission, in terms of the number of planned outpatient visits, A&E attendances, planned and emergency readmissions, and the total time spent in hospital.

We now outline how we will address each of the specific objectives listed in section 3.1.

1. Time trends in acute secondary care for patients with chronic liver disease and its outcomes: We will use the linked datasets to describe for each year in the study period the number of CLD patients who had an emergency admission, the proportion of these patients who had an admission to critical care and its duration, total length of hospital stay, readmission rate and total time spent in hospital within the first year, the rate of liver transplantation, and in-hospital and 1-year mortality.

2. Regional variation in acute secondary care for patients with chronic liver disease and its outcomes: We will estimate in the last 5 years of data the rate of emergency admissions for CLD per 100 000 people per year in 44 regions of England. We will estimate regional emergency admission rates without and with adjustment for patient and regional characteristics. In addition, we will analyse regional differences in outcomes.

3. Impact of regional clinical networks on referral patterns: The development of regional networks, shaped as hub-and-spoke models, will be explored by observing referral patterns after a first emergency admission of patients with CLD. We will identify the hub (a hospital that typically receives referrals) and the spokes (hospitals that typically refer patients) in each clinical network. The configuration and characteristics of these networks will be compared.

4. Impact of regional, hospital and patient characteristics on critical care use of chronic liver disease patients who had a first emergency admission: Multilevel logistic regression models will be used to explore which of the regional characteristics, hospital characteristics, and patient characteristics are associated with critical care use.

5. Critical care use and clinical outcomes after a first emergency admission in patients with CLD: We will characterise hospitals according to the proportion of patients that are admitted to critical care and whether they were admitted to critical care early or late in order to explore to what extent hospitals with more frequent and earlier critical care admissions of CLD patients after an emergency admission have better short-term outcomes. The results will be analysed using multilevel logistic regression including the level and timing of critical care use as hospital-level characteristics with adjustment for key patient characteristics.

6. Use of liver transplantation after a first emergency admission in patients with CLD: Using the linked UK Transplant Registry data, we will explore the regional variation in the use of liver transplantation in the first year after a first emergency admission. We will use multilevel logistic regression models to explore to what extent the regional variation is associated with specific patient and health service characteristics.

7. Impact of coordinated specialist outpatient review after discharge on readmissions, referral for transplantation, and mortality: To answer this question, we will compare the outcomes of patients who are discharged alive from hospital after their first emergency admission from hospitals that offer coordinated specialist outpatient review with patients from hospitals where this type of outpatient review is not available. We will use multilevel Cox regression to estimate differences in time to readmission, referral for transplantation, and death.

5 STUDY SCHEDULE

Please see section 4 above and monthly time line attached as appendix 1

6 CONSENT

Not applicable: study working with existing routine data only.

Application is being made for Section 251 support from CAG.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

The study will include all patients older than 18 years with chronic liver disease (CLD) who were admitted with a first emergency hospital admission between 1 April 2009 and 31 March 2022.

7.2 Exclusion Criteria

A previous emergency hospital admission with chronic liver disease in the two preceding years.

People who have chosen to adopt the National Data Opt-Out.

8 RECRUITMENT

Not applicable: study working with existing routine data only.

A data flow diagram is appended as Appendix 2.

Hospital Episode Statistics (HES) data will be requested from NHS Digital for patients with a Chronic Liver Disease (CLD) diagnosis anywhere in their episodes in the study period (1 April 2009 to 31 March 2021). CLD diagnosis will be defined as ICD-10 codes in the range between B15-B19 or between K70-K77.

Analysts at NHS Digital will identify the patient cohort. They will send the identifiers of these patients (without any clinical data) to the Intensive Care National Audit and Research Centre (ICNARC) for linkage to ICNARC data.

Patients undergoing a liver transplant in England between one year before the study period to one year after the study period will be identified in The UK Transplant Registry, by NHS Blood and Transplant. The identifiers of these patients will be sent (without clinical data) to NHS Digital for linkage to HES.

De-identified cohorts of patients will be sent from NHS Digital, ICNARC and NHS Blood and Transplant to LSHTM for analysis, containing no patient identifiers. Pseudonymised study IDs will be used by the research team at LSHTM to link the three datasets.

9 STATISTICAL METHODS

Please see section 4 above. Further, an overview of the statistical plan is presented below.

We will include all patients older than 18 years with chronic liver disease (CLD) who were admitted with a first emergency admission (EA) in the study period from 1 April 2009 to 31 March 2022. Patients will be considered to have CLD if they have a Hospital Episode Statistics (HES) inpatient record with an ICD-10 codes in the range between B15- B19 or between K70-K77. An EA will be identified based on an administrative HES code related to the method of admission. We will consider an EA to be a first-time occurrence if there is no record of a similar admission, with a minimum of in two preceding years of data available (the "look-back" period).

We will create coding schemes that describe the clinical characteristics of the patients, including the nature and severity of the CLD, their comorbidities, and their adversity-related health issues. Coding schemes will also be developed to capture critical care admissions, predominantly based on data items available through linkage with Intensive Care National Audit and Research Centre (ICNARC) data but enhanced by also including information available in HES records of hospital admission and adult critical care episodes. In addition, we will derive measures that capture specific patterns of secondary care use in the year immediately after the first EA, in terms of the number of planned outpatient visits, and A&E attendances, the number of planned and emergency readmissions, and the total time spent in hospital.

Specific research questions:

1. Time trends in acute secondary care for patients with chronic liver disease and its outcomes:
We will use the linked datasets to describe for each year in the study period from 1 April 2009 to 31 March 2022, the number of CLD patients who had an EA, the proportion of these patients who had an admission to critical care and its duration, total length of hospital stay, readmission rate and total time spent in hospital within the first year, the rate of liver transplantation, and in-hospital and 1-year mortality. Changes in these results over time (including changes in the period 2020-2022 as a result of the Covid-19 pandemic) will be determined with Poisson, logistic or linear regression models, depending on the nature of the dependent variable.

2. Regional variation in acute secondary care for patients with chronic liver disease and its outcomes:
First, we will estimate the rate of EAs for CLD per 100 000 people per year in 44 regions. The numerator will be the number of CLD patients with a first EA and the denominator populations will be derived by aggregating the updated 2011 Census results for patients of 18 years and older in each region. We will use multilevel Poisson regression models to produce empirical Bayes estimates for regional EA rates without and with adjustment for patient and regional characteristics. We will analyse regional differences in critical care use during the EA, total length of hospital stay, readmission rate and total time spent in hospital within the first year, the rate of liver transplantation, and in-hospital and 1-year mortality. Multilevel regression models will be used to quantify the regional variation and to produce empirical Bayes estimates for each region. We will assess the impact of the Covid-19 pandemic on regional variation in EA rates and outcomes.

3. Impact of regional clinical networks on referral patterns: The development of regional networks, shaped as hub-and-spoke models, will be explored by observing referral patterns after a first EA of patients with CLD. We will create "super-spells" for each patient and identify within this super-spell the hospital of the EA and the hospital trust where most of the care was provided. These results will be used to identify the hub (a hospital that typically receives referrals) and the spokes (hospitals that typically refer patients) in each clinical network. The configuration and characteristics of these networks (e.g., in terms of regional coverage, number and characteristics of referred patients, type of

care provided predominantly in the hub and spokes, changes to referrals pre- and post- Covid-19)) will be compared.

4. Impact of regional, hospital and patient characteristics on critical care use of chronic liver disease patients who had a first emergency admission: We will explore the association between which of the regional characteristics (e.g., network arrangements, prevalence of CLD, use of transplantation), hospital characteristics (e.g., transplant centre status, specialist staffing, ICU capacity, ICU case-mix), and patient characteristics (e.g., type of CLD and comorbidity, age, sex, socioeconomic deprivation) are associated with the proportion of cases admitted to critical care, their clinical condition at critical care admission, the duration of critical care, and the proportion of cases for whom critical care was withdrawn. We will also explore changes in critical care use as a result of the Covid-19 pandemic. Multilevel logistic regression models will be used to estimate adjusted odd ratios that capture the impact of the regional, hospital and patient characteristics and the Covid-19 pandemic on critical care use.

5. Critical care use and clinical outcomes after a first EA in patients with CLD: We will characterise hospitals according to the proportion of patients that are admitted to critical care and whether they were admitted to critical care early or late in order to explore to what extent hospitals with more frequent and earlier critical care admissions of CLD patients after an EA have better short-term outcomes (in-hospital mortality and readmissions, total time spent in hospital and mortality during the year following the EA). The results will be analysed using multilevel logistic regression including the level and timing of critical care use as hospital-level characteristics with adjustment for key patient characteristics, including age, sex, socioeconomic deprivation, and comorbidity.

6. Use of liver transplantation after a first EA in patients with CLD: Using the linked UK Transplant Registry data, we will explore the regional variation in the use of liver transplantation in the first year after a first EA. We will use multilevel logistic regression models to explore to what extent the regional variation is associated with specific patient and health service characteristics , and whether patterns of transplantation changed in response to the Covid-19 pandemic. We will use Cox regression with sequential stratification to estimate the impact of liver transplantation on survival. Sequential stratification is a relatively new method which has wide applicability to observational studies where the time to an event (e.g., death) is of interest and the treatment being compared (i.e., liver transplant) is time dependent.

7. Impact of coordinated specialist outpatient review after discharge on readmissions, referral for transplantation, and mortality: We will compare the outcomes of patients who are discharged alive from hospital after their first EA from hospitals that offer coordinated specialist outpatient review with patients from hospitals where this type of outpatient review is not available. We will use multilevel Cox regression to estimate differences in time to readmission, referral for transplantation, and death.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Consultation with people with liver disease was undertaken at the very earliest initial planning stages of this project. We first held informal discussion with people hospitalised with CLD at King's College Hospital, and with their next of kin, and following an encouraging response developed an initial research plan.

Through our research partners, the British Liver Trust, we then conducted an online survey of 57 people with CLD from across the UK to understand their attitudes to the goals and basic research methods under consideration. This sample was representative of the patients with CLD who would be in the proposed study cohort in respect of age, sex and cause of liver disease. More than 80% had required hospitalisation as a consequence of CLD. More than 90% felt it "extremely important" to understand regional variations in outcome of CLD. More than 90% supported the research and felt it to be addressing an important subject, endorsing the approaches proposed to be utilised, including the use of de-identified linked electronic health records. Thirty-three of the respondents volunteered to join an online patient consultation group for the research project.

A face-to face focus group was then conducted with 19 people who had LT for CLD, many of whom had experienced EA at an early stage of their illness. This group also confirmed support for the proposed research and its methodology. They also expressed enthusiasm for continued patient participation in the process of research and their feedback reinforced the importance of adequate notification steps and methods for "opt out" of use of personal data for those who did not wish to contribute. As outlined below, the research plan now incorporates an extended PPI component, specific patient notification steps and processes of opt-out.

A patient representative with lived experience of CLD, emergency admission and liver transplant is now a grant co-applicant and member of the research team, as is a representative of a patient organisation, the British Liver Trust (BLT). As members of the research team they will be involved in all stages of the research cycle including prioritising research questions, advising upon and managing the research process and routes to data opt-out, analysing and interpreting the results of research, with a prominent role in dissemination of findings.

A Patient Advisory Group (PAG) is to be recruited that will include people with liver disease and lived experience of drug and alcohol services and homelessness. The PAG will be convened at 6 monthly intervals to consider and advise on research questions, conduct and the actions that should follow its findings, feeding back to the research team. Recognising patients and the public as key stakeholders in the research, the dissemination plan includes webinars, presentations and reports for patients and patient organisations. We will involve our PPI and patient representatives to ensure that we engage all relevant organisations and that the style and format of our publications is accessible to these audiences.

11 FUNDING

The study funding has been reviewed by the KCH R&I Office and deemed sufficient to cover the requirements of the study.

The research costs for the study have been supported by The National Institute for Health and Care Research (NIHR 132969), confirmed 4th April 2022 for £1.163,742.27.

Breakdown of funding as awarded is detailed in Appendix 3.

12 DATA HANDLING AND MANAGEMENT

Details of case ascertainment and outline data flows are shown in section 8 and appendix 2 respectively. The research team analysing the data will only have access to de-identified data. Personal data will only be used for data linkage carried out by trusted third parties. Application will be made to the Confidentiality Advisory Group (CAG) for processing of the data without consent under Section 251 of the Health and Social Care Act 2001.

The de-identified clinical data will be stored on a secure server at LSHTM. The secure server will ensure appropriate levels of IT security and complies with the IG toolkit. Only the researchers required to carry out data analysis at LSHTM will have access to the linked data on the secure server. These researchers will have accredited researcher status, have undergone information governance training, and will comply with GDPR.

After the study has ended the data will be retained on the secure data server at LSHTM. Access to the data will be strictly controlled by the Principal Investigator of the study (William Bernal, KCH) and by the co-Principal Investigator (Jan Van der Meulen, LSHTM). Access will only be given to members of the research team whose role includes data analysis. The Principal Investigator and the co-Principal Investigator will regularly monitor the audit logs they are sent.

The co-Principal Investigator will have control of and act as custodian for the final data generated by the study. In this study, the following parties are involved as data controllers and processors:

Organisation Name	Role	Function	Contact
NHS Digital	Controller	1. Creation of data group 2. Creation of Pseudonym Code 3. Provider of Pseudonym Code and NHS Number to NHS BT and ICNARC	DPO Name Jon Moore (enquiries@nhsdigital.nhs.net)
NHS Blood and Transplant	Controller	1. Provision of data based on NHS D List and sender of details to	DPO Name Katrina Smith (informationgovernanceteam@nhsbt.nhs.uk)
ICNARC	Controller	1. Provision of data based on NHS D List and sender of details to	DPO Name Lee Shailer (DPO@icnarc.org)
Kings College Hospital	Controller	1. Oversight of Research Study	1.PI Name Professor William Bernal (william.bernal@nhs.net) 2. Nicholas Murphy-O'Kane, Data Protection Officer (Kch-tr.dpo@nhs.net)
London School of Hygiene and Tropical Medicine	Processor	1. Recipient of data from NHS	DPO Name Peter Wright (DPO@lshtm.ac.uk)

		D, NHS BT, and ICNARC 2. 2. Complete analytic actions as directed by KCH	

13 MATERIAL/SAMPLE STORAGE

Not applicable: study working with existing routine data only.

14 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

- The Sponsor considers the procedure for obtaining funding from NIHR to be of sufficient rigour and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies (listed below). Approval from each will be obtained before the study commences.

- Health Research Authority
- Research Ethics Committee
- Confidentiality Advisory Group

15 ADVERSE EVENTS AND INCIDENT REPORTING

15.1 Definitions of Adverse Events

Not applicable: study working with existing routine data only.

15.2 Assessments of Adverse Events

Not applicable: study working with existing routine data only.

15.3 Procedures for recording adverse events

Not applicable: study working with existing routine data only.

15.4 Procedures for recording and reporting Serious Adverse Events

Not applicable: study working with existing routine data only.

15.6 Reporting Urgent Safety Measures

Not applicable: study working with existing routine data only.

15.7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and R&I Office should be notified immediately of any case where the above definition applies during the study conduct phase.

15.8 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

16 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. The Project team will meet at least monthly, at which time there will be a fixed agenda item for review of all untoward incidents.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

Further monitoring support will be delivered by the independent Study Steering Committee which will meet 6-monthly to review milestones, deliverables and consider the implications of findings and their dissemination, including research designs, project research management, development of participant information resources, research reports, and dissemination of research findings.

17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

This will include ensuring all relevant mandatory training has been undertaken and maintained, specifically in relation to Good Clinical Practice (GCP) and Information Governance (IG).

18 INDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office

19 ARCHIVING

Please see section 12 above.

20 PUBLICATION AND DISSEMINATION POLICY

Based on our results, we will formulate recommendations on how the care of acutely ill people with CLD admitted to hospital as an emergency can be improved. Our strategy to disseminate findings will be based on a number of principles:

- We will build awareness of the project among patient groups and professional bodies in the project's early phase through direct communications and presentations.
- At key "junction points" in the research plan – e.g., at conclusion of specific work packages or at the commencement of others - there will be focussed dissemination activity to raise awareness and inform the next phases of research.
- We will organise an end-of-project workshop to formulate recommendation for practice. Participants of this workshop will be recruited from existing networks and relationships available to the members of the Research Team and Steering Group, including NHS England's Specialised Commissioning Team (or its relevant successor), BASL, the British Society for Gastroenterology (BSG) and the Intensive Care Society (ICS). This workshop will produce clear messages that fit our wide range of audiences (e.g., patient and public, commissioners, clinicians, regulators and policy makers). The recommendations will be summarised in a summary report that will be disseminated across all our stakeholders.
- Messages will be shared with people with CLD and clinicians through the extensive and developed communication channels of the British Liver Trust.
- Our channels for dissemination will include traditional media and academic journals, professional newsletters, social media, targeted emailing and dedicated project web pages.

Our findings will be disseminated as follows:

- A final research report for the NIHR HS&DR programme detailing research methods, findings and conclusions of all four WPs, including recommendations for practice and an extensive summary for patients and the wider public.
- Policy advice targeting NHS England at national level to the Specialised Commissioners via the chair of the Hepato-Pancreato-Biliary Clinical Reference Group (Prof Foster, Chair of the project's Steering Group).
- At a regional level by engagement with regional medical directors through formal meetings to discuss our findings and inform change at the local commissioning level.

- In addition to changes in formal commissioning, we will engage lead hepatologists in NHS Trusts via the BASL and BSG liver networks and ensure they are aware of our findings and the value of introducing change to their organisations.
- Feedback to NICE with regards to findings relating to NICE Pathways on the management of acutely ill patients in hospital, and NICE guidelines on gastrointestinal bleeding, acute kidney injury, complications of cirrhosis, and recognising and responding to deterioration.
- A training package and associated resources aimed at relevant professional bodies, including the BSG, BASL, ICS, and NHS Blood and Transplant, and which can be utilised by clinicians and drug and alcohol services to give information, address stigma and improve patient engagement.
- Presentations and resources for patient organisations and patients, including the British Liver Trust and related organisations to help inform and empower patients and improve patient engagement. We will utilise our PPI and Steering Group, charity representatives and consult key stakeholder to increase dissemination coverage and ensure style and format are accessible.
- Research papers for peer-reviewed academic journals, articles for clinical journals, and conference presentations.

21 REFERENCES

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22 APPENDICES

1. Study Timetable
2. Data Flow Diagram
3. Funding Breakdown

Appendix 1: PROTOCOL VERSIONS

Versions No	Version Date	Status
1.0	22/06/22	Initial submission to HRA
1.2	22/09/22	NSA 01: Minor amendment including change of age inclusion as advised by CAG. Change of opt out criteria from study specific to national opt out.
1.3	1/10/23	NSA 02 Page 1: Addition of statement clarifying NIHR funding ; amendment of protocol version and date Page 22: amendment of version control table Amendment to footer to include new version, date and iras ID.

The following pages contain the protocol for the second study within the programme grant.

Title: MAP-CLD Social Science

IRAS ID: 312387

MAP-CLD social science study-protocol v.3.1 29-8-2023 FINAL

MAP-CLD Social Science Study Protocol

- **This protocol has regard for the HRA guidance and order of content for qualitative protocols**

FULL/LONG TITLE OF THE STUDY

Management of Patients with Chronic Liver Disease admitted to hospital as an emergency

SHORT STUDY TITLE / ACRONYM

MAP-CLD Social Science

Version 3.1, 29/08/2023

RESEARCH REFERENCE NUMBERS

IRAS Number:	312387
KCH Ref:	KCH23-049
FUNDERS Number:	NIHR123969

This project is funded by the NIHR [20/02 April 2020 HS&DR Researcher-led (Standard) NIHR 123969]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

- **LIST of CONTENTS**

- **KEY STUDY CONTACTS**

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Study Co-ordinator	Vernie Ramalingam Tel: 0203 299 2038 Email: vernie.ramalingam@nhs.net
Sponsor	R&I Office at King's College Hospital NHS Foundation Trust
Funder(s)	NIHR
Key Protocol Contributors	Prof. William Bernal, william.bernal@nhs.net Dr. Rebecca Lynch, r.j.lynch@exeter.ac.uk Dr. Grace Redhead, g.o.redhead@exeter.ac.uk
Committees	MAP-CLD Steering Committee

STUDY SUMMARY

Study Title	Management of patients with chronic liver disease admitted to hospital as an emergency
Internal ref. no. (or short title)	MAP-CLD Social Science
Study Design	Ethnography and semi-structured interviews
Study Participants	Sites of care and clinical decision-making for Chronic Liver Disease (CLD) in four hospitals (e.g. clinics, wards, offices, online meetings), NHS staff and patients at these sites. Out-patients with CLD who have survived emergency hospital admission.
Planned Size of Sample (if applicable)	Four hospital research sites, up to 40 outpatients, up to 15 inpatients, up to 20 clinicians
Follow up duration (if applicable)	N/A
Planned Study Period	March 2023-Sept 2024
Research Question/Aim(s)	The project's overall aim is to improve the national organisation and delivery of care for acutely ill people with CLD.

	In relation to this wider project aim, the Social Science study aims to: ● Identify processes of care that may be used to address the existing marked inequalities in health, improve patient experience, engagement with healthcare and survival; ● Explore understandings of patient experience in order to identify barriers to the delivery of effective care

FUNDING AND ROLE OF STUDY SPONSOR AND FUNDER

The study funding has been reviewed by the King's College Hospital NHS Foundation Trust R&I Office, and deemed sufficient to cover the requirements of the study.

The research costs for the study have been supported by The National Institute for Health and Care Research (NIHR 132969), confirmed 4th April 2022 for £1,163,742.27.

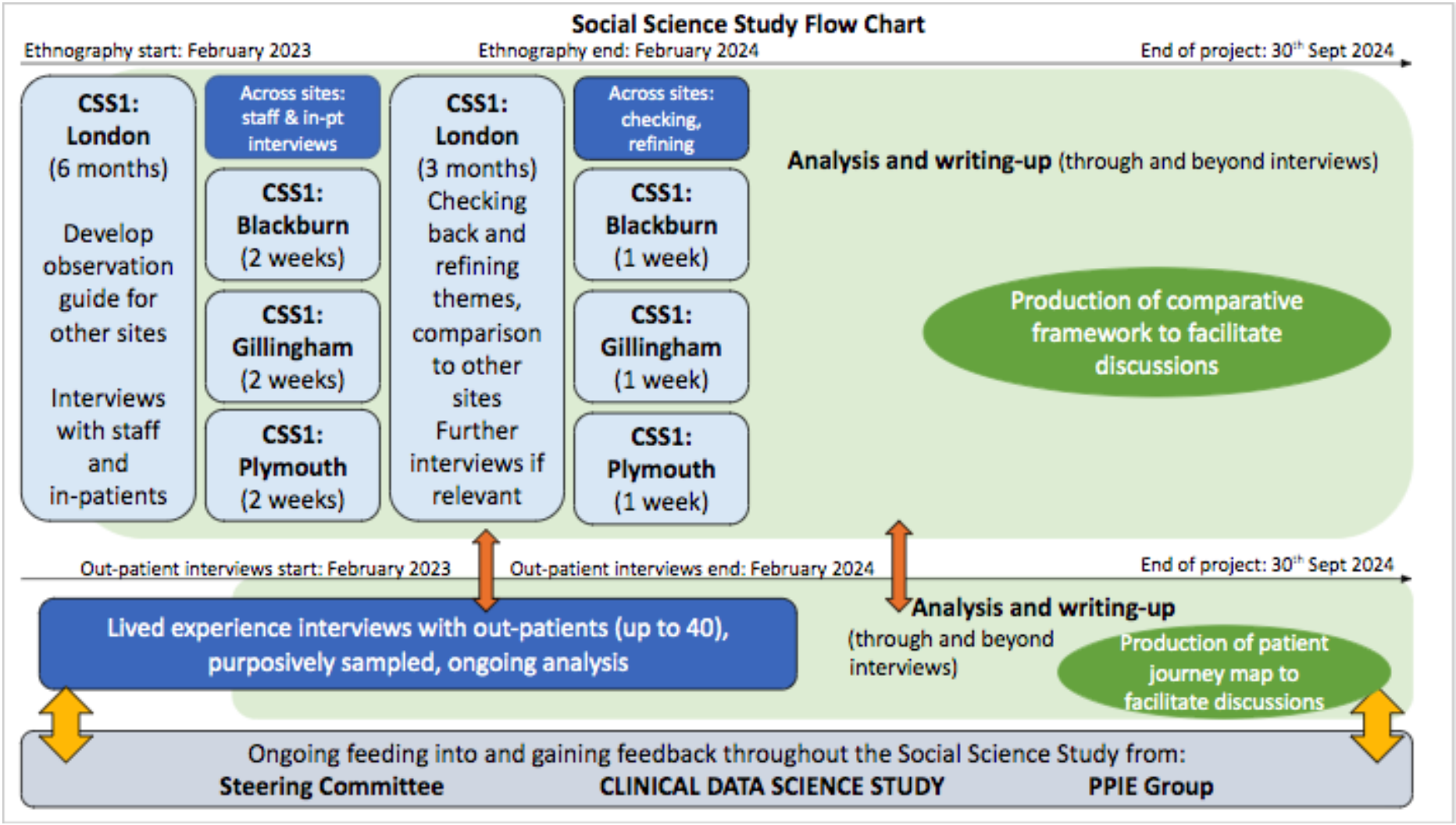
ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

An independent Study Steering Committee will meet 6-monthly to review milestones, deliverables and consider the implications of findings and their dissemination, including research designs, project research management, development of participant information resources, research reports and dissemination of research findings.

A patient representative with lived experience of CLD, emergency admission and liver transplant is a grant co-applicant and member of the research team, as is a representative of a patient organisation, the British Liver Trust (BLT). As members of the research team they will be involved in all stages of the research cycle including prioritising research questions, advising upon and managing the research process and routes to data opt-out, analysing and interpreting the results of research, with a prominent role in dissemination of findings.

We will consult with two PPIE groups, one based at British Liver Trust, and the other based at Kings College Hospital. We will meet with these groups at 6 monthly intervals, and they will consider and advise on research questions, conduct and the actions that should follow its findings. We will involve these representatives to ensure that we engage relevant patient organisations, and that the style and format of our outputs is accessible to these audiences.

KEY WORDS:	Ethnography, interviews, social science, qualitative, chronic liver disease, health inequality.


Social Science Study Flow Chart
Ethnography start: February 2023
Ethnography end: February 2024
End of project: 30th Sept 2024
CSS1: London (6 months)
Develop observation guide for other sites
Interviews with staff and in-patients
Across sites: staff & in-pt interviews
CSS1: Blackburn (2 weeks)
CSS1: Gillingham (2 weeks)
CSS1: Plymouth (2 weeks)
CSS1: London (3 months) Checking back and refining themes, comparison to other sites Further interviews if relevant
Across sites: checking, refining
CSS1: Blackburn (1 week)
CSS1: Gillingham (1 week)
CSS1: Plymouth (1 week)
Analysis and writing-up (through and beyond interviews)
Production of comparative framework to facilitate discussions
Out-patient interviews start: February 2023
Out-patient interviews end: February 2024
End of project: 30th Sept 2024
Lived experience interviews with out-patients (up to 40), purposively sampled, ongoing analysis
Analysis and writing-up
(through and beyond interviews)
Production of patient journey map to facilitate discussions
Ongoing feeding into and gaining feedback throughout the Social Science Study from:
Steering Committee
CLINICAL DATA SCIENCE STUDY
PPIE Group

STUDY PROTOCOL

Management of patients with chronic liver disease admitted to hospital as an emergency

● 1 INTRODUCTION

Liver disease is a serious and increasing health problem in the UK. However, people with liver disease often do not know that they are affected until they need to be admitted to hospital as an emergency. These people are often very ill, and a quarter of them die within two months of coming into hospital as an Emergency Admission (EA). The care they get when they are in hospital, and after being discharged, varies greatly across the country. This variation in care has major effects on how long they survive. Survival of those who live in the most deprived areas is half that of those who live in the most well-off ones. We want to understand how and why the place where people live and the care that is available to them affect the way they are treated and their survival.

Developing services for patients with chronic liver disease (CLD) that are safer, more effective, and more patient-centred involves improving our understanding of three interacting complexities: the complexity of CLD and its treatment options, the complexity of the life situation of many CLD patients, and the complexity of the healthcare system. Advancing knowledge in this field and making evidence-based recommendations requires different research methods and disciplines to investigate these related issues. Our mixed-method project brings together two complementary studies- a Clinical Data Science study and a Social Science study- that between them will investigate how and why patient outcomes vary after EA for advanced CLD. This protocol refers to the Social Science study only.

The Social Science study consists of two qualitative work packages (WPs) that will collect accounts of the lives of patients and their experiences of CLD and its management both in and beyond the health care system. Using interviews and ethnographic observations, it will provide a better understanding of the interactions between patients with CLD and health care professionals. We will generate new evidence through ethnographic observations of liver care in practice in four NHS hospitals situated in four different regions of the UK, supplemented by interviews with admitted CLD patients and with clinical staff who make decisions about patients' care (Ethnography WP). We will also explore the impact of CLD on peoples' lives by interviewing CLD patients after discharge from hospital after an EA about their understanding of illness and how these affect actions taken to manage health and engagement with clinical services (Out-Patient Interviews WP), which will inform initiatives to improve services.

● 2 BACKGROUND AND RATIONALE

The increasing prevalence of liver disease in the UK, the resulting increase in morbidity and mortality, and the regional variation in survival has been extensively reviewed in reports of the Lancet Commission on Liver Disease in the UK and the Atlas of Variation in Risk Factors for Liver Disease in England (Williams et al, 2014; PHE, 2017). Below we summarise these reports as well as evidence from an extended review of the literature that was carried out to support this application. This review

highlighted serious questions about the current provision and delivery of care for patients with CLD, especially in patients who were admitted to hospital as an emergency.

Mortality rates from CLD in the UK have increased 400% since 1970, and in people younger than 65 years have risen almost five-fold (Williams et al, 2014; PHE, 2017). Most patients die in working age and CLD is now the third biggest cause of premature mortality. In 2018, liver disease was the leading cause of death for those age 35-49 years. However, the prevalence of liver disease and its outcome is not uniform across the UK. Studies in England have shown wide variation: premature mortality varies 7.7-fold and hospital admissions 8.5-fold by Clinical Commissioning Group (CCG). This variation is closely linked to the level of socio-economic deprivation. People with CLD who live in the most deprived areas of England die nearly 10 years earlier and have a mortality rate that is twice as high compared to those who live in the most affluent ones (Williams et al, 2014; PHE, 2017).

CLD has a wide range of different aetiologies. People with CLD, particularly if it is alcohol-related, often first come to medical attention with an unplanned emergency admission (EA) to hospital when their disease is already advanced. Over a quarter of these patients die within 60 days of their first EA (Roberts et al, 2019; Shah et al, 2019). Re-admissions are common and associated with a worse prognosis, and nearly 70% of patients who survive a first EA will die within 5 years (Roberts et al, 2019).

Provision of specialist care for people with CLD admitted as emergencies shows wide variation across the UK with major imbalances between service provision and local disease burden (Williams et al, 2017). A study of CLD patients admitted to hospital between 2004 and 2012 in England and Wales suggested that early input of liver specialists – hepatologists or gastroenterologists – may improve patient care and is associated with a reduction in early mortality by more than 20% (Roberts et al, 2019). However, more recent evidence indicates that specialist care is still lacking, with very few districts general hospitals having dedicated hepatology services, and very limited provision for out-of-hours or weekend care (Peng et al, 2019).

An evidence-based care bundle ('BASL Care Bundle') has been developed for the early care of patients with CLD after being admitted as an emergency. An evaluation in seven hospitals in North West England shows that the care bundle's introduction may be associated with reduced mortality in "outlier hospitals", but it has not been evaluated elsewhere (Kalis et al, 2020; Dyson et al, 2016).

People with CLD are often severely ill when first admitted and up to a third may require transfer to a high-dependency unit (HDU) or ICU for "critical care" support. However, there is variation in ICU admission rates and not all receive the critical care that they may benefit from, particularly if their CLD is alcohol-related (NCEPOD, 2013; Berry et al, 2016). A National Confidential Enquiry into Patient Outcome and Death (NCEPOD) review of deaths in patients with alcohol-related CLD identified systematic stigma and linked mortalities (NCEPOD, 2013). Appropriate escalation of care with ICU admission often did not occur, even if indicated, and when a patient had been admitted, treatment was often inappropriately limited or withdrawn. Nihilism is not justified as ICU survival for CLD in England has shown progressive improvement (McPhail, 2018).

After hospital discharge, continued input from liver specialists is also important. Research from outside the UK suggests that prompt, coordinated specialist outpatient review is associated with lower readmission rates, healthcare costs and improved survival (Tapper et al, 2016; Ramachandran et al, 2018; Kanwal et al, 2016; Morales, 2018). In the UK, care and support for outpatients with CLD are poorly characterised but appear very variable. For example, in people whose CLD is severe, referral to liver transplant (LT) centres by local specialists for possible LT is key but there is a more than 5-fold difference in the rates of LT between CCGs – a difference that does not correlate with local prevalence of CLD (PHE, 2017).

Evidence explaining why this research is needed now

Since 2014, the Reports of the Lancet Commission into Liver Disease in the UK have raised concerns about the increasing mortality from CLD, particularly after an EA, drawing attention to the marked regional variation in survival and of the limited and unequal provision of the specialist care.

There is a need to re-configure the currently limited UK services so that they deliver care associated with the best possible outcomes in a consistent way across the country. UK-based initiatives to address these shortfalls have been proposed but to date their adoption has been patchy and their large-scale and long-term effects are unknown. These initiatives include the care bundle developed by the British Association for the Study of the Liver (BASL) and NICE Pathways as well as the recent recommendation for regional liver centres linked to a hub-and-spoke network of surrounding district general hospitals (Vaughn-Sandler et al, 2014). Wider initiatives to re-configure clinical services for maximum benefit for this often disadvantaged patient group – particularly in relation to outpatient care – have not been tested in the NHS.

There is an urgent need to investigate these issues qualitatively, identifying the key concerns and experiences of both patients and in care settings which contribute to the disparities and poor outcomes visible across England. This includes the currently poorly characterised stigma that confronts many people with CLD once admitted to hospital and the difficulties of engagement with healthcare that result. Our ethnographic observations of liver care services and interviews with CLD patients will inform how liver service can be designed best to meet CLD patients' needs, so that they can benefit from timely escalation of care or referral for liver transplantation.

Two qualitative WPs will collect accounts of the lives of patients and their experiences of CLD and its management both in and beyond the health care system. Using interviews and ethnographic observations, it will provide a better understanding of the interactions between patients with CLD and health care professionals. We will generate new evidence through ethnographic observations of liver care in practice in four NHS hospitals situated in four different regions of the UK, supplemented by interviews with admitted CLD patients and with clinical staff who make decisions about patients care (ethnography WP). We will also explore the impact of CLD on peoples' lives by interviewing CLD patients after discharge from hospital after an EA about their understanding of illness and how these affect actions taken to manage health and engagement with clinical services (lived experience interviews WP), which will inform initiatives to improve services.

Throughout the research programme, cross-cutting approaches with the involvement of people with CLD in the design, conduct and interpretation of the research and the continuous interaction between the different WPs will be used to share learning in real-time from one to another to shape and refine research questions and interpretation. Patient and public involvement and engagement (PPIE) representatives are directly involved as part of the Research Team and the Steering Group. In addition, a PPIE Advisory Group will meet regularly at key junction points of the different WPs to review results and advise on planned research activities. We will disseminate our findings to key audiences as the individual WPs progress are completed, using both established networks and novel events. As well as sharing findings at existing clinical and academic conferences, an end-of-project workshop will be held with relevant stakeholders to develop and refine recommendations for care improvement and optimal service configuration.

3 THEORETICAL FRAMEWORK

This programme of study focuses on the value of lived experience and observation of clinical practices and decision-making in order to identify the variables that lead to poor patient outcomes in CLD. This study takes two methodological approaches – ethnographic observation and in-depth interviewing – which draw two theoretical frameworks which link into each other.

The first theoretical framework draw in is practice theory, which focuses on what people do and how this links to wider actions, structures and meaning, rather than focusing solely on what people say. Emerging from the use of ethnography in anthropology and sociology, practice theory has been increasingly utilised in researching health care and public health. Such studies view 'the patterning of daily lives (and their implications for health) as outcomes of the coordination and synchronisation of social practices which persist over time and space, and which are reproduced and transformed by those who 'carry' them' (Blue et al, 2014). By observing practices in the care of CLD through ethnographic research, this project will identify new sites of intervention with the potential to shift unequal outcomes and identify how practices are shaped by structural and cultural contexts. In the context of the interviews, this will mean that will not only attending to what people say about their experiences but also to what they describe doing.

Secondly, we draw on the principles of grounded theory, which seeks to respond to issues of importance in participants' lives, rather than solely focusing on generating data on identified as significant by the investigators. This means that as interviews and observations proceed, the study will respond to the issues identified and raised by participants and will adapt to investigate these emerging issues in more depth (Williams et al, 2022). This approach, which focuses on 'giving voice' to groups who are marginalised from current service provision, is particularly appropriate given that the central question this project is investigating is the evident inequality in outcomes for CLD.

● 4 RESEARCH QUESTION/AIM(S)

The project's overall aim is to improve the national organisation and delivery of care for acutely ill people with CLD. It seeks to establish determinants of care processes and outcomes, recognising that these may be characteristics of treatments at patient level or characteristics of service provision at the provider level.

In relation to this wider project aim, the Social Science study aims to:

- To identify processes of care that may be used to address the existing marked inequalities in health, improve patient experience, engagement with healthcare and survival;
- To explore understandings of patient experience in order to identify barriers to the delivery of effective care

The results of the research will locate ways through which the organisation and delivery of services for patients with CLD can be made more responsive to CLD patients' needs. These will inform the development of recommendations for practice change that will make CLD services more patient-centred, safer, and more effective.

4.1 Objectives

The objectives of the Social Science study are:

- To investigate the interactions between patients and clinical staff and how key decisions are made with respect to treatment, especially ICU admission, in people with CLD after an EA
- To explore the impact of CLD on peoples' lives, their understanding of illness and how these affect actions taken to manage health and engagement with clinical services in survivors of an EA.

The first objective will be undertaken primarily through the ethnographic work taking place in clinical sites while the second will be undertaken primarily through in-depth interviews with out-patients.

4.2 Outcome

Based on our results from both the Clinical Data Science and Social Science studies, we will formulate recommendations on how the care of acutely ill people with CLD admitted to hospital as an emergency can be improved. Our strategy to disseminate findings is detailed in Section 9 below.

● 5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

This study comprises two work packages (WPs) that address the two key objectives of the study. The first of these uses ethnographic methods (participant observation and interviews) to explore interactions between patients and clinical staff and how decisions are made around care (Ethnography WP). The second uses in-depth semi-structured interviews to explore the impact of CLD on peoples' lives, understandings of illness and how these affect actions taken to manage health and engagement with clinical services (Lived Experience Interviews WP).

Ethnography WP

The Ethnography WP will generate new data through ethnographic observations of liver care-in-practice in four Case Study Sites (CSS) situated in four different regions of the UK, supplemented by interviews with in-patients with CLD and with clinical staff who make decisions about patients' care. Exploration of care-in-practice within different kinds of liver services and recording of real-world examples of patient-clinician interactions will allow points of tension and avenues for potential improvement, including improving patient engagement with care, to be identified. These will inform the development of resources for patients and service providers and assist in the interpretation of patient journeys gathered through the Lived Experience Interviews WP and identified in the Clinical Data Science element of the wider project.

Ethnographic observation allows examination of practices as they take place. It can focus on key actions, interactions, conversations, and practices that are less obvious to those directly involved (Hammersley and Atkinson, 2007). Ethnographic approaches use a combination of methods (observation, interviews, analysis of key documents and texts, immersion of the researchers in the research context) and allow an opportunity to explore the day-to-day running of liver disease services in practice, (Swinglehurst et al, 2010; Wolf et al, 2012; Swinglehurst and Greenhalgh, 2015; Surr et al, 2021) e.g., who (and what) is present at different times and places, what is talked about, by whom, when and where. It also allows discussion of these events with those who have been involved in them through speaking to patients with CLD and clinical staff involved in care, so that relevant lines of enquiry emerging from observations can be followed-up.

Furthermore, ethnographic findings from each CSS can be contextualised in the wider landscape of health care needs and provision within each case study area. This helps to locate CLD care and service provision in relation to structural issues and wider inequalities that may be engendered through day-to-day healthcare interactions and decision-making. Such nuance and potential reasons for geographical variation in the delivery of CLD care are difficult to establish through analysis of large data sets (as occurs in the Clinical Data Science element of the wider project). Ethnographic work across different sites will provide a grounded sense of how and why particular CLD services may operate as they do, allowing greater contextualisation and insight into the findings of the Clinical Data Science work.

Ethnographic observations will focus on interactions between patients and clinical staff, how clinical practices are undertaken, and how decisions about care are reached. This ethnographic work will be undertaken by an experienced medical anthropologist (RL), drawing on approaches from practice theory (Mol, 2002; Nicolini, 2013). Practice theory approaches focus on what people do and how this links to wider actions, structures and meaning, rather than focusing on what people say to derive such links. Emerging findings from the observations will be presented and discussed with the PPIE group and the wider research team at key points in the project.

Ethnographic observation will be conducted in four CSS in different regions across the UK (hospitals with liver services in London, Plymouth, Blackburn, and Gillingham in Kent). Ethnographic observation will involve spending time on the wards with patients, attending ward rounds, following ('shadowing') key members of staff and selected patients as they move between different areas of the hospital, attending key meetings where treatment decisions are made, and observing key interactions between patients and other people they encounter on the ward. Observation of these key aspects will be compared across the four case study sites, using a framework developed from ethnographic work in the first case study site in London and in discussion with the PPIE groups and members of the wider project team.

The specific spaces of observation will inevitably differ slightly across the CSS, depending on the services offered and the different spaces that emerge as important in relation to CLD care through the observations themselves. It is not assumed that it is possible to know all the meetings that will impact on patient care in a particular ward prior to commencing work in each site. An important element of the ethnographic work is that it will map out key spaces of relevance and key individuals and interactions through which care decisions are made and patient:clinician engagement take place.

The selection of each CSS in respect to the configuration and provision of services, populations served and patient outcomes has been carefully considered to reflect the diversity of care across England and the range of issues and tensions that need to be considered in making recommendations for service improvements. Details of each of these sites and the rationale for selecting these is given in the Study

Setting section below. Time spent in each site and movement between these has also been carefully planned. Foundational ethnographic work will be conducted over approximately 6 months at CSS1. A flexible approach to the timing of this fieldwork has been taken, so that if necessary work may be split or separated out over a longer time period, should coronavirus rates restrict ethnographic observations. It is anticipated that in the event that Covid restrictions to the site come into place these would be of a short-duration, as occurred in previous outbreaks, and RL would be able to attend virtual MDT meetings and speak to staff through Zoom during this time if required. The foundational ethnographic work at CSS1 has three key goals that contribute to subsequent ethnographic work in the remaining three sites:

- to gain a better understanding of key interactions in relation to care and how decisions about treatment are made;
- to identify practices to be compared across sites;
- to develop and refine topic guides and recruitment approach for interviews with out-patients as part of the Lived Experience Interviews WP.

A guide developed through this initial observation will then be used to undertake rapid, focused ethnographic work in the three other sites- the peripheral specialist unit (CSS2), and two non-specialist units (CSS3&4) where fewer CLD patients receive care. Three weeks of ethnographic work will be conducted in each of these additional sites, which will be split over an initial two-week period with a follow-up observation week undertaken some months later, when the first round of observation has been undertaken in all sites. This will allow further directions that may have emerged within one site to be followed up and explored in the other CSS. This approach to the different sites will also allow for flexibility to conduct the ethnographic work around potential restrictions that may be introduced as a response to the coronavirus.

To gain a greater understanding of the observations, we will also conduct short interviews with CLD in-patients and hospital staff. Interviews with staff will be used to explore further how and why there might be variation in the care of people with CLD and why a particular course of action might have been undertaken or a particular interaction observed. Complex and interconnected aspects of service delivery, including availability of services, clinical training, experiences and expectations, and moral attitudes are possible explanations for variation in care, and interviews will increase understanding of these and how their potential impact on delivery of care. In each site we will interview clinical staff who make key decisions about the care for people with CLD, such as ICU admission, care duration, and referral for liver transplantation. Interviewees will include gastroenterologists and hepatologists, ICU specialists, nurses and additional inpatient team members. In addition, we will interview admitted patients whose care has been directly affected by these decisions and are judged by clinical staff to be well enough to participate. This will allow us to directly compare accounts of staff with accounts of patients, to gain insight into both sides of observed interactions and activities.

Up to 15 interviews with patients and 20 interviews with health care staff will be carried out across the study sites by RL. The results of these interviews will support analysis and guide the interpretation of the results of the Clinical Data Science study (through highlighting aspects that may contribute to differences identified in patient pathways and outcomes by data analysis) and inform the in-depth patient interviews undertaken in the Lived Experience Interviews WP. We anticipate that the majority of these interviews will be conducted in the first CSS, with the potential for a select number of briefer interviews as necessary in other sites.

Observations and brief interviews where recording is not permitted/feasible (e.g. in a busy ward, during shadowing) will be recorded by RL in fieldnotes in a fieldwork diary, which will be retained by RL throughout her time in the field as a confidential record. Fieldnotes will be de-identified, scanned and uploaded to secure University of Exeter folders at regular intervals throughout the project. Interviews, such as those with clinical staff, that can be held in rooms on the hospital sites that facilitate confidential conversation without interruption (such as side rooms on wards or consulting rooms in out-patient clinics) will be audio-recorded with the participant's permission. These interviews can also be conducted through Zoom if interviewees prefer or if coronavirus restrictions prevent face-to-face interviewing. Audio-recordings of the interviews will be sent for external transcription by a company used to dealing with confidential and patient data. Recordings are encrypted and uploaded to their site through the project's password protected account. The resulting transcriptions (also encrypted) can later be securely downloaded and decrypted through a separately emailed code. All interviewees will be assigned a participant study number which will be used to identify their interview recording and subsequent transcript. RL will de-identify the transcripts on their return and these will then be stored securely under the participant's study number on University of Exeter servers. A record of those interviewed and their signed consent form will also be stored electronically, separately from the interview transcripts, in secure, restricted access folders held by the University of Exeter. At no point will the local clinical team be informed of a participant's involvement with the study, and no documentation from the study will be included in patient records.

Further contextual work on each case study site (e.g., wider patient demographic data, population served by each hospital, structure of services and community care) will be compiled with the assistance of a Clinical Research Fellow (attached to our associated Clinical Data Science Study), to place the findings from each site into context. Salient comparative aspects of this context will be brought together with key themes, points of tension and practices from the observations and interviews, as part of a within-case analysis.

Recording field notes and analysis:

Anthropological approaches to ethnography emphasise that analysis cannot be separated from the doing of the research itself. Recording fieldnotes is already inevitably a process of selection and analysis that occurs in the field, with insights gained from previous observations, knowledge gained from elsewhere (such as relevant literature) and key points of action or involvement of key individuals informing what is recorded and when. Over time in the field what is recorded becomes more refined, with increased attention paid to those practices that occur again and again or which appear to produce particular outcomes. Practice-based approaches within anthropology stress a focus on what is being done in the field and what does or 'enacts'. This framing will both guide what is recorded and how this is explored through analysis, with particular attention paid to key values and assumptions.

Comparison across sites (across-site analysis) will be undertaken through a focus on key topics and source of data (e.g., observation of particular events or decision about care, interviews with staff or patients about patient communication). Plotting these findings as a grid will create an analysis framework document. This multi-dimensional approach of both within-case and across-case analysis will allow contextualization and depth, highlight where and why care (and outcomes) might differ, examples of good practice and what 'works', as well as identifying potential key points for re-evaluation, discussion, and intervention in improving care. This framework document will be presented to the PPIE group and wider project team and will provide detail and context for the conceptual map of individual patient journeys undertaken in the Clinical Data Science study and in the

Lived Experience Interviews WP. An adapted version of the framework document will be presented in the end of project workshop.

Key outputs from the work package will include the within-case and across-case analysis framework document, and, with the Clinical Research Fellow and assistance of the wider team, the development of a training package and associated resources which can be utilised by drug and alcohol services and clinical staff. In all outputs, data will be anonymised, and care will be taken to ensure that patients themselves are unidentifiable.

Patient lived experiences WP

This WP will explore the impact of CLD on peoples' lives, their understanding of their illness and how these affect actions taken to manage health and engagement with clinical services. Through interviews with CLD outpatients who have survived EA, we will compile detailed, nuanced, and rich accounts that 'give voice' to this under-represented and often stigmatised group through illustrating the patient experience in training and resources for services and key stakeholders. These accounts will help inform improvements in care that are guided by what has worked and has not worked for patients, as well as assisting in interpretation of the findings of the ethnographic and Clinical Data Science WPs.

People with CLD come from a range of different backgrounds and have had different experiences, but many have complex and difficult lives marked by severe disadvantage, stigma, and negative experiences with health care services. Approximately 90% of CLD is lifestyle-related, most frequently as a result of alcohol and drug use and obesity (PHE, 2020), and wider assumptions about this patient group, and notions of blame for their conditions can be interwoven into experiences of care and condition management (Sogolow et al, 2010) and negatively impact on help-seeking (Vaughn-Sandler, 2014).

In order to describe and explore these patient experiences and how these may link to clinical decision making and service provision, audio-recorded, in-depth, semi-structured interviews will be conducted with up to 40 CLD out-patients who have survived EA across the four case study sites. This form of interviewing, led by an experienced social science team used to working on sensitive topics with disadvantaged groups (GR and RL) allows patients to raise and elaborate on those aspects that are meaningful and important to them, as well as enabling the interviewer to prompt responses on specific topics (Green, 2018).

Interviews will follow a topic guide which has been informed by initial preparatory interviews and consultations with different clinical staff, key stakeholders and a patient expert, as well as accompanied observations within the first CSS consultations, and a review of relevant literature. The interview topic guide prompts responses on patient history and lived experience of living with CLD, treatment pathways and interactions and engagement with clinicians, actions taken to manage health, and sense of self and identity as a CLD patient. Interview participants will be purposefully sampled to ensure inclusion of patients who may have had different experiences based on specific individual factors. We will therefore include we interview both male and female outpatients as well as those of different ages, with different types or liver disease and who live in different areas. These characteristics will be explored in the interviews in relation to socio-economic disadvantage and exclusion, including how disadvantage may be compounded intersectionally through these characteristics (Shim, 2014).

Clinical staff in each CSS will identify and distribute recruitment packs to outpatients meeting the study inclusion criteria (detailed below). Patients are asked to contact the study team to express interest in participating and will be purposively sampled to include maximum variation of patient characteristics across the interview cohort as discussed above. To support recruitment of people with past or current experience of drug and/or alcohol use, we will also work with services for these patients to recruit participants in the two of our CSS where cirrhosis and / or alcohol related issues are significantly higher than the England mean (Blackburn and London) and where, despite both having high rates, outcomes for the patients in these two sites differ considerably.

Our hospital sites will notify us if translation of interviews and recruitment materials into commonly used languages in their areas is necessary. Translation of recruitment materials will be conducted at Exeter. If interpreters are needed for interviews, we will utilise the services and/or mechanisms used by the clinical team, including informal translation by a family or friend, and the Language Line Solutions service used in NHS Trusts. If such translation of interviews is required, and incurs a fee, we will reimburse the sites for this. Interviews will be conducted in a venue chosen by interviewees: at home, in clinics or in another location where a confidential interview can take place and be audio-recorded. Interviews can be conducted over the phone or through Zoom if interviewees prefer or if coronavirus restrictions prevent face-to-face interviewing.

Data collection and analysis will follow the principles of grounded theory, so that interview topic guides and prompts will become increasingly refined through the interview process (Charmaz, 2014). Data management software (NVivo 12) will be used to facilitate coding of the dataset and subsequent identification of key themes. Initial coding will be undertaken by GR in discussion with RL.

The team will meet regularly through the patient interview period to discuss progress and emerging themes, which can be interrogated in more depth as interviews progress. Conceptual maps of key points in the care journey for patient interviews with similar experiences and/or characteristics will be developed from the interview data. Concept maps organize and visually represent knowledge, indicating key concepts or ideas and illustrating how these connect to each other (Novak, 2007).

These visual representations of key patient journey points will be presented and discussed with the PPIE group and wider team to facilitate understanding of, and reflection on, research findings, providing a means through which to compare and contrast the patient journey across the different WPs and where interventions to improve patient care might be introduced. As well as detailing key findings and instances of significance for patients, this WP will therefore also highlight implications for informing initiatives to improve services and will be used to contextualise findings across other WPs.

This WP will yield findings of direct relevance to clinical practice through contextualising patient experience of CLD and their engagement with treatment and services in relation to the complexities of patients' everyday lives. Highlighting how clinical interactions and movement between services are experienced by patients, difficulties and barriers faced and the resources and interactions that have been helpful will allow resources and training to be developed for clinical professionals that will seek to address potential misconceptions and lack of understanding of patient experiences and facilitate better engagement with this patient group. Findings will linked to those in the ethnographic WP to develop a training package and associated resources. In all outputs, data will be anonymised, and care will be taken to ensure that patients themselves are unidentifiable.

Local permission has been received to conduct ethnographic work across all four case study sites (Appendix 2). Ethical permission to conduct this work is being sought through the HRA.

- **6 STUDY SETTING**

Ethnography WP Study Setting

Ethnographic observation will be conducted in four CSS purposively selected to reflect the diversity of care provision and patient outcomes across England:

CSS 1: King's College Hospital is a large teaching hospital in inner city London, serving an ethnically diverse population with high levels of socioeconomic deprivation. It combines a busy gastroenterology/hepatology service and a specialist hepatology/liver transplantation centre at the Institute of Liver Studies, which supports one of the largest liver transplant programmes in Europe. As well as 3 general intensive care units (ICU) with a total of 60 beds, there is a specialist 19 bedded Liver ICU dedicated to the care of patients with liver disease with a local, regional and national referral base. The rate of admissions to King's of patients with cirrhosis and alcohol related issues is significantly higher than the England mean.

CSS 2: Derriford Hospital is the largest teaching hospital in the South-West Peninsula and serves Plymouth and nearby areas of Devon and Cornwall. The catchment population is characterised by diversity – both rural and urban, wealthy and with pockets of deprivation, and wide variance in health and life expectancy. Hepatology services for much of the south-west of England are provided by the South West Liver Unit, a large specialist liver unit delivering hepatology, hepatobiliary surgery and assessment and follow-up liver transplantation services. Liver transplantation surgery and post-operative care is provided at King's College Hospital in London. Its population rates for cirrhosis-related admissions do not differ significantly from the England mean but mortality rates are significantly lower.

CSS 3: The Royal Blackburn Teaching Hospital is an acute district general hospital in Blackburn, Lancashire. It serves an urban multi-cultural population that is amongst the 10% most deprived in the UK, with its CCG having the 5th highest mortality rate from liver disease in England and amongst the very highest rates of hospital admissions with cirrhotic liver disease. Clinical care for acute admissions with cirrhosis is delivered by a multi-disciplinary team from the hepato-pancreatic biliary service. There is a newly formed alcohol and addiction team providing in-patient services and liaison with community addiction teams.

CSS 4: The William Harvey Hospital is an acute district general hospital in Ashford, Kent. It serves a mixed urban/rural population of 95% white-ethnic origin with pockets of significant deprivation. CLD mortality does not differ from the national mean but rates of admission of patients with alcohol-related diagnoses and from CLD are significantly lower than the national average. Cirrhosis care is delivered by a combined gastrointestinal and liver services consultant team and is working toward level 1 accreditation from IQILS.

Data from the different sites will provide insight to regional inequalities, different demands of services, interaction between staff and patients, decision-making around care, and ongoing patient engagement. Since care for CLD, and different geographical regions and populations have different issues and demands, recommendations that work in one context may not work in another. Incorporating a diversity of CLD care contexts will allow us to explore different tensions and concerns that different services and populations may face. This will allow us to consider points of similarity and difference, potential points of intervention and considerations that may need to be made in relation to our recommendations.

Lived Experience Interviews WP Study Setting

For outpatient interviews, participants will live in the vicinity of the four sites identified above – in South London, in the South-West peninsular, in Blackburn and in Kent. Interviews will take place in a location convenient and comfortable for the participant – usually their home. This ensures that the interview does not place undue expectation of travel or exertion upon the participant. Visiting the participant at home may also give the interviewer insight into factors affecting the participant's health and healthcare – for example its accessibility, distance from the healthcare institutions they visit, the local environment and access to transport and amenities.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

For clinical staff:

Delivers care to CLD patients at hospital case study site

For inpatients:

Patient is under the care of liver service(s) in the hospital under study

Well enough to participate and consent to be interviewed (as determined by their treating physician)

Over age 18

Has experienced emergency admission for liver disease

For outpatients:

Patient is being seen by the outpatient liver clinic(s) under study

Well enough to participate and consent to be interviewed (as determined by their treating physician)

Over age 18

Has experienced emergency admission for liver disease

7.1.2 Exclusion criteria

For clinical staff:

Does not deliver care to CLD patients at hospital case study site

For inpatients:

Patient is not under the care of liver service(s) in the hospital under study

Not well enough to participate and consent to be interviewed (as determined by their treating physician)

Not under age 18

Has not experienced emergency admission for liver disease

For outpatients:

Patient is not being seen by the outpatient liver clinic(s) under study

Not well enough to participate and consent to be interviewed (as determined by their treating physician)

Not under age 18

Has not experienced emergency admission for liver disease

7.2 Sampling

The four case study sites have been carefully chosen to reflect different patient populations, patient outcomes, different services offered and geographical spread. Four sites were able to give us this variation while still enabling us to undertake comparative analysis. Time dedicated to ethnography across these sites has been carefully divided between these to facilitate ongoing comparison and reflection across the sites.

Across the four case study sites: Outpatient interviews: up to 40

Interviews informing the ethnography: Clinicians: up to 20; inpatients: up to 15

7.2.1 Size of sample

As a qualitative study, the distribution of interviews does not rely on sample size calculations for study design. However, we are seeking a distribution of interviews across the four sites of the project in to learn about how patients' experience treatment differs across regions with different CLD patient outcomes. For the ethnographic work strand, more interviews with clinicians based at KCH will take place than elsewhere, as RL is based at KCH for an immersive 6 months and then visits the 3 other sites for comparative data collection over shorter periods of time (2 weeks at each site, followed by a further week).

Given the variation we are looking for within the sample of patients and clinical staff, we estimate that the numbers above will be maximum number required sto allow us to reach data saturation. If we reach data saturation before the number of participants indicated above, we will not continue to ask patients/staff to participate.

7.2.2 Sampling technique

This study will conduct purposive sampling to interview participants from all four of the hospital sites, with a range of CLD types and across a range of ages (greater detail on this is given in the Study Design section above). By mapping and comparing interview responses against such demographic data, we will seek to explore in detail how inequality operates in CLD treatment and care.

7.3 Identification

7.3.1 Sample identification

Ethnography

The researcher and/or the lead clinician identified in the CSS will introduce the research to any patients or healthcare staff encountered as part of observation. Posters explaining the research will be placed in research areas.

For clinical staff interviews:

RL will draw on her time conducting ethnographic fieldwork in the four hospital sites to identify members of staff who may be willing to be interviewed. Staff will be selected to reflect involvement in a range of different forms of care and with different roles. RL will approach potential interviewees in their place of work/through work email addresses.

For inpatient interviews:

As part of their routine clinical work, clinicians treating outpatients will identify patients that fulfil the inclusion and exclusion criteria. These potential participants will first be approached by one of these staff members during routine contact and will ask patients if they are happy to speak to RL about the research project. RL will talk through the project and what their involvement would be, should they be willing to participate. RL will leave an information sheet and will return at a specified time (at least 24hrs later), to answer any further questions and, if the patient is willing, to undertake the interview/arrange another time for the interview, if the participant consents. If the patient does not want to speak to RL, they will be asked to indicate this to a member of staff. RL will check with clinical staff regarding patient wellbeing prior to meeting with patients.

For outpatient interviews:

As part of their routine clinical work, clinicians treating outpatients will identify patients that fulfil the inclusion and exclusion criteria.

These potential participants will first be approached by one of these staff members during routine contact. The staff member will explain the project to them and provide them with an invitation and information sheet. The patient will contact the research team via the contact information provided and complete an Expression of Interest form. This stage does not constitute consent to giving part – only to being called by a member of the team.

At no time will the research team have access to patient notes.

Participant eligibility screening process

As mentioned above, clinicians treating patients will identify patients that fulfil the inclusion and exclusion criteria according to patient notes. These clinicians will only consider patients under their care and who they see as part of routine practice.

Researchers will review the Expressions of Interest forms submitted by potential participants. Purposive sampling will be undertaken by researchers based on information that patients have chosen to disclose for the purpose of this sampling (age, treating hospital, first three digits of postcode, type of CLD).

7.3.2 Consent

Processes for informed consent

For all interviews conducted as part of the study, RL and GR will be responsible for obtaining formal, written consent from participants in line with the protocol. Interview participants will have received written study information, and had the study explained to them, at least 24 hours before they give their consent. On the day of the agreed interview, the researcher will again explain the study and check the potential participant's understanding of the purpose and nature of the research, and check that consent is voluntary and informed.

Participants will be asked to sign the consent form after re-reading the Participation Information Sheet. If at any time during the study participants ask to stop the interview, they can do so without needing to provide a reason. They may also withdraw their interview data up to four weeks after the interview without needing to provide a reason.

For the observation study work, RL will obtain written consent from the lead staff member or patient she is shadowing at the outset of the study. Following this, she will gain verbal consent at the start of each observation of team meetings or shadowing. For additional clinicians or patients who are encountered during this shadowing, the staff member, patient or RL will introduce the project and researcher to those present, give them a written leaflet with project information, and ask for verbal consent for the observation. Patients will have the opportunity to pre-emptively opt out of the observation study by contacting RL or a member of their care team, and this will be communicated on posters displayed in the study area. If any member of staff or patient does not consent, their contributions or data will not be recorded, and the researcher will leave the study area for the duration of the encounter.

Timeline for informed consent

Staff members and patients who are being shadowed will be informed of the study and given 24 hours to deliberate about their participation before the commencement of observation. For people encountered in observations, posters explaining the research will be present in spaces, and the staff member and/or researcher will explain the research and ask for verbal consent, and emphasise that giving or not giving consent will not affect any care provided. This means that people encountered during the observation process will not have the standard 24 hours to decide. Staff members, inpatients and outpatients participating in in-depth interviews will have a minimum of 24 hours to deliberate their participation before an interview begins. Interviewees will have the option to withdraw their data at the end of the interview (and up to four weeks after the event) and/or to stop the interview at any point.

Gauging capacity for consent

In order to ensure that inpatients and outpatients have the capacity to consent, clinicians will be asked at the identification stage to only select potential participants with the capacity for consent – in this instance, not affected by hepatic encephalopathy. If during the interview the interviewer judges that there may be concern about the participant's capacity for consent, they will raise their concern with the participant's clinical team (whilst being careful not to disclose any topics discussed in the interview).

- **8 ETHICAL AND REGULATORY CONSIDERATIONS**

- **8.1 Assessment and management of risk**

Risks of the study to the participant and mitigations for risk

Emotional distress – Risk and burden for all participants (patients and clinicians) include the potential for distress when discussing experiences of providing/receiving care.

Mitigation: The interviewer will assure the participant at the start of the interview that they can choose not to answer questions, or pause or stop the interview, without explanation, and the interviews will be structured with open-ended questions that allow the participant to shape the content of the interview. Both interviewers are trained qualitative researchers with previous experience of conducting sensitive interviews. They will be able to provide contact numbers for additional support should interviewees need them.

Physical risk – Patients may find a long interview tiring. In addition, some people with CLD may be immunocompromised, and individuals with CLD have a higher rate of mortality from COVID19 than those without CLD.

Mitigation: Interviews will be conducted at a time and place that suits the interviewee. For clinical staff and inpatients, this will depend on the possibilities available in the different hospital sites. For outpatients, interviews may take place in the participant's home, over the phone or in clinics,

depending on what interviewees prefer. The project will operate with reference to the situation of COVID-19 at the time of the study. If meeting in person, researchers experiencing COVID-19 symptoms will test themselves for COVID-19 using lateral flow tests for the two days before the interview. The research team will continue to review the position of COVID-19 and any new variants in the UK and introduce other measures, such as remote interviewing, where necessary.

Professional conflict of interest – For observing or interviewing clinicians, there is a potential for professional conflicts of interest, if they feel invited to report on clinical practices they do not agree with.

Mitigation: The project researcher will emphasise that the purpose of the study is not to discover or report poor quality practice, and that if concern does arise for staff participants they should follow Trust guidelines and support.

Risk of disclosure of harm – There is a risk that participants may disclose an intention to harm themselves or others.

Mitigation: The project has asked clinicians selecting potential participants to exclude individuals who may pose a risk to themselves or others. If this situation arises, participants will notify clinical staff in the patient's hospital, whilst taking care to maintain confidentiality regarding other topics discussed in the interviews.

8.2.1 Research Ethics Committee (REC) and other Regulatory Review, Compliance, and Amendments

Before the start of the study, a favourable opinion will be sought from a HRA REC for the study protocol, informed consent forms and other relevant documents. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained.

The Chief Investigator will notify the REC of the end of the study (30 September 2024). If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Before any patients are recruited into the study, the Chief Investigator will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator and RL, in agreement with the sponsor, will use the Amendment Tool on the IRAS website to guide the form of amendment required and to notify the REC and NHS R&D offices through the online submission system. The Chief Investigator and RL will work with sites (R&D departments at NHS sites as well as the study team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting

and ensure adequate data quality. The Project team will meet at least monthly, at which time there will be a fixed agenda item for review of all untoward incidents.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

Further monitoring support will be delivered by the independent Study Steering Committee which will meet 6-monthly to review milestones, deliverables and consider the implications of findings and their dissemination, including research designs, project research management, development of participant information resources, research reports, and dissemination of research findings.

8.3 Peer review

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

- The Sponsor considers the procedure for obtaining funding from NIHR to be of sufficient rigour and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies (listed below). Approval from each will be obtained before the study commences.

- Health Research Authority
- Research Ethics Committee

8.4 Patient & Public Involvement

<u>Early/developmental work on the project and project proposal:</u>

Consultation with people with liver disease was undertaken at the very earliest initial planning stages of this project. We first held informal discussion with people hospitalised with CLD at King's College Hospital, and with their next of kin, and following an encouraging response developed an initial research plan.

Through our research partners, the British Liver Trust, we then conducted an online survey of 57 people with CLD from across the UK to understand their attitudes to the goals and basic research methods under consideration. This sample was representative of the patients with CLD who would be in the proposed study cohort in respect of age, sex and cause of liver disease. More than 80% had required hospitalisation as a consequence of CLD. More than 90% felt it "extremely important" to understand regional variations in outcome of CLD. More than 90% supported the research and felt it to be addressing an important subject, endorsing the approaches proposed to be utilised, including the use of de-identified linked electronic health records. Thirty-three of the respondents volunteered to join an online patient consultation group for the research project.

A face-to face focus group was then conducted with 19 people who had a liver transplant for CLD, many of whom had experienced EA at an early stage of their illness. This group also confirmed support for the proposed research and its methodology.

Following successful funding of the project, recruitment methods, interview topic guides and ethnographic foci for the social science element of the project were developed and refined following discussions with patients with lived experience of CLD, clinical staff able to advise on patient:staff interactions and members of the British Liver Trust reflecting on their own work with patients.

<u>Ongoing PPIE involvement in the project:</u>

A patient representative with lived experience of CLD, emergency admission and liver transplant is a grant co-applicant and member of the research team, as is a representative of a patient organisation, the British Liver Trust (BLT). As members of the research team they will be involved in all stages of the research cycle including prioritising research questions, advising upon and managing the research process and routes to data opt-out, analysing and interpreting the results of research, with a prominent role in dissemination of findings.

Our project PPIE group will be convened at 6 monthly intervals throughout the project. The group will consider and advise on research questions, conduct and the actions that should follow its findings, and feeding back to the research team. Recognising patients and the public as key stakeholders in the research, the dissemination plan includes webinars, presentations and reports for patients and patient organisations. We will involve our PPIE and patient representatives to ensure that we engage all relevant organisations and that the style and format of our publications is accessible to these audiences.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. These will be adequately documented and reported to the Chief Investigator and Sponsor immediately.

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality. The Project team will meet at least monthly, at which time there will be a fixed agenda item for review of all untoward incidents.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach

Further monitoring support will be delivered by the independent Study Steering Committee which will meet 6-monthly to review milestones, deliverables and consider the implications of findings and their dissemination, including research designs, project research management, development of participant information resources, research reports, and dissemination of research findings.

-

8.6 Data protection and patient confidentiality

During recruitment, personal contact details will be used to recruit participants (with their consent) through the Expression of Interest form and retained to maintain continuity with patient participants during the final phase of the project. These details will only be obtained from the participants and used within their consent, and only those details provided by the participant will be used.

During the project, the original paper versions of this data will be kept securely in a locked cabinet on university premises and in an encrypted electronic form on a university server. These locations and procedures will ensure that personal contact information will always be kept in a separate location and format to that of the primary data. The only link between the two will be in the form of a participant number.

If personal information about patients shared in an interview (e.g. staff member uses patient as an example to make a point), personal information about the patient will be removed/anonymised after transcription.

Data collected in the field during interviews and ethnography will be stored on an encrypted electronic notebook, and then transferred to servers at the University of Exeter at the earliest opportunity for storage, and then deleted from the notebooks. Back-ups will be made regularly as per University of Exeter policy.

Interviews will be audio-recorded using a digital, encrypted, password-protected iPhone. Files will be securely transferred onto university servers and encrypted. An encrypted copy of each audio file will be sent to an external transcription service for transcription, and permission will explicitly be sought for this in the consent form. This external transcription service will be a recognised and accredited service and will be asked to sign a confidentiality agreement in advance. These audio files will be sent and received as encrypted, password-protected files.

RL will be the custodian of the data generated by the study. Access to the primary data generated by both WPs will be restricted to RL and GR. This will include contact information provided by participants and demographic details disclosed in patient questionnaires. Excerpts of transcripts, codes and themes generated through data analysis and analytical summaries and presentations of findings may be shared, on occasion, within the wider project team and PPIE group, to gain feedback and further insight into particular findings. This data will be anonymised.

We will store audio recordings until the end of the study (30 September 2024), when these will then be destroyed. Transcripts, contextual demographic data and field notes will be retained for 10 years following the end of the project. These will be anonymised and archived securely on University of Exeter servers.

De-identified data will be archived by the University 2 years after the project has ended and held for up to 10 years.

8.7 Indemnity

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office.

8.8 Access to the final study dataset

Due to the sensitive nature of the dataset, only RL and GR will have access to the full social science dataset, and no member of the extended project team or Steering Group will be able to access the data set. No researchers will be able to use the data to conduct secondary analysis.

9 DISSEMINATION POLICY

Based on our results, we will formulate recommendations on how the care of acutely ill people with CLD admitted to hospital as an emergency can be improved. Our strategy to disseminate findings will be based on a number of principles:

- We will build awareness of the project among patient groups and professional bodies in the project's early phase through direct communications and presentations.
- At key "junction points" in the research plan – e.g., at conclusion of specific work packages or at the commencement of others - there will be focussed dissemination activity to raise awareness and inform the next phases of research.
- We will organise an end-of-project workshop to formulate recommendation for practice. Participants of this workshop will be recruited from existing networks and relationships available to the members of the Research Team and Steering Group, including NHS England's Specialised Commissioning Team (or its relevant successor), BASL, the British Society for Gastroenterology (BSG) and the Intensive Care Society (ICS). This workshop will produce clear messages that fit our wide range of audiences (e.g., patient and public, commissioners, clinicians, regulators and policy makers). The recommendations will be summarised in a summary report that will be disseminated across all our stakeholders.

- Messages will be shared with people with CLD and clinicians through the extensive and developed communication channels of the British Liver Trust.
- Our channels for dissemination will include traditional media and academic journals, professional newsletters, social media, targeted emailing and dedicated project web pages.

Our findings will be disseminated as follows:

- A final research report for the NIHR HS&DR programme detailing research methods, findings and conclusions of all four WPs, including recommendations for practice and an extensive summary for patients and the wider public.
- Policy advice targeting NHS England at national level to the Specialised Commissioners via the chair of the Hepato-Pancreato-Biliary Clinical Reference Group (Prof Foster, Chair of the project's Steering Group).
- At a regional level by engagement with regional medical directors through formal meetings to discuss our findings and inform change at the local commissioning level.
- In addition to changes in formal commissioning, we will engage lead hepatologists in NHS Trusts via the BASL and BSG liver networks and ensure they are aware of our findings and the value of introducing change to their organisations.
- Feedback to NICE with regards to findings relating to NICE Pathways on the management of acutely ill patients in hospital, and NICE guidelines on gastrointestinal bleeding, acute kidney injury, complications of cirrhosis, and recognising and responding to deterioration.
- A training package and associated resources aimed at relevant professional bodies, including the BSG, BASL, ICS, and NHS Blood and Transplant, and which can be utilised by clinicians and drug and alcohol services to give information, address stigma and improve patient engagement.
- Presentations and resources for patient organisations and patients, including the British Liver Trust and related organisations to help inform and empower patients and improve patient engagement. We will utilise our PPIE and Steering Group, charity representatives and consult key stakeholder to increase dissemination coverage and ensure style and format are accessible.
- Research papers for peer-reviewed academic journals, articles for clinical journals, and conference presentations.
-

10 REFERENCES

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- **11. APPENDICIES**

11.1 Appendix 1- Required documentation

Documentation required prior to initiating a participating site:

- Research CVs of Dr. Rebecca Lynch and Dr. Grace Redhead (project researchers)
- Expression of Interest Form for outpatients interested in participating in the project
- Email to non-selected outpatient interviewees
- Ethnographic study information poster
- Participant information sheets for ethnographic work (clinical staff being shadowed, patients being shadowed, clinical staff interviews, inpatient interviews)
- Participant information sheets for out-patient interviews (outpatients, friends and family members)
- Consent forms for ethnographic work (clinical staff being shadowed, patients being shadowed, clinical staff interviews, inpatient interviews)
- Consent forms for out-patient interviews (outpatients, friends and family members)
- Interview topic guides (outpatient; in-patient; clinical staff)
- Demographic questionnaire to be completed by inpatient and outpatient interviewees
- List of support services for interviewees (1x sheet for patients, 1x sheet for clinical staff)

11.2 Appendix 2 – Amendment History

This will be amended with letters from the four local sites when they are received.

East Lancashire Hospitals NHS
NHS Trust

Dr S A McClements
Hepatology
Digestive Diseases MEC
Royal Blackburn Hospital
Haslingden Road
Blackburn BB2 3HH

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deborah.mcleish@elht.nhs.uk

24 March 2021

NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
University of Southampton
Alpha House, Enterprise Road
Southampton,
SO16 7NS

To whom it may concern,

Re: NIHR132969; Management of patients with chronic liver disease admitted to hospital as an emergency.

This is to confirm that my Trust will be happy to provide access to our centre for research team members for the above study. We will facilitate the observational and interview elements of the ethnographic components of the research.

Blackburn with Darwen and Burnley local authorities represent the main conurbations served by East Lancashire Hospitals Trust. Both consistently remain in the most deprived 10% of authorities within England on IMD ranking (Index of Multiple Deprivation). Health care inequality within the region is evidenced by prevalence and incidence rates for cancer, cardiovascular disease and liver disease that consistently remain above national rates. Within East Lancashire there are pockets of affluence highlighting stark local health inequalities; for instance in the most deprived areas, life expectancy for men is 10.2 years lower and 7.1 years lower for women, when compared to the least deprived areas.

East Lancashire is a richly diverse area, the main urban centres having benefitted from high volume immigration from South East Asia in the 1950's and 1960's. Consequently, there are vibrant communities of second and third generation immigrants; 31 % of people in Blackburn identified as BME in the 2011 census.

The liver service forms part of the Gastroenterology department with shared inpatient beds on the Royal Blackburn site. Out-patient services run through the Trust's 6 sites in East Lancashire, with further outreach from the viral hepatitis team to the wider Lancashire and

King's College Hospital NHS
NHS Foundation Trust

Liver Transplantation and
Hepatobiliary / Pancreatic Surgery

Mr Andreas Prachalias
Clinical Director of Liver Services
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King's Switchboard: 020 3299 9000

Date: 7th April 2021

NIHR Evaluation
Trials and Studies Coordinating Centre (NETSCC)
University of Southampton
Alpha House, Enterprise Road
Southampton, SO16 7NS

Dear Sir / Madam

Re: NIHR132969; Management of patients with chronic liver disease admitted to hospital as an emergency.

I am writing to you in support of the above study. My Care Group will provide access to the members of the research team and will facilitate the observational elements of the ethnographic components of the research.

The Institute of Liver Studies at Kings College Hospital is a high-volume tertiary centre for the care of patients with chronic liver disease with a specialist Intensive Care Unit dedicated to their care and supports one of the largest liver transplant programmes in Europe. In addition, this incorporates the largest HPB unit in the country.

Kings College Hospital is also a busy general hospital serving an inner city population with high levels of deprivation, and the researchers will also have access to general Critical Care and standard wards to conduct research there.

Please do not hesitate to get in touch if you have any further questions.

Yours sincerely

Mr Andreas Prachalias
Clinical Director of Liver, Gastroenterology and Endoscopy Services
Consultant in HPB & Liver Transplant

East Kent Hospitals University NHS
NHS Foundation Trust

Department of Gastroenterology

Tel: 01233 616625

William Harvey Hospital
Kennington Road
Willesborough
Ashford
Kent
TN24 0LZ
General Enquiries: 01233 633331

Private and Confidential

Dated: 1.04.21

To whom it may concern,

Re: NIHR132969; Management of patients with chronic liver disease admitted to hospital as an emergency.

This is to confirm that East Kent Hospitals University NHS Foundation Trust will be happy to provide access to research team members for the above study. We will facilitate the observational and interview elements of the ethnographic components of the research.

William Harvey Hospital has a dedicated liver service and currently working towards phase 1 accredition for Improving quality of liver service (IQLS). There are approximately 8 patients with decompensated liver disease admitted each month through the emergency department . We have Consultant led liver clinics for decompensated liver disease, complex hepatology cases such as overlap syndrome, viral hepatitis etc. We have nurse led Cirrhosis HCC surveillance clinics and Hepatitis B/C clinics. We have several hepatology audit projects which we are currently working on. We are an approved site for the national PBC audit and UK wide PBC research study.

We look forward to participating in this study and offer the support required to the research team.

Yours sincerely

Dr Jayshri Shah
MD DNB MRCP CCST
Consultant Hepatologist and Gastroenterologist

University Hospitals Plymouth NHS Trust

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Professor Matthew Cramp, MD FRCP 01752 432722
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Dr Ashwin Dhanda, PhD MRCP 01752 432723

Hepatology Nurse Specialists secretary: 01752 431930
Alcohol Liaison Service: 01752 439933

Hepatobiliary Surgeons
Mr David Stell PhD FRCS
Mr Matthew Bowles, MB FRCS
Mr Somaiah Arnoori, MS MD FRCS
Mr Chris Briggs, MB Ch B MD FRCS

Claire Goulding HPB Cancer Nurse Specialist
Liz Whitby, HPB Cancer Nurse Specialist
Surgical Secretaries: 01752 432071

Ref: MEC Typed: 30/03/2021

NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC)
University of Southampton
Alpha House, Enterprise Road
Southampton. SO16 7NS

To whom it may concern

Re: NIHR132969; Management of patients with chronic liver disease admitted to hospital as an emergency.

This is to confirm that my centre will be happy to participate in the above study. We will provide access for research team members to conduct the study and will facilitate the observational and interview elements of the ethnographic components of the research.

Derriford Hospital is the largest teaching Hospital in the south west. The South West Liver Unit serves its local catchment population of Plymouth and nearby areas of Devon and Cornwall, a population characterised by diversity – both rural and urban, some more wealthy areas but with large pockets of deprivation, and wide variance in health and life expectancy. Hepatology services for much of the south west of England are provided by the South West Liver Unit, a large specialist liver unit delivering hepatology, hepatobiliary surgery and assessment and follow-up liver transplantation services.

Please do not hesitate to get in touch if you have any further questions.

Yours faithfully,

Professor Matthew E Cramp MD FRCP
Consultant Hepatologist and Professor of Hepatology

11.4 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0 (prior to HRA approval)	3/4/23	Grace Redhead	Email address correction for Grace Redhead – g.o.redhead@exeter.ac.uk not g.redhead @exeter.ac.uk
2	3.0 (prior to HRA approval - changes made in response to initial REC review)	24/4/23	Grace Redhead	p.24, changed from 'observing' to 'shadowing' p.24, added that RL will give patients encountered during observation a written leaflet about project p.24, added that patients may pre-emptively opt out of observation study by contacting RL or a member of their care team and that this option will be included on posters displayed in study area. p.24, removed that RL will 'wait at a distance' and replaced with RL will 'leave the study area'
3	3.1	29.8.23		p.1 addition of statement acknowledging NIHR funding

All protocol amendments will be listed here should a new version of the protocol be produced. Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC.