Version 5. 30/11/2023

Protocol: Liver Research Cymru.

Duration 12 months (commencing 1st April 2023 Through to 30th March 2024).

Source of Funding: This study/project is funded by the NIHR Health Technology Assessment (HTA) Programme (NIHR 154876). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care

This programme relates to building of a research collaborative in Wales: Liver Research Cymru

The method by which we aim to achieve this is set out in the detailed research plan and the 3 workplans are reproduced below.

Only in workplan 3 will we look to describe new studies and any associated protocols can be uploaded as they develop.

Andrew Yeoman

October 2023

1. Building the Research Community (Yeoman, Nollett)

There is a need to establish a partnership network of health care professionals, researchers, and the public across Wales. Clinical partners will include consultant Hepatologists, GPs, microbiologists/ blood borne virus (BBV) teams, public health consultants and allied health care practitioners, including hepatology and BBV specialist nurses. Representation will be from all Welsh health boards. Broader clinical stakeholders, including public health clinicians will receive feedback through the bi-monthly LDIG meetings. Academic partners will be drawn from the Centre for Trials Research and the Division of Population Medicine, Cardiff University, Swansea Centre for Health Economics, Population Data Science and the SAIL Databank, Swansea University. The partnership's initial focus will be to strengthen and build the necessary links to lead research focussed on screening, early diagnosis and prevention, and rapid evaluation of clinical pathways. The partnership will actively seek to build links with established clinical research expertise in Wales, including palliative care and oncology. The project management group will meet monthly and lay the foundation for the network model. The broader stakeholder group will contribute to data review and a research synthesis away day, and individuals will be invited to contribute to focused elements of project development. The partnership will connect and learn from successful research teams that have addressed similar priorities for other diseases, for example, the screening, diagnosis, and early prevention of cancer research team at the Division of Population Medicine, Cardiff University.

Existing collaborators/stakeholders already supporting this work are: Dr Sue Channon, clinical psychologist and process evaluation expert; Prof Sunil Dolwani, Gastroenterologist and Director of Health Wise Wales; Dr Alan Woodall, GP and Clinical Director of R&D Powys Teaching Health Board.

Clinical collaborators have already also been identified for each health board in Wales and are as follows; Aneurin Bevan UHB- Dr Andrew Yeoman. Betsi Cadwalladr UHB - Dr Thirologanathan Mathialahan, Cardiff and Vale UHB - Dr Tom Pembroke, Cwm Taf Morgannwg UHB- Dr David Samuel, Hywel Dda UHB- Dr Ian Rees, Powys UHB- Dr Alan Woodall, Swansea Bay UHB-Dr Chinlye Ch'ng.

There is a need to further develop research leadership and skills within the hepatology community in Wales. Mentorship will be provided by the senior research team (Carson-Stevens, Fitzsimmons & Hood) with an additional view to recognition of needs for training and upskilling. The management of the network will be facilitated by the project manager (ABUHB).

As well as developing the research partnership within Wales, Liver Research Cymru will build and strengthen relationships with existing research groups active in this field across the UK. In this regard the lead applicant (Yeoman) is already a member of the British Society of Gastroenterology (BSG)/British Association for the Study of the Liver (BASL) Research Development Group and also co-chairs a special interest group (SiG) on Early Detection of Liver Disease in the UK. Although this is currently an informal group as the respective professional bodies have not been able to commission new SiG's due to financial constraints, the co-chair is currently the BSG Vice President for Hepatology and the current President of BASL is also supportive of the activity.

The SiG exists to share best practice across the UK and to help set the direction of future work in regards clinical pathways and research. Tangible outputs from the group to date comprise 2 publications. The first was on the methods of early detection of liver disease (Macpherson et al. Frontline Gastroenterol. 2022 Jan 24;13(5):367-373) and the second a systematic review of existing pathways (Abeysekera et al. Lancet Gastroenterol Hepatol. 2022 Aug;7(8):770-780).

The SiG comprises membership from each of the 4 nations within the UK and has representation from the key research groups currently working in the field of early detection of liver disease (Dundee, Leeds, Royal Free and University College London, Portsmouth, Nottingham, Newcastle). As such there is an established and collaborative network available for Liver Research Cymru to build upon and develop ever stronger relationships and collaborations.

Patient and Public Involvement is an integral part of the network model and is included to contextualise findings from the data from a patient/service-user perspective, prioritise and develop research questions, input into grant applications and drive participation in liver disease research. To expand on the initial patient representation, a public advisory group will be established consisting of 8 people with personal experience of liver disease or caring for those with liver disease. The aim is to encompass representation from every health board in Wales, those of working age, underserved groups, and the predominant aetiologies of liver disease in Wales.

Outputs:
The Liver Research Cymru network aims to develop an inclusive and cohesive group within 6-months to review the data generated in WP2 and contribute to the design and prioritisation of studies leading to NIHR phase 2 bids in objective 3 (Figure 1). In addition, we aim to use

this network to springboard a bid to establish this network as a Health and Care Research Wales Research Unit.

2. Connecting & Understanding the Data (Akbari, Pembroke)

The Wales Liver Disease Registry methodology has built upon the International Classification of Diseases (ICD) version 10 (ICD-10) code mapping in the HepaHealth project and 2021 expert panel consensus (Pimpin et al., 2018, Hagström et al., 2021). Codes reflecting the natural history of liver disease have been defined to enable monitoring of disease progression over time from underlying aetiology (i.e. alcohol related liver disease, hepatitis C infection) to cirrhosis, portal hypertension, decompensation, liver cancer and death. ICD-10 mapping to Read codes has been completed.

The Secure Anonymised Information Linkage (SAIL) Databank is one of the richest anonymised individual-level, population-scale Trusted Research Environment (TRE) in the world, containing a variety of health and social care, administrative, geo-environmental and specialist data sources (saildatabank.com Ford et al., 2009, Rodgers et al., 2012). SAIL contains 86% of primary care and 100% of secondary care data for all Welsh residents and those receiving NHS Wales services. The wealth of information available in the SAIL Databank includes lifestyle and clinical data (alcohol excess, BMI, injecting drug use, smoking and diabetes), prescribing data, clinical results extracted directly from laboratory reporting systems (e.g. abnormal liver function tests and thrombocytopenia) and environmental and socio-economic deprivation data. Operative codes and pathology data will be included in the data set.

The Liver Disease Registry methodology will be applied to the SAIL Databank. This will enable the capture of outpatient diagnoses of liver diseases at an earlier stage of presentation (Ratib et al., 2014). Discrete pre-diagnosis stages of i) liver risk factors, alcohol, obesity/metabolic and injecting drug use, and ii) routine blood test abnormality will be defined. The coding methodology will be reviewed as it is integrated with the primary care data. Further adjustments will be made to ensure complete capture of all relevant Read codes, associated risk factors and investigations into a research ready data asset (RRDA).

We will test the scope and utility by using this research ready data asset to address three key objectives:

1) Describe key clinical and socio-demographic features associated with liver disease diagnosis, later stage presentation, mortality on first hospital admission and disease progression.

Descriptive logistic regression models will investigate a number of potential explanatory variables including (but not limited to) social deprivation and difficult to reach geographic locations, (coastal and post-industrial towns and inner cities). Of particular interest is describing features associated with developing compensated advanced chronic liver disease (cACLD). These patients are a key group to target for early diagnosis in primary care, and these analyses will improve understanding of disease progression, (including HCC development) and potentially lead to future research on appropriate screening strategies. Overall, these descriptive analyses will help us to better understand who is at greater risk of liver disease diagnoses and liver disease-related poor outcomes and will inform subsequent funding applications to allow targeting of the population most at need.

2) Assess ability to evaluate clinical pathways

To support service change and improvements to clinical care, we will develop a data platform from which service change, and the associated health economic implications, can be rapidly evaluated and directly inform subsequent improvements. We will test and refine our ability to do this by evaluating the All Wales abnormal LFT pathway. This pathway was implemented in a staggered manner allowing for analysis of intervention and comparator groups using data from the SAIL databank. The analysis will include clinical and cost-effectiveness outcomes. Following this work, we will develop procedures to enable rapid clinical and economic analyses of future pathways – not just in Wales, but across the UK using routinely collected data and SAIL as the trusted research environment (Innes et al., 2022, Petta et al., 2021).

3) Develop frameworks to assess time to diagnosis and disease progression

Linked primary care, secondary care, laboratory, pathology, and mortality data may allow us to describe the clinical encounters from first presentation with a liver-related symptom to first liver disease diagnosis and assess the potential for earlier diagnosis and treatment, as well as the resource use and associated costs. The main objectives of this work will be descriptive to better understand the data, the size, complexity, and value of repeated measures, and to draw on expertise from other disease areas to define parameters of interest (e.g., code lists of agreed liver-related symptoms, the period that most accurately reflects time to diagnosis). The overall aim of this work is to complete the necessary pilot and feasibility work to put us in an excellent position to apply for funding for subsequent early diagnosis research, which will use causal inference methods to fully and robustly understand pathways to diagnosis and treatment, and identify areas for intervention.

Following this work, the public advisory group will meet to help interpret the findings from the data integration and give their own perspectives (from their lived experience) on the liver journey, including missed opportunities for diagnosis.

This data analysis will enhance the understanding of the natural history of liver disease and cost-of-illness in Wales. This workstream will develop the methodologies to synthesise high-quality data, underpinning future work in the timeframe of the NIHR phase 2 funding call. In particular, sample size and potential bias and approaches to mitigate bias will be identified, as well as opportunities to utilise routine data to provide the outcome data for prospective studies. We aim to develop liver disease progression and features of mortality data relevant to under researched areas, including palliative care and networks for advanced complex liver disease outside of the liver transplant setting. Approaches to identify risk factors for missed opportunities in diagnosis will be identified.

It is anticipated that this analysis of liver health in Wales will identify gaps in service provision and needs for service development. These potentially low-hanging opportunities to bring about rapid and high-impact service development will be implemented through the existing LDIG network and the impact assessed through the Liver Research Cymru collaboration.

3. Prioritising & Designing Studies (Ahmed, Currie)

Following the initial establishment of the Liver Research Cymru partnership and the development of the liver disease RRDA, a specific workstream will convene to identify specific research questions that can be enabled using the RRDA and how it could be potentially expanded and iteratively developed as new priorities are identified. The priority of these questions and study design will reflect the newly formed collaborations within Wales and

reflect the clinical needs established in the Liver Disease Implementation Group with patient advisory group input. The key goal is to develop a research application in the NIHR phase 2 call. It is anticipated that the primary focus of this research will reflect the need to improve the early diagnosis and screening of liver disease in Wales. Complementary research questions will incorporate i) modelling of the services required to meet the growing incidence of liver disease including assessment of cost-effectiveness and ii) identification and engagement with under-served groups at increased risk of liver disease.

This work package will facilitate research prioritisation among the partners and external stakeholders. Initial long-lists of research priorities will be identified from James Lind Alliance priority setting partnership reports, NICE clinical guideline research recommendations, national Special Interest Groups (SiG's) and national liver disease delivery plans. They will be considered in the context of data insights from work package 2 around burden and need. Liver Research Cymru will also prioritise working with other groups funded by this call to deliver appropriate research activity within Wales to maximise recruitment.

The public advisory group will hold a third meeting to prioritise research questions from a patient/carer perspective and reference the long lists identified. A fourth meeting of the public advisory group will be held to gather patient/carer input into the design of the proposed research and final grant application.

Prioritised research will be designed with methodological input from the Centre for Trials research, Centre for Health Economics, Division of Population Medicine, and external experts as required. WP leads will link with existing Health and Care Research Wales infrastructure, such as the Research Support & Delivery Service, to design decentralised studies that minimise the burden on participants and the NHS. This builds on our experiences supporting the UK-wide PANORAMIC trial, which recruited and followed up 25,000 people (1,800 in Wales) from primary care in 5-months without face-to-face contact. In the design of future studies we will use our links with the Population Data Science Group and the SAIL Databank and our substantial experience of using routine health data (including NHS Digital, Clinical Practice Research Datalink (CPRD), QResearch etc.) to maximise the capture of participant information, including patient reported outcome measures, and follow-up data from routine records (including data for health economics), using SAIL as a dedicated TRE for studies that recruit participants from outside Wales.

Summary

Liver Research Cymru will develop a new research network combining clinical hepatology experience with established research expertise in Wales. The application and development of the novel Liver Registry methodology within the SAIL Databank will provide a unique liver disease RRDA encompassing risk factors for primary and secondary care diagnoses, prescribing, laboratory, geo-environmental and mortality data. Methodology and preliminary data review by a broad range of methodological experts will inform the development of research projects as part of NIHR phase 2 bids. Further expansion to acquire and use UK-wide data will be explored, with the SAIL Databank TRE able to be used to store and access anonymised data from anywhere in the world. This project in itself will provide important up to date epidemiological data relevant to developing hepatology services in Wales and across the UK in the evolving post-COVID-19 environment.