Research Partnership on Caring for Cirrhosis Closer to Home

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Abstract

Chronic liver disease is an ignored epidemic with significant premature mortality. The majority of deaths from liver disease result from cirrhosis or its complications. The therapeutic strategies that have been studied to slow disease progression in cirrhosis have been carried out in highly selected patient population in specialised liver centres. Currently in the UK, most of the clinical care for patients with cirrhosis is concentrated in secondary care and this has exacerbated the disparity between the clinical need and provision of specialist liver services across the UK. In line with the 2019 NHS Long Term Plan, delivering community-based interventions for patients with cirrhosis will boost out-of-hospital care and dissolve the historic divide between primary and secondary care. In the current climate of unprecedented pressure on both primary and secondary care, the optimal ways to integrate and deliver these community-based interventions are unknown.

The Research Partnership on Caring for Cirrhosis Closer to Home (COACH) was established to develop the capacity and capability to deliver high quality research in the field of community care for patients with cirrhosis.

COACH developed a PPIE stakeholder network in collaboration with other local liver partnership. These networks facilitated research priority setting events which highlighted the need for treatment options for patients with decompensated cirrhosis and delivery of treatment closer to patient's home. This culminated in the development of research proposals and funding applications to the NIHR.

The COACH partnership has created a multidisciplinary collaborative hub of research expertise in advanced liver disease. This provides a foundation for future research activities in this area.

Plain Language Summary

Liver disease is a serious but often an overlooked health problem that causes many early deaths. Most of these deaths happen because of cirrhosis, a late stage of liver damage. So far, most treatments for cirrhosis have only been tested in small groups of patients treated at specialist hospitals. In the UK, care for cirrhosis is mainly provided in hospitals, which has led to unequal access to specialist liver care across the country.

The NHS Long Term Plan (2019) calls for more care to be delivered in the community, closer to where people live. This would ease pressure on hospitals and build innovative services closer to where patients live. However, the best way to provide this kind of care in the community is still unclear.

To tackle this, we formed the COACH Partnership (Caring for Cirrhosis Closer to Home). Our goal was to support high-quality research into community-based care for people with cirrhosis. COACH worked with local liver groups and patients to understand what matters most. They found a strong need for better treatments for people with advanced liver disease and more care delivered at home or nearby.

COACH has since helped create research projects and apply for funding to the National Institute for Health and Care Research (NIHR). We have also built a strong team of experts working together on liver disease, creating a solid base for future research.

Keywords

Cirrhosis, Trials, PPIE, Community Care

Background

Chronic liver disease is an ignored epidemic, with significant premature mortality. In England, in 2020, liver disease was the second leading cause of working lives lost, overtaking ischaemic heart disease and accidental poisoning[1]. Over the last 50 years, deaths from liver disease have increased by 400% which is in stark contrast to other major chronic conditions in which deaths have either remained stable or decreased[2]. The majority of liver deaths result from cirrhosis or its complications. The natural history of cirrhosis is characterised by an asymptomatic phase without any clinical manifestation of the disease. This is followed by the decompensated phase characterised by the occurrence of complications including ascites, variceal bleeding, hepatic encephalopathy, and/or hepatocellular carcinoma. Decompensation is associated with reduced survival[3]. Management of decompensated cirrhosis is largely driven by treatment of individual complications as they occur. The therapeutic strategies that have been studied to slow the disease progression include non-selective beta-blockers (NSBB)[4, 5], transjugular intrahepatic portosystemic shunts (TIPS)[6, 7] and intravenous albumin infusions[8, 9]. These studies are invariably carried out in highly selected patient population concentrated in specialised liver centres, which limits the generalisability of the study findings.

In the UK, chronic disease management is one of the cornerstones of primary care work, with management pathways and treatment services available locally and incentivised nationally[10]. This has led to a more standardised evidence-based care for people living with a range of chronic conditions such as type 2 diabetes and congestive cardiac failure. However, there is a glaring lack of incentivisation of managing liver disease as a chronic disease across most of the UK, with no current or historical Quality and Outcome Framework (QOF) targets for liver disease [11]. Many GPs report a gap in confidence and knowledge in managing chronic liver disease [12]. Therefore, the majority of the clinical care for patients with cirrhosis is concentrated in secondary care. This has exacerbated the postcode lottery of specialist liver services with the service provision and clinical need being disjointed across the UK[2].

The proposed partnership focussed on studying the delivery of community-based interventions for patients with cirrhosis. This will be in line with the recommendations from the 2019 NHS Long Term Plan to boost out-of-hospital care and dissolve the historic divide between primary and community health services[13]. This community-based model is likely to

involve complex interventions, including complexity in the number of components in the intervention involved, the target patient population and the permitted level of flexibility in the intervention delivery[14]. Potential interventions could include (but are not limited to):

- Delivery of intravenous albumin infusion in the community, either in patient's home or in community hubs.
- Self-management co-ordinated through community hubs. This can be facilitated by novel digital monitoring system[15].

In the face of current challenges in the NHS with unprecedented pressure both on primary and secondary care, optimal ways to integrate and deliver these community-based interventions are unknown. Conventional randomised controlled trials (RCTs) may not be suitable to answer these questions and therefore alternative study designs such as self-controlled study, historical controls or cluster randomisation should be explored.

We developed a sustainable, cross-sectoral partnership with diverse expertise to address these challenges. The partnership was underpinned by concepts of equality, diversity and inclusion among the patient population, healthcare providers and also the researchers as highlighted by the NIHR[16].

The proposed partnership brought together three regions seeking to improve care for patients with decompensated cirrhosis by delivering care closer to home: London [University College London (Prof Alastair O'Brien, AOB), Ealing (Dr Nina Stafford)], Yorkshire [Leeds (Dr Ian Rowe, IR), York, Scarborough (Dr Robert Driver)] and the East Midlands [Nottingham (Dr Naaventhan Palaniyappan, NP, Prof Guruprasad Aithal, GPA), Grantham, Lincoln]. The partnership adopted a hub and spoke model. In each region, the research-experienced centres supported by clinical academics (NP, GPA, AOB and IR) buddied with research-naïve sites. This approach provided opportunities to focus on new research sites and to disseminate the research culture across these sites, and ultimately improve care and health outcomes.

These specific areas have been chosen as they are areas where liver disease is prevalent, and the population has historically been underserved by research activity. Leeds and Nottingham are among the top three regions with the highest hospital admission rates due to liver disease in England. These regions represent geographical areas with significant population diversity in ethnicity and socioeconomic status [17, 18].

The proposed partnership aimed to break the perceived barrier between primary and secondary care in jointly delivering clinical research and foster stronger integration between partners in primary and secondary care. Nottingham City GP Alliance (NCGPA) was our primary care partner in Nottingham (Dr Jonathan Harte, Medical Director of NCGPA). NCGPA consists of 37 GP practices covering a population of 355,000.

Dr Kirsty Sprange (KS) from Nottingham Clinical Trials Unit (NCTU) provided methodological oversight and supported the provision of research training for members of the partnership through NCTU.

Project aims & objectives

The overarching aim of our NIHR liver partnership was to establish and develop a partnership across diverse geographical areas with capacity and capability to deliver high quality research in the field of community care for patients with cirrhosis.

Our specific objectives were as follows:

1. To develop a sustainable, cross-sectoral collaborative research partnership which includes geographic patient populations historically underserved by clinical research activity.
2. To understand the strengths, weaknesses, barriers and enablers of research readiness within the current clinical research infrastructure to address the complexities of community-based interventions for patients with cirrhosis.
3. To share topic and methodological expertise across the partnership and consequently develop organisations with capacity and capability to deliver nationally generalisable studies.
4. To identify key research questions in collaboration with stakeholders, co-design and submit high-quality competitive research proposals to future NIHR call on liver disease.

Patient and Public Involvement/Engagement

Our aim was for patient and public involvement and engagement (PPIE) to be conducted in a way that it promotes meaningful and active involvement of patients with cirrhosis and those important to them. Within the Nottingham Biomedical Research Centre (BRC), the patient advisory group (PAG) and PPIE task group of the Gastrointestinal and Liver Theme have been integral to research focussed on liver diseases. Nottingham has hosted the James Lind Alliance Priority Setting Partnership in 'Alcohol-related Liver Disease' and 'Non-alcohol-related Liver and Gallbladder Disorders' (2016-2017) and the GI & Liver Theme PAG has participated in these priority setting activities. Over the past 10 years, PAG has supported 158 research applications. In addition, we have continued to learn through PPIE events including ‘Ethnicity and Chronic Conditions’ (May, June, Oct 2020), ‘Multi-morbidity’ (Focus groups, Dec 2020) and ‘Research Lounges’ (March, July 2021).

In developing the partnership, we worked with 8 PPIE representatives (patients with chronic liver disease and carers). We held a virtual PPI focus group and the PPIE representatives reviewed the lay summary and plans for public involvement in the research partnership. With the support of Nottingham BRC, all PPIE representatives were reimbursed for their contributions to this partnership.

Stakeholder engagement

After receiving the award, a partnership coordinator was appointed to oversee day-to-day activities associated with COACH.

The core members of COACH attended the launch of the four NIHR liver partnerships that were associated with NIHR Nottingham Biomedical Research Centre (BRC). The event was attended by diverse stakeholders associated with the partnerships including academics, clinicians, community leaders, and patients with lived experience. At this meeting, Dr Palaniyappan presented the rationale behind the COACH partnership. Round table discussions concluded the day with discussions around strategies to improve inclusivity in liver research.

Research Strategy and Priority

The established PPIE network, and wider academic and non-academic partners were invited to a discovery event to identify the research priorities. Patients and people with lived experience, including the carers were given time and space to express their thoughts on research topics in an open forum.

The main points that were raised during this meeting were

1. "*We did not realise how poor the prognosis is for patients with decompensated cirrhosis.*"

   Patients and carers were shocked at the difference between the prognosis of patients with compensated and decompensated cirrhosis. Decompensation leads to hospitalisation, which can have further negative consequences in terms of nosocomial infections.

2. "*I am shocked at the lack of treatment options for patients who are seriously ill with decompensated cirrhosis.*"

   There is a lack of disease modifying treatments for patients with decompensated cirrhosis beyond alcohol abstinence for patients with alcohol-related liver disease. Liver transplant is only available for a very small proportion of patients mainly due to lack of donor organs. Despite years of research, there is lack of progress in identifying a disease modifying treatment that is widely available, much to the disappointment of the patients.

3. "*The difference in specialist liver care and research across the country is huge*."

   The map highlighting the variation in liver services across the country generated a lot of discussion in the room because there was a general assumption that the care across the NHS is homogenous.

The priorities identified during this meeting were

(i) Urgent need for new therapeutic options for patients with decompensated cirrhosis including repurposing of existing medications for new purposes.

(ii) Delivery of treatment in the community closer to patient's home. Patients and carers were unanimous in expressing their preference of community-based treatment compared to treatment in the hospital.

(iii) The important outcomes identified, in order of priority, were
   a. Improved survival
   b. Shorter hospital stay and preventing of recurrent hospitalisation
   c. Improved quality of life.

Information gathered from these sessions directly led to the funding application that was submitted from the COACH partnership.

Long-term albumin infusion in the community for patients with cirrhosis and ascites (ALBI-HOME) (submitted to NIHR Health Technology Assessment)

Chief Investigator – Dr Naaventhan Palaniyappan & Prof Alastair O'Brien

Co-investigators – Prof Guruprasad Aithal, Prof Matthew Cramp, Dr Ian Rowe, Dr Robert Driver, Prof Ewan Forrest, Prof Alan Montgomery, Dr Kirsty Sprange, Dr Chris Partlett, Dr Edward Cox, Dr Suman Prinjha, Ms Rebecca Haydock, Ms Samantha Drewett

Summary

Information gathered from the PPIE activities via COACH partnership directly informed this application. It was developed to address the patient priority of new effective treatment in decompensated cirrhosis and delivery of such treatment at home.

A core working group was established involving academics and clinicians with expertise in hepatology, trial methodology, qualitative analysis and health economics. Providers of homecare nursing were involved. PPIE support was provided by the GI/Liver Patient Advisory Group (PAG) from the NIHR Nottingham BRC. Application development was led by Dr Naaventhan Palaniyappan with ongoing mentorship from Prof Alastair O'Brien.

A full-day workshop was attended by the core working group to develop the research question according to the PICO framework. The protocol for the application was subsequently refined through regular online meetings.

There is evidence to suggest that weekly albumin infusion improves survival, reduces hospital admissions and improves quality of life. The current evidence has led to the adoption of long-term albumin treatment as standard of care in Italy[19] and Australia[20], with considerable enthusiasm within the hepatology community worldwide However, this potentially life-saving treatment will not currently be introduced in the UK for 2 main reasons:

1. Uncertainties regarding the clinical effect of HA, especially in patients with alcohol-related cirrhosis which accounts for 85% of patients in UK studies (ATTIRE, ASEPTIC and BOPPP).
2. Lack of capacity in the NHS to deliver this treatment in secondary care.

To address these concerns, we proposed an adequately powered randomised controlled trial to assess the clinical and cost-effectiveness of long-term albumin delivered in patients' homes. With a positive outcome, we anticipate widespread adoption of this innovative treatment strategy for these patients who lack alternative effective treatment.

Homecare delivery was an innovative approach to address the challenges within the NHS regarding the delivery of weekly albumin infusions. Such services are already used in other fields including cancer treatment and antibiotics. We felt that homecare delivery would be an inclusive approach aimed at reducing barriers to attending hospital for treatment for patients from underserved groups.

Proton-pump inhibitor Use in Cirrhosis

Proton-pump inhibitors (PPI) are liberally prescribed in patient with cirrhosis without a clear evidence-based indication. Observational and retrospective studies have highlighted the potential harm of PPI in patients with cirrhosis, with 4 meta-analyses identifying a significant association between PPIs and spontaneous bacterial peritonitis (SBP)[21-24]. Increased risk of SBP has been attributed to the PPI-related microbiotic shift leading to small intestinal bacterial overgrowth, bacterial translocation, and systemic inflammation [25-27]. Other infection risks associated with PPI therapy include pneumonia [28, 29] and *Clostridium difficile* colitis [30]. Adverse clinical outcomes have also been observed with PPI use in cirrhosis with increased hepatic encephalopathy (HE) [31, 32] and mortality [33-35]. However, studies were limited by retrospective or case–control design [36-40] and prospectively conducted studies did *not* show increased incidence of SBP[38, 41]. PPIs are more likely to be prescribed following variceal haemorrhage, which itself increases risks of infection, HE and mortality, thus limiting interpretation due to confounding by indication[42-45].

Therefore, there remains considerable uncertainty over the true risks of PPI use among patients with cirrhosis. This is important as use could be causing widespread harm or alternatively, PPI may be unnecessarily withheld when there is a valid indication. This uncertainty can be resolved with a randomised controlled trial (RCT).

We have been exploring a clinical trial of discontinuation of PPI therapy. This trial lends itself extremely well to primary care as a very large population of patients with cirrhosis would be needed. We have held extensive discussions with colleagues in primary care, who have expressed their reservations in recruiting these patients into clinical trials without oversight from the hepatologists.

To address these uncertainties, Research for Patient Benefit (RfPB) funding application is being planned. The main focus of this application would be to determine if discontinuation of PPI therapy is feasible in patients with cirrhosis.

Conclusion & Future plans

The COACH partnership has successfully achieved its objectives. Firstly, we have engaged with stakeholders and people with lived experience to prioritise research areas around cirrhosis. The team that has been built will continue to support future research activities. Secondly, we have created an environment of mentorship to support each other to enable capacity building and personal development.

The success of COACH goes beyond the outcome of the funding application that were submitted. Although the funding for the liver partnership has ceased, the network that has been built will continue to enable ongoing collaborative research in this field.

Ethics and consent

No activities within this report required ethical approval.

Data availability

No data was included in this study.

Competing interests

No competing interests were disclosed.

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Author roles

Palaniyappan N: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing-Original Draft and Review & Editing; **Aithal GP**: Investigation, Conceptualization, Writing – Review & Editing; **Rowe I**: Investigation, Writing – Review & Editing; **Driver R**: Investigation, Writing – Review & Editing; **Stafford N**: Writing – Review & Editing; **Sprange K**: Methodology, Writing – Review & Editing; **Drewett S**: Methodology, Writing – Review & Editing; **O'Brien A**: Investigation, Conceptualization, Writing – Review & Editing.

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