Research Partnership on Caring for Cirrhosis Closer to Home (COACH)

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

2. PROPOSED PARTNERSHIP

The proposed partnership brings 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 will adopt a hub and spoke model. In each region, the research-experienced centres supported by clinical academics (NP, GPA, AOB and IR) will be buddied with research-naïve sites. This approach provides 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 will break the perceived barrier between primary and secondary care in jointly delivering clinical research and will foster stronger integration between partners in primary and secondary care. Nottingham City GP Alliance (NCGPA) will be 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. We will work with NCGPA to identify similar GP alliances in different regions within the partnership.

Dr Laura Nellums will lead the development and embedding of patient and public involvement and engagement (PPIE) within each region. LN will draw on her work involving migration and health and wider disparities in access to care and health outcomes. Dr Kirsty Sprange (KS) from Nottingham Clinical Trials Unit (NCTU) will provide methodological oversight and will support the provision of research training for members of the partnership through NCTU.

3. AIMS & OBJECTIVES

Aim

The overarching aim is 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.

Objectives

- To develop a sustainable, cross-sectoral collaborative research partnership which includes geographic patient populations historically underserved by clinical research activity.

- 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.
- To share topic and methodological expertise across the partnership and consequently develop organisations with capacity and capability to deliver nationally generalisable studies.
- 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.

4. PARTNERSHIP PLANS & ACTIVITIES

We propose 3 interlinked phases within the partnership. The timetable details the foci of each phase

- Phase 1 (Months 1-2) – **Working together** to establish the partnership and co-produce ground rules.
- Phase 2 (Months 3-12) – **Developing together** to understand and build the research capacity and capability across the partnership.
- Phase 3 (Months 9-18) – **Building together** to establish research questions and develop research proposals.

Phase 1 – Working together

We will establish the partnership infrastructure and the members of partnership will form the key contacts within each region. We will hold networking events across the partnership to invite key stakeholders in each region including primary care clinicians, allied healthcare professionals, commissioners, hepatology day case units, community hubs, home care delivery teams and PPIE representatives. We will co-produce ground rules for working together collaboratively. COACH website will be designed to enable cross partnership communication. The website will be hosted by Nottingham NIHR Biomedical Research Centre.

Phase 2 – Developing together

We will understand and strengthen the research capacity and capability of the partnership by mapping current services, providing structured training and mentorship for clinicians and allied healthcare professionals. This phase will also involve training and capacity building for patient and public stakeholders, including those from historically underserved groups, who will be engaged throughout the project and inform the work. These activities will be conducted in collaboration with key people identified in phase 1 and ensure that the research proposals that are developed in phase 3 will be clinically relevant.

Mapping current services & research capacity

Ambulatory and community care for patients with decompensated cirrhosis vary widely across locations in both organisational structures and delivery of the service. Numerous specialities will be involved including primary care, community nursing and hospital-based specialties of hepatology and palliative care.

We will carry out an online survey across the partnership to map the totality of community care available for patients with cirrhosis. The survey will be aimed at primary and secondary care to understand current and any planned future service provision in this domain.

We will understand the research readiness by mapping the current research activity including key people, regional and national research infrastructures (Clinical Research Networks and NIHR), existing research collaborators and PPIE. The data will be analysed using the COM-B model framework[19]. The COM-B model represents the observation that behaviour change

occurs when individuals and organisations have the **C**apability, **O**pportunity and **M**otivation to make and sustain the change. The COM-B framework will be used to determine the barriers, enablers, and priorities across the partnership. The data will be used to create a database of aspiring researchers with their specific training and support needs for Phase 3.

Structured training

The partnership will offer funded structured training and development opportunities to members. These courses will build on the free NIHR online courses on "Improving Healthcare Through Clinical Research" and "What is Health Research?". The NCTU offers a range of well-established trial methodology short courses including the Fundamentals of Clinical Trials, Introduction to Clinical Trials (online), Introduction to Clinical Trial Statistics and Qualitative Research within RCTs. The primary focus of these courses is the design and conduct of large multicentre clinical trials including complex intervention trials which will be the main type of trials to be designed by the partnership in phase 3. Training will be offered to upskill those new to research to support their personal development as well as their engagement in co-production of proposals in phase 3.

The partnership will also support capacity building and training around PPIE and meaningful collaboration with patient and public groups from diverse communities. This will include facilitating access to key resources (e.g. NIHR, INVOLVE) and training (NIHR's interactive course), as well as local training provided within the partnership (e.g. the University of Nottingham's 'Patient, Carers and Public Involvement in Research' course, and ARC East Midlands learning and development network for patient and public involvement in health and social care research).

In addition, the partnership will share already established research seminars and events to support knowledge and skills development. Examples include the Divisional Seminar Series at the School of Medicine, University of Nottingham. Aligning with NIHR guidance, training will be provided for researchers, clinicians, and members of patient and public groups, which will support their involvement in Phase 3.

Knowledge exchange

Using the co-production principle of reciprocity[20], knowledge exchange will be fostered by buddying sites with research expertise with research-naïve sites to optimise skill-sharing, efficiency and develop research strategies. We will embrace diversity and enable involvement of key stakeholders, including not only researchers and clinicians, but also patient and public groups from underrepresented communities. This will enable bidirectional knowledge exchange, which will benefit both the researchers and stakeholders. Inclusivity will be a key element of this partnership, and this requires us to be readily accessible.

Time and mentorship for clinicians

The partnership will support early career and leading clinical academics with protected time to develop their own research project and proposals. This will also encourage front line clinicians to work on the research proposal development alongside their clinical commitment. Each region will be allocated funds to undertake local training to become research ready. This will mostly constitute training in (but not limited to) Good Clinical Practice (GCP), Equality, Diversity and Inclusion (EDI), audit training and allocation of protected research time.

The partnership will include a focus on mentorship from experienced clinical academics and researchers with expertise in developing and evaluating complex interventions in decompensated cirrhosis. Experienced partners will support early career researchers

including primary care clinicians to develop and/or jointly lead grant applications in this area. Mentorship, supportive leaders and role models are key facets in developing research and clinical academic leaders of the future [21, 22].

Phase 3 – Building together

Phase 3 will explore and finalise research priorities and relevant research questions across the partnership. This will begin with a research question generation exercise, progressed through proposal development workshops. The proposal will be refined with the support of clinical trial units with PPIE embedded throughout. The research proposals will be developed for the future NIHR call on liver disease with a focus on Efficacy and Mechanism Evaluation (EME) and Health Technology Assessment (HTA) streams.

Research question generation

We will organise a research question generation exercise underpinned by the Child Health and Nutrition Research Initiative (CHNRI) methodology [23]. The partnership will work with 'Expert Stakeholders' (relevant personnel, organisations and professional bodies beyond our partnership) to prioritise research questions relating to community care in decompensated cirrhosis. The key stages include:

- Defining the scope and research question criteria within the partnership, including population of interest, any geographical limits and timescales.
- Integrating the proposed research questions by combining duplicates and removing questions that are out of scope.
- Scoring of the proposed research questions by Expert Stakeholders in terms of answerability, feasibility, and implications for research being conducted in areas where health needs are greatest.

Proposal development

Proposal development workshops will be held to shape the top priority research questions identified from the research question generation exercise.

We will hold three workshops, which will be hosted by NCTU to develop study questions and methodology, focusing on key elements of population, intervention, comparator and outcome (PICO). These PICO workshops have been employed successfully by NCTU in other clinical areas to co-create detailed proposals for trials, ensuring buy-in from the clinical community. We will invite topic and methodological experts including partnership members, methodologists (quantitative and qualitative), clinical trials units (Nottingham & Leeds), advisors from Research Design Service, primary and secondary care clinicians, allied health professionals and patient and public representatives. Attendees will work with methodologists in small groups to iron out the study design including the methodology (qualitative/quantitative/mixed methods), outcomes to be measured, interventions, analysis plan and data management.

Following the PICO workshops, draft proposals will be prepared in anticipation of the Part two NIHR commissioned call. The draft proposals will be sent for peer review by partnership members and Expert Stakeholders including public and patient representatives. The clinical trials unit will provide additional written feedback. The applicants will work within the partnership to strengthen the proposals based on the feedback obtained.

5. DISSEMINATION

The ground rules established in phase 1 will include a strategy for dissemination and communication to support research capacity and capability within partner sites, and patient and public groups. Dissemination to the wider clinical and academic community will occur via networking events and by maintaining a social media presence. Additional dissemination will include sharing of learning through academic papers and presentations at conferences, specifically in relation to the barriers and enablers of community care for patients with cirrhosis. The work will also be disseminated through engagement with patient and public groups, which will be informed by the input of our PPIE stakeholders in the partnership.

The lead applicants of the funded partnerships will present nationally at a virtual British Association for the Study of the Liver (BASL) event arranged by co-applicant Dr Ian Rowe. Through these local and national (NIHR and BASL) forums we are confident that our proposed partnership will benefit from shared learning across liver partnerships. We fully expect that the partnership infrastructure that is built will last beyond the funding duration (18 months) and will enable ongoing collaborative research.

6. PROJECT MANAGEMENT

NP will provide overall leadership supported and mentored by GPA, IR and AOB. The core team will meet virtually every 2 months and ad hoc as required. At these meetings, the team will be joined by spokes and other partners that are relevant to the phase of the project. The regular meetings will ensure that the partnership is on track to meet its timeline, budget and outputs. By intention, the partnership will function in most part by virtual meetings to maximise geographical inclusivity and minimise travel cost. The research partnership coordinator will manage the day to day running of the partnership.

7. REFERENCES

1. Liver disease: Applying All Our Health. 1st September 2022]; Available from: https://www.gov.uk/government/publications/liver-disease-applying-all-our-health/liver-disease-applying-all-our-health.
2. Williams, R., R. Aspinall, M. Bellis, G. Camps-Walsh, M. Cramp, A. Dhawan, J. Ferguson, D. Forton, G. Foster, S.I. Gilmore, M. Hickman, M. Hudson, D. Kelly, A. Langford, M. Lombard, L. Longworth, N. Martin, K. Moriarty, P. Newsome, J. O'Grady, R. Pryke, H. Rutter, S. Ryder, N. Sheron, and T. Smith, Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. The Lancet, 2014. 384(9958): p. 1953-1997.
3. D'Amico, G., A. Morabito, M. D'Amico, L. Pasta, G. Malizia, P. Rebora, and M.G. Valsecchi, New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. Hepatology International, 2018. 12: p. S34-S43.
4. Kumar, M., S. Kainth, A. Choudhury, R. Maiwall, L.G. Mitra, V. Saluja, P.M. Agarwal, S.M. Shasthry, A. Jindal, A. Bhardwaj, G. Kumar, and S.K. Sarin, Treatment with carvedilol improves survival of patients with acute-on-chronic liver failure: a randomized controlled trial. Hepatol Int, 2019. 13(6): p. 800-813.
5. Turco, L., C. Villanueva, V. La Mura, J.C. García-Pagán, T. Reiberger, J. Genescà, R.J. Groszmann, B.C. Sharma, C. Merkel, C. Bureau, E. Alvarado, J.G. Abraldes, A. Albillos, R. Bañares, M. Peck-Radosavljevic, S. Augustin, S.K. Sarin, J. Bosch, and G. García-Tsao, Lowering Portal Pressure Improves Outcomes of Patients With Cirrhosis, With or Without Ascites: A Meta-Analysis. Clinical Gastroenterology and Hepatology, 2020. 18(2): p. 313-327.e6.
6. Trebicka, J., W. Gu, L. Ibáñez-Samaniego, V. Hernández-Gea, C. Pitarch, E. Garcia, B. Procopet, Á. Giráldez, L. Amitrano, and C. Villanueva, Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. Journal of hepatology, 2020. 73(5): p. 1082-1091.
7. Bureau, C., D. Thabut, F. Oberti, S. Dharancy, N. Carbonell, A. Bouvier, P. Mathurin, P. Otal, P. Cabarrou, J.M. Péron, and J.P. Vinel, Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology, 2017. 152(1): p. 157-163.
8. Caraceni, P., O. Riggio, P. Angeli, C. Alessandria, S. Neri, F.G. Foschi, F. Levantesi, A. Airoldi, S. Boccia, G. Svegliati-Baroni, S. Fagiuoli, R.G. Romanelli, R. Cozzolongo, V. Di Marco, V. Sangiovanni, F. Morisco, P. Toniutto, A. Tortora, R. De Marco, M. Angelico, I. Cacciola, G. Elia, A. Federico, S. Massironi, R. Guarisco, A. Galioto, G. Ballardini, M. Rendina, S. Nardelli, S. Piano, C. Elia, L. Prestianni, F.M. Cappa, L. Cesarini, L. Simone, C. Pasquale, M. Cavallin, A. Andrealli, F. Fidone, M. Ruggeri, A. Roncadori, M. Baldassarre, M. Tufoni, G. Zaccherini, and M. Bernardi, Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet, 2018. 391(10138): p. 2417-2429.
9. Caraceni, P., A. O'Brien, and P. Gines, Long-term albumin treatment in patients with cirrhosis and ascites. J Hepatol, 2022. 76(6): p. 1306-1317.
10. NHS Digital. QOF 2020–21 Results. 1st September 2022]; Available from: https://qof.digital.nhs.uk/.
11. NHS Digital. Quality and Outcomes Framework, 2019–20. Official statistics. 2020;. 1st September 2022]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2019-20/main-findings.

12. Standing, H.C., H. Jarvis, J. Orr, C. Exley, M. Hudson, E. Kaner, and B. Hanratty, GPs' experiences and perceptions of early detection of liver disease: a qualitative study in primary care. British Journal of General Practice, 2018. 68(676): p. e743-e749.
13. NHS Long Term Plan 2019. 1st September 2022]; Available from: https://www.longtermplan.nhs.uk/.
14. Skivington, K., L. Matthews, S.A. Simpson, P. Craig, J. Baird, J.M. Blazeby, K.A. Boyd, N. Craig, D.P. French, E. McIntosh, M. Petticrew, J. Rycroft-Malone, M. White, and L. Moore, A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ, 2021. 374: p. n2061.
15. Kazankov, K., S. Novelli, D.A. Chatterjee, A. Phillips, A. Balaji, M. Raja, G. Foster, D. Tripathi, R. Boddu, R. Kumar, R. Jalan, and R.P. Mookerjee, Evaluation of CirrhoCare® - A digital-health solution for home management of patients with cirrhosis. Journal of Hepatology, 2022.
16. Best Research for Best Health: The Next Chapter. 1st September 2022]; Available from: https://www.nihr.ac.uk/documents/best-research-for-best-health-the-next-chapter/27778.
17. Regional ethnic diversity. 6th September 2022]; Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest.
18. What are the regional differences in income and productivity? 6th September 2022]; Available from: https://www.ons.gov.uk/visualisations/dvc1370/.
19. Michie, S., M.M. van Stralen, and R. West, The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci, 2011. 6: p. 42.
20. Guidance on Co-producing a Research Project. 2018 30 Aug 2022; Available from: https://research.hscni.net/sites/default/files/Copro_Guidance_Mar18.pdf.
21. Cowley, A., C. Diver, A. Edgley, and J. Cooper, Capitalising on the transformational opportunities of early clinical academic career training for nurses, midwives and allied health professionals. BMC Medical Education, 2020. 20(1): p. 418.
22. Lopes, J., V. Ranieri, T. Lambert, C. Pugh, H. Barratt, N.J. Fulop, G. Rees, and D. Best, The clinical academic workforce of the future: a cross-sectional study of factors influencing career decision-making among clinical PhD students at two research-intensive UK universities. BMJ Open, 2017. 7(8): p. e016823.
23. Rudan, I., J.L. Gibson, S. Ameratunga, S. El Arifeen, Z.A. Bhutta, M. Black, R.E. Black, K.H. Brown, H. Campbell, I. Carneiro, K.Y. Chan, D. Chandramohan, M. Chopra, S. Cousens, G.L. Darmstadt, J. Meeks Gardner, S.Y. Hess, A.A. Hyder, L. Kapiriri, M. Kosek, C.F. Lanata, M.A. Lansang, J. Lawn, M. Tomlinson, A.C. Tsai, and J. Webster, Setting priorities in global child health research investments: guidelines for implementation of CHNRI method. Croat Med J, 2008. 49(6): p. 720-33.