An Alcohol-Related liver disease Multi-Stakeholder Hub (ARMS-Hub) to enhance research activity in underserved communities in the UK

1. Background and Rationale

Alcohol use is the third leading cause of early death in the UK and is the main driver of chronic liver disease, estimated to affect 600,000 people in England alone.[1] Alcohol use costs the NHS £3.5 billion per year.[2] There were 69,130 hospital admissions due to Alcohol-related Liver Disease (ArLD)[3] with 5,608 deaths in 2020/21 in England.[4] Inpatient mortality is as high as 23%[5] and many of these were first presentations of advanced ArLD cirrhosis indicating low rates of early identification and intervention.[6]

In 2014, the Lancet Liver Commission recognised alcohol misuse as a condition with high prevalence that needed to be urgently addressed.[1] In 2017, the James Lind Alliance conducted a priority setting partnership to identify the top ArLD research questions.[7] Since then, sadly, little progress has been made in health policy or research and ArLD admissions and mortality continue to rise year on year.[8]

ArLD is a condition affected by social, gender and ethnic disparities. People with lower socioeconomic status (low educational level or unemployed) are ten times more likely to develop ArLD[9] and subsequently die from it.[10] There has also been increasing incidence of ArLD in ethnic minorities and women, with disparities in access to alcohol treatment.[11]

Despite the high prevalence and healthcare burden of ArLD, there has been a paucity of research addressing prevention, morbidity and mortality. International data assessing research activity and liver disease burden found a marked inattention to ArLD compared to other liver diseases.[12] The same is true in the UK; data from the NIHR Clinical Research Network (CRN) found only eight trials with a total of 868 participants in ArLD opened since April 2018, of which one was commercial. In contrast, 36 trials (18 commercial) in fatty liver disease recruited 3021 participants during the same period.

Reasons for inattention to ArLD are multifactorial but certainly include stigma and lack of interest from industry. Stigma impacts healthcare of ArLD patients at all stages of disease from early detection to intervention.[13,14] Public stigma that ArLD is self-inflicted may influence allocation of industry and non-commercial funding. NHS Scotland has made the first steps to change public opinion by challenging stigma around alcohol use.[15] Wider engagement of public, healthcare professionals (HCPs) and industry is required to impact the stigma associated with harmful alcohol use and its consequences.

CRN data shows that research activity in ArLD since 2018 is concentrated in academic centres e.g. Imperial, Liverpool and Plymouth. Conversely, five CRN regions recruited fewer than 30 participants to ArLD studies since 2018: West Midlands, Kent, Surrey and Sussex, East of England, Wessex, and Thames Valley and South Midlands. Consider the largest UK trial in ArLD to date as a case study: Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH).[16] Recruiting over 1100 participants across 65 hospitals in England, Scotland and Wales, academic centres (e.g. Imperial, Liverpool, Glasgow, Nottingham and Newcastle) recruited well compared to district general hospitals (e.g. Basildon, Lincoln and Newport). There was under-representation of hospitals from Kent, Surrey and Sussex, Thames Valley and South Midlands, and West Midlands. This coincides with areas of high ArLD hospital admissions and mortality (e.g. Coventry, Wolverhampton, Luton).[10] This demonstrates that research interest and expertise rather than disease prevalence dictates ArLD clinical trial activity.

Furthermore, ArLD is a complex condition requiring a multidisciplinary approach including hepatologists, addiction psychiatrists, alcohol nurses, allied health professionals and community workers. Current research mainly occurs in specialty silos and fails to draw together the multidisciplinary team needed to conduct successful ArLD research. There are large gaps in ArLD research including qualitative research, research in non-hospital settings, participation of non-medical HCPs and involvement of community services and the voluntary sector. This helps to explain the lack of progress in answering top research priorities such as methods to deliver healthcare education about excessive alcohol use and community-based care models.[7]

There is an urgent unmet need to increase and enhance ArLD research in the UK. This proposal is an opportunity to explore and challenge stigma in ArLD research and to increase engagement in areas of high prevalence and low research activity. It will create multidisciplinary partnerships across different settings that will develop interdisciplinary research proposals addressing key research priorities to improve care and treatment and so reduce morbidity and mortality from ArLD.

2. Aims and Objectives

2.1. Aim

To establish an ArLD multi-stakeholder hub of multidisciplinary experts and patient representatives that will increase and enhance ArLD research in the UK through identification of research priorities and developing study proposals targeting these (figure 1).

2.2. Objectives

1. Identify and develop interdisciplinary partnerships including community, voluntary sector and social care organisations
2. Explore stigma in ArLD research and methods to overcome it
3. Develop a diverse and representative ArLD PPIE group
4. Build research capacity by engaging less research-active clinicians, non-medical healthcare professionals and community workers
5. Develop interdisciplinary research proposals targeting key research priorities to enhance ArLD research in the UK in preparation for Part 2 of this research call

3. Research Plan / Methods

3.1. Work package 1: Establishment of multi-stakeholder ArLD hub (ARMS-Hub)

A dedicated research coordinator will map existing ArLD clinical and/or research networks. We will encourage an allied health professional (AHP) to take the role of the coordinator to help identify and engage AHP networks in ArLD research. Members of the Project Steering Group (PSG; see section 6) will use their contacts and professional networks to identify existing networks across disciplines and settings including hepatology, addictions, biomedical science, community services and charities/voluntary sector and among different professional groups including AHPs, nursing, psychology and research methodologists.

The PSG has already identified the following groups that will be invited to contribute: British Association for the Study of the Liver ArLD Special Interest Group, Royal College of Psychiatrists Addiction Faculty, British Liver Nursing Association, Society for the Study of Addiction, Alcohol Health Alliance, British Dietetic Association, Chartered Society of Physiotherapy and Royal College of Occupational Therapists. We will also seek international collaborators through our international networks lead. Through funders, charities and our networks, we will search for active or recently completed relevant projects. We will engage with teams leading these projects such as the Changing Futures Programme, a Government-funded initiative to tackle health inequalities in people with multiple disadvantage including alcohol misuse.

Representatives from each network/discipline will be invited to join the ARMS-Hub. We will also invite representatives from relevant national charities and voluntary organisations including Alcohol Change UK, Alcoholics Anonymous, Mind and Shelter.

The Hub will have strong PPIE representation of a diverse group of patients with lived experience of ArLD and their carers (see Work package 2).

ARMS-Hub member meetings (~20 attendees) will take place five times virtually within the first nine months. After establishing terms of reference and defining goals of ARMS-Hub the first three meetings will address the following issues. (1) ‘Is stigma still a problem in developing and conducting ArLD research and how can we overcome this?’ (2) Methods to engage less research-active sites and non-medical healthcare professionals in ArLD research (see Work package 3). (3) Methods to engage under-served communities with ArLD in research. The fourth meeting will generate and prioritise ArLD research questions (in the light of findings from earlier workshops on stigma and engagement). The final meeting will develop study proposals targeting the identified research priorities that will be finalised in a Research Symposium (Work package 4).

The Research Coordinator (supervised by the qualitative research lead) will facilitate the first three meetings. Three facilitated groups at each meeting will discuss each theme and generate ideas and potential solutions considering feedback from PPIE meetings (Work package 2). Subsequent meetings will rotate attendees to other groups to enable all attendees to contribute to each theme and build on previous discussion. The fourth meeting will use Nominal Group Technique (NGT)[17] to generate and prioritise research questions. This approach generates ideas while giving all participants an equal voice.[18] In brief, we will use a four-stage NGT approach: (1) generating ideas, (2) individual feedback, (3) group discussion and (4) voting to establish consensus. In the final meeting, ARMS-Hub members will divide themselves into working groups ensuring a balance of expertise including PPIE representatives and methodological support to develop study proposals to address the identified research priorities. A study outline will be developed by the end of this meeting, which will continue to be developed through collaborative virtual working, until finalisation at the Research Symposium. Studies will be designed with careful consideration of learning from earlier meetings and PPIE input around stigma and research engagement.

ARMS-Hub will develop a strong web presence with a dedicated public website that will showcase the expertise of the Hub and become a focal point for connecting with potential collaborators. We will build a map of existing networks, groups and organisations and invite researchers to share their details to promote engagement. Information and resources such as opportunities to join working groups or attend training events will be shared with a focus on early- to mid-career researchers and HCPs.

Deliverables: (1) A multi-stakeholder hub of experts and PPIE in ArLD. (2) An understanding of how to overcome stigma in ArLD research. (3) Methods to engage less research active sites and staff groups. (4) Methods to engage under-served communities. (5) An interactive website to showcase the Hub's activities. (6) A shortlist of ArLD research priorities and outlines of study proposals to address these.

Milestone: Establishment of ARMS-Hub and completion of five meetings by Month 9.

3.2. Work package 2: Patient and Public Involvement and Engagement (PPIE) group

We recognise that people with ArLD form a diverse group from different socioeconomic backgrounds and communities, who do not always engage with healthcare services. A recent engagement project completed by the CI included a scoping review, which found few proven methods to engage under-represented groups in research; a stakeholder consensus meeting recommended training peers to recruit people in their own communities as the best strategy to improve engagement. It is important that we hear the full range of ArLD patient voices so have developed a strategy to ensure diverse representation. The strategy will be supported by a designated Equality, Diversity and Inclusion (EDI) Lead, who will use his experience of understanding ethnic disparities in liver disease identification and outcomes to ensure inclusion of a diverse spectrum of people with ArLD. We will work within the framework of recent EDI policies from BASL, BSG and NIHR.

The recruitment strategy will involve three methods. Firstly, the PSG will use their existing contacts, PPIE groups and support networks to identify suitable PPIE representatives. Our PPIE co-applicant will play a leading role in identifying local and national patient groups (e.g. Alcohol Research UK, South Asian Health Foundation). Secondly, we will advertise through the British Liver Trust patient forum, a group of over 500 patients with liver disease. Thirdly, we will identify support workers in community alcohol services and homelessness services in several areas of high ArLD prevalence around the country. We will provide them with an explanation of the project and PPIE roles and ask them to recruit people with ArLD known to them.

We anticipate inviting 15-20 people to form the PPIE group and acknowledge that membership may be dynamic with members leaving and joining the group throughout the project. We will support involvement of people with lived experience with a flexible approach. To promote accessibility we will hold both in person and virtual events and will consider other methods of interaction such as using messaging apps after consultation with the group. The first meeting will introduce members to PPIE, research and their role in this project followed by two meetings to gain PPIE input into methods to overcome stigma in ArLD and how to engage diverse groups of ArLD patients. Facilitation techniques such as 'trios' and 'station rounds' will be used to support active engagement with each topic. Both techniques support group members to play an active role in generating and sharing ideas through small group work and feedback to the wider group. Ideas will be shared bidirectionally with the ARMS-Hub group meetings that address these topics. Meetings will be chaired by the PPIE co-applicant (supported by a Deputy PPIE Representative) and facilitated by our designated PPIE Lead.

In addition, at least two members of the PPIE group and the PPIE co-applicant will attend hub meetings to act as a liaison between the wider PPIE group (Work package 1).

Deliverables: (1) Representative ArLD PPIE group. (2) Patient-orientated methods to overcome stigma and engage ArLD patients in research.

Milestones: (1) Establishment of PPIE group by Month 4. (2) Completion of group meetings by Month 7

3.3. Work package 3: Building research capacity

A series of four knowledge exchange workshops will be held from Month 6 to 10. Each workshop will bring together Hub members with ~15 clinicians, HCPs, and service users from less research-active sites. Participants will be identified from NIHR CRN research activity data linked with ArLD hospital admission data to find sites of low recruitment to ArLD studies with higher-than-average hospital admissions. We will invite clinicians, nurses, AHPs and community workers from each site.

Workshops have the following objectives: (1) to increase knowledge of ArLD research and how to get involved, (2) to set up formal mentorship relationships and Action Learning Sets, (3) to understand barriers and facilitators to research engagement.

To understand barriers and how to overcome them, we will take a 'World Café' approach. In brief, the most common barriers will be identified at the start of the workshop and a table allocated to each identified barrier and groups facilitated to explore each barrier and develop strategies to resolve it. Groups then move around the room to different tables (to explore different barriers) after an allocated time.

Attendees will be offered a formal mentorship arrangement with a member of the Hub specific to their requirements (e.g. early career AHP mentee paired with senior AHP researcher mentor). Mentorship pairs will meet at least once during this project to define goals and actions. A long-lasting relationship will be encouraged beyond the scope of this project. Interested parties will also be able to access the scheme through the Hub website. Mentorship opportunities will range from supporting HCPs in applying for research funding to experienced researchers leading a multicentre trial. The mentorship lead will implement the programme with input from the scientific lead. Mentors/mentees will be provided resources and training in mentorship and will also take part in two Action Learning Sets in month 8 and 9. Action learning involves working on identified challenges, using the knowledge and skills of a small group of people (5-7) combined with skilled questioning, to produce fresh ideas and find solutions to individual problems that will enable applying that learning to planned practice. The focus is on learning from experience and putting it into action immediately. It may provide fresh insights to achieve different solutions and a chance to progress new opportunities/ideas within the ARMS-Hub.

Deliverables: (1) Knowledge exchange workshops. (2) Formal mentorship relationships. (3) Action Learning Sets. (4) Understanding of barriers/facilitators to research engagement.

Milestone: Completion of workshops by Month 10.

3.4. Work package 4: Developing ArLD research proposals

In Month 12, we will organise a one-day symposium to finalise research proposals to enhance ArLD research in the UK. The event will take place in-person with the option of joining virtually to allow wide inclusion of participants. We will invite all ARMS-Hub and PPIE group members and advertise the event widely through the Hub's affiliated organisations and networks. Our co-applicants from RDS-SW and Peninsula Clinical Trials Unit will ensure representation from RDS and Clinical Trials Units to contribute to the research proposals.

The morning session will share learning from the Hub, PPIE group and research building workshops (Work packages 1-3). In the afternoon session, working groups will review and finalise study proposals that were generated in Work package 1. This wider involvement and consultation with stakeholders will ensure that the study is relevant, well designed and achievable.

Deliverables: (1) Knowledge exchange through one-day symposium. (2) ArLD research proposals for submission to the second call of NIHR funding.

Milestone: Completion of Research Symposium by Month 12.

4. Dissemination, Outputs and anticipated Impact

The key output from this project will be finalised study proposals related to high priority research questions, including consideration of stigma and research engagement, for submission to the second stage of NIHR funding. Findings will be widely disseminated to the clinical and scientific community through national conferences and open access publication in peer-reviewed medical literature. We will disseminate a lay summary to all networks involved in the Hub and through our PPIE group to local communities and local, regional and national patient groups. We will develop a Hub website and social media accounts to engage with HCPs and patients.

We intend to sustain the Hub beyond allocated funding by requesting a small amount of administrative support from Hub partners including BASL and charities.

5. Project Management

The CI takes overall responsibility for the management of this project. He will be supported by a PSG consisting of all co-applicants that will meet virtually every two months for the duration of the project. A research coordinator will be appointed ready to commence post at the start of the project.

6. Ethics / Regulatory Approvals

This project does not involve identifying patients through NHS or social care services and does not include them in research. Therefore, NHS Research Ethics Committee approval is not required.

7. Project / Research expertise

Our multidisciplinary project team of clinicians and academics represents the main stakeholder groups in the Hub with a PPIE co-applicant. We include co-applicants representing the Research Design Service and Peninsula CTU, who will support this partnership and assist in developing future proposals.

8. Success criteria and barriers to proposed work

We will demonstrate success by achieving lasting impact on ArLD research in the UK, through tackling stigma and barriers to engagement, capacity building and research proposals. Within 5 years, we aim to submit more than 5 interdisciplinary ArLD research proposals for funding, which will include methods to (1) target historically poorly research-engaged teams/regions, (2) challenge and overcome alcohol-related stigma and (3) improve access to research of ArLD patients from under-served communities.

We have detailed plans to identify and engage networks, organisations and PPIE representatives. Should we have difficulty recruiting diverse PPIE representatives, we will use existing relationships with community groups to assist with peer recruitment and support their inclusion through non-traditional methods such as messaging apps. Should networks or organisations fail to engage with Hub meetings we would ask them to provide written contribution and feedback.

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10. References

1. Williams R, Aspinall R, Bellis M, et al. 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. *Lancet* 2014; **384**(9958): 1953-97.
2. Foundation for Liver Research. Financial case for action on liver disease: Foundation for Liver Research, 2017.
3. Office of National Statistics. England hospital episode statistics 2020-2021, 2022.
4. Public Health England. Monitoring alcohol consumption and harm during the COVID-19 pandemic: Public Health England, 2021.
5. Roberts SE, John A, Brown J, Napier DJ, Lyons RA, Williams JG. Early and late mortality following unscheduled admissions for severe liver disease across England and Wales. *Alimentary pharmacology & therapeutics* 2019; **49**(10): 1334-45.
6. Subhani M, Elleray R, Bethea J, Morling JR, Ryder SD. Alcohol-related liver disease mortality and missed opportunities in secondary care: A United Kingdom retrospective observational study. *Drug Alcohol Rev* 2022; **41**(6): 1331-40.
7. James Lind Alliance, National Institute for Health Research. Research priorities for alcohol related liver disease: NIHR, 2016.
8. Williams R, Aithal G, Alexander GJ, et al. Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK. *Lancet* 2020; **395**(10219): 226-39.
9. Askgaard G, Fleming KM, Crooks C, et al. Socioeconomic inequalities in the incidence of alcohol-related liver disease: A nationwide Danish study. *Lancet Reg Health Eur* 2021; **8**: 100172.
10. Public Health England. The 2nd Atlas of variation in risk factors and healthcare for liver disease in England. PHE Publications: Public Health England, 2017.
11. Kardashian A, Serper M, Terrault N, Nephew LD. Health disparities in chronic liver disease. *Hepatology* 2022.
12. Ndugga N, Lightbourne TG, Javaherian K, et al. Disparities between research attention and burden in liver diseases: implications on uneven advances in pharmacological therapies in Europe and the USA. *BMJ Open* 2017; **7**(3): e013620.
13. Schomerus G, Leonhard A, Manthey J, et al. The stigma of alcohol-related liver disease and its impact on healthcare. *Journal of hepatology* 2022; **77**(2): 516-24.
14. Houghton C, Taylor A. Stigma and social barriers to accessing timely healthcare for alcohol dependence and misuse: a narrative review. *Gastrointestinal Nursing* 2021; **19**: 512-7.
15. NHS Scotland. Challenging drug and alcohol stigma. 2022. https://www.nhsinform.scot/campaigns/challenging-drug-and-alcohol-stigma.
16. Thursz M, Forrest E, Roderick P, et al. The clinical effectiveness and cost-effectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2 x 2 factorial randomised controlled trial. *Health technology assessment* 2015; **19**(102): 1-104.
17. Delbecq AL, Van de Ven AH, Gustafson DH. Group techniques for program planning : a guide to nominal group and Delphi processes. Glenview, Ill.: Scott, Foresman; 1975.
18. Cantrill JA, Sibbald B, Buetow S. The Delphi and nominal group techniques in health services research. *Int J Pharm Pract* 1996; **4**: 67-74.