

Research Plan

The Midlands Liver Research Alliance - A partnership to optimise obesity-related liver disease research; targeting areas of high incidence and underserved communities.

Background

In the Western world, liver disease is the only chronic condition demonstrating a yearly increase in prevalence, making it the fifth leading cause of death after heart, cancer, stroke, and respiratory disease¹. The major contributor to this trend is a global surge in Non-Alcoholic Fatty Liver Disease (NAFLD). Recent estimates suggest a world-wide prevalence of ~32% in adults^{2,3}. The main trigger is escalating obesity rates, with NAFLD being present in the majority of individuals. These statistics are problematic given that NAFLD directly increases the likelihood of developing chronic conditions and reduces life expectancy⁴.

Non-alcoholic fatty liver disease represents a spectrum of pathological hepatic phenotypes that range from simple steatosis to decompensated cirrhosis and hepatic cell carcinoma. The infiltration of excess fat into the liver is a common denominator in all forms of NAFLD; however, the presence of simple steatosis alone, without accompanying hepatic injury is benign or may progress slowly⁵. In contrast, the additional presence of hepatic inflammation and hepatocyte injury is recognised as a key indicator of a more aggressive NAFLD phenotype that is destined to progress to more advanced stages of NAFLD⁶. Non-Alcoholic Steatohepatitis (NASH), develops in ~25% of individuals with steatosis and predisposes to premature mortality, principally relating to liver and cardiovascular causes⁷.

The development of hepatic inflammation, hepatocyte injury and hepatic fibrosis are triggered in response to various pathological processes that are stimulated by hepatic lipotoxicity and extra-hepatic metabolic derangements⁶. Prominently, insulin resistance and metabolic syndrome are intimately related to NAFLD and the progression to more advanced stages of disease. The prevalence of NASH is therefore exceptionally high in individuals with type 2 diabetes (~37%) which is a serious concern given that dual disease presence accelerates NAFLD progression, worsens glycaemic control, provokes a need for more intensive pharmacotherapy, heightens cardiovascular risk, and reduces longevity⁸⁻¹⁰.

NAFLD, Obesity and Type 2 Diabetes (T2D)

NAFLD is readily referred to as the hepatic manifestation of metabolic syndrome as a result of shared common comorbidities (visceral adiposity, insulin resistance, dyslipidaemia and cardiovascular disease) with NAFLD implicated as both a cause and consequence^{11,12}. The prevalence of NAFLD is rapidly rising, in parallel with similar trends of obesity and T2D¹³⁻¹⁵. Obesity and T2D are contributing factors to the development of NAFLD, and its progression to non-alcoholic steatohepatitis or advanced disease¹⁶. Given the overweight and obesity rates in the UK (63% of adults) of which 1 in three adults are estimated to have early stage NAFLD, combined with NAFLD and non-alcoholic steatohepatitis prevalence of above 60% in T2D, highlights a major public health concern^{17,18}.

Obesity, T2D and dyslipidaemia are the strongest modifiable risk factors for NAFLD¹⁹, present in ~50% of individuals with obesity²⁰ and ~94% of individuals with severe obesity (BMI \geq 40 kg·m²)²¹. It must be noted that non-modifiable risk factors such as age, sex (e.g. male), ethnicity (e.g. Hispanic/south Asian), low socioeconomic status and geographical location (e.g. coastal regions²²) are also associated with greater prevalence and severity of NAFLD^{20,23-25}. With the overweight and obesity levels in the UK and the associated modifiable risk factors, there is a national need and urgency to prioritise obesity related liver disease research.

NAFLD Management

At present, no pharmaceutical therapies are licensed specifically for NAFLD. Physical activity and weight loss therefore remain the cornerstone of disease management²⁶. Specifically, a weight loss

goal of ~5% is recognised as necessary to reduce liver fat, whereas greater weight loss (7-10%) is deemed necessary to meaningfully influence hepatic inflammation and/or fibrosis. Most population-based health behaviour interventions (diet and activity) can achieve 5-10% weight loss, and low energy diets can achieve significant weight loss short term (10-15%). However, weight loss maintenance is difficult to achieve for most. Although not a scalable therapy, evidence from bariatric surgery demonstrates the potent benefit of significant weight loss on NAFLD, in people with severe obesity²⁷. Such dramatic and sustained weight loss (15-25%) drastically improves / resolves steatosis, NASH, and hepatic fibrosis in 92%, 81% and 65% of cases²⁸. Usefully, the emergence of new, highly effective obesity pharmacotherapies (conferring up to 15% weight loss) provides an opportunity to tackle NAFLD on a larger scale, through sustained weight reduction. The GLP-1 receptor agonists, liraglutide (3 mg) once daily and semaglutide (2.4mg) once weekly have recently been approved for weight management. Phase 2 trials highlight the potential for incretin based therapies including dual receptor agonists to improve steatosis and hepatic inflammation, however, higher levels of weight loss and longer treatment duration may be needed to improve hepatic fibrosis^{29, 30}. The combination of novel weight loss agents with health behavior interventions holds therapeutic potential³¹.

Midlands underserved and hard to reach populations

The disparity in population level NAFLD burden is apparent, with incidence, prevalence and severity disproportionately affected by sex, ethnicity, socioeconomic status and geographical location³². The West Midlands is the most ethnically diverse region outside of London where 21% of residents are of Asian, Black, Mixed or Other ethnicity, whilst the West (10.8%) and East Midlands (6.5%) are amongst the areas with the highest Asian population³³.

Individuals of South Asian ethnicity in high-income countries have higher levels of insulin resistance than white Europeans; attributed to differences in adipose tissue metabolism and body composition^{34, 35}. NAFLD prevalence is therefore greater in South Asian populations (~53%¹⁸), with predisposition to developing obesity-related disease earlier than western populations³⁵⁻³⁷. Therefore, standard body mass index (BMI) thresholds do not adequately define NAFLD risk in South Asians. The NIHR Clinical Research Network Targeting Tool for liver disease shows the geographical spread of adults classified as overweight (≥ 25 kg/m²) in England. Of 152 localities four of the top five span the East and West Midlands (Sandwell, Stoke-on-Trent, Northeast Lincolnshire and Dudley); without ethnically adjusting for BMI²².

The Chief Medical Officer's annual report 2021³⁸ highlighted high rates of preventable diseases and low life expectancy in coastal regions, encouraging strategies to address health inequalities (particularly research disparities). In England, Lincolnshire is a coastal region with low liver research activity³⁹, high levels of deprivation and very high obesity prevalence. Northeast Lincolnshire's adult obesity prevalence is the 4th highest in the England, with high mortality rates from chronic liver disease (ranked 18th of 146 areas reported in England), particularly mortality in the under 75s (ranked 17th of 149 areas reported), which explains the high proportion of hospital admissions from NAFLD³⁹. Nottingham is ranked 2nd in England for NAFLD hospital admissions. In summary, the Midlands has high levels of ethnic and socioeconomic diversity, multiple areas of deprivation and underserved communities including coastal regions. This context supports our proposal to develop a Midlands-based multi-disciplinary research partnership to address obesity-related liver disease and research disparities.

Proposed research partnership

The Midlands Liver Research Alliance utilises existing NIHR infrastructure and collaborative partners from across the Midlands as an effective base to create a novel partnership. At its core are three Biomedical Research Centres (BRC). Nottingham and Birmingham BRCs have extensive expertise and international recognition in liver research (led by Professor Aithal and Professor Newsome respectively), and Leicester's BRC (led by Professor Davies) has world-leading expertise in obesity and lifestyle health behaviour research. The partnership will also include other Midlands-based specialists, methodologists (such as Professor Kim Thomas, expert in clinical trial methodology, core

outcome set development and priority setting partnerships), social scientists (Dr Darko, expert in ethnicity, health and inequalities), weight management experts (such as Dr David Webb, Consultant Physician and clinical lead tier 3 weight management), Clinical Trials Units expertise (Birmingham and Lincoln) and support from both liver and obesity charities (figure 1). The partnership hosts key areas of resource and expertise: imaging, pharmacotherapy and health behaviour interventions.

The NIHR Nottingham Biomedical Research Centre has a theme dedicated to Magnetic Resonance Imaging (MRI). Much of this work is led by medical physicists hosted in the Sir Peter Mansfield MRI Centre, within the University of Nottingham. The remit of this theme is to develop new imaging protocols to facilitate clinical diagnoses, and to subsequently evaluate clinical utility. These techniques therefore enable earlier and more accurate detection and monitoring of disease mechanisms / outcomes, non-invasively. With specific reference to liver disease, the Sir Peter Mansfield MRI Centre have pioneered techniques for the non-invasive assessment of key disease pathways and targets using MRI, magnetic resonance spectroscopy (¹H-MRS, ³¹P MRS, ¹³C MRS), and magnetic resonance elastography. Specific examples include: liver fat, liver fat composition, liver glycogen, liver fibro-inflammation, liver Adenosine triphosphate metabolism, tricarboxylic acid cycle flux and beta-oxidation, glutathione flux (oxidative stress). Key aims within the cardiovascular theme of Leicester BRC include the improvement of diagnoses and identification of effective treatments. The development and utilisation of novel imaging techniques is central to these ambitions. The Glenfield Hospital hosts the Leicester BRCs imaging suite which includes state-of-the-art 1.5 and 3T MRI, computerised tomography and ultrasound scanners. These facilities permit the detailed assessment of cardiovascular structure, function, and metabolism. Professor Gerry McCann, cardiovascular theme lead, has a programme of research investigating the interaction between obesity, T2D, and cardiac dysfunction. For the present application, cardiovascular disease is the leading cause of morbidity and mortality in patients with NAFLD; and therefore, tackling cardiovascular pathology is an important target for this patient population. If successful the partnership will reach out to the Midlands Medical Imaging Network, a Collaborative initiative championed by Midlands Innovation which comprises expert representatives from Birmingham, Aston, Leicester, Kent, Loughborough, Lincoln, Nottingham, and Warwick. This network which brings together inter-disciplinary expertise from across the Midlands region in the acquisition, analysis and interpretation of medical imaging data in health and pathology, will be key to pursuing imaging research in individuals with obesity related liver disease.

Effective obesity pharmacotherapies leading to clinically significant weight loss have been approved over recent years (Glucagon-like peptide-1 receptor analogues (GLP-1 RA) liraglutide 3mg once daily and semaglutide 2.4mg once weekly). Liraglutide 3mg can lead to 6-8% weight loss and weight maintenance in combination with moderate intensity lifestyle interventions⁴⁰⁻⁴². Semaglutide 2.4mg once weekly results in weight loss between 14.9%-16% when combined with variable intensity lifestyle interventions^{43, 44}. Moreover, tirzepatide 5-15mg, a dual agonist of GLP-1/gastric inhibitory peptide which has recently been approved in the US for management of T2D^{45, 46}, can result in 15-20.9% weight loss when used in people without diabetes in combination with moderate intensity lifestyle interventions⁴⁷. Professor Davies and Leicester NIHR Biomedical Research Centre (BRC) have extensive expertise on the use of these medications in people with obesity and/or T2D (SCALE-Diabetes, STEP-2, STEP-1, STEP-3, STEP-4, SURPASS-2)^{40, 43-45, 48, 49}. Professor Davies has been global PI in a number of these studies^{40, 48}. Moreover, Loughborough University and Leicester BRC have expertise in developing lifestyle interventions (DELIVER study, NCT04004273) for liver-related outcomes and also combining them with weight-loss medications in real word settings to optimise weight-related outcomes and quality of life (STRIVE study)⁵⁰. Early phase trials with liraglutide and semaglutide have demonstrated that these medications have favorable effects on hepatic histology in people with NASH, at least on hepatic steatosis and inflammation, without, however improving hepatic fibrosis^{29, 30}. A number of the studies assessing the impact of glucagon-like peptide-1 receptor analogues on liver disease have been led by Professor Newsome's team (Birmingham BRC)^{29, 30} in collaboration with Professor Aithal (Nottingham BRC)³⁰. A phase 3 study with

semaglutide 2.4mg once weekly in people with NASH is currently taking place (ESSENCE trial, NCT04822181). Tirzepatide 5-15mg has also been shown to reduce the liver fat content by 8% (assessed through liver MRI) in people with T2D⁵¹.

This partnership will utilise and build upon the successful NIHR Diet and Activity Research Translation (DART) collaboration which combines a network of BRCs across England, with non-BRC academic institutions, research groups, clinicians and researchers. DART's membership boasts world-class resources and expertise in the fields of human interventional research, epidemiology and clinical trials, the reach and impact also extends into devolved nations. The collaboration with DART will add reciprocal value enabling access to an existing network and extensive specialist research resource, and extend existing Clinical Research Network (CRN) speciality group work streams around obesity-related disease.

Collaborators from across the Midlands, with support from the NIHR Leicester Patient Recruitment Centre, Centre for Ethnic Health and Clinical Research Network, will enable access to a diverse population that spans areas with high rates of liver disease and low research activity, e.g. Lincolnshire and Leicestershire. These collaborators have the capacity to deliver research outputs including phase 3-4 commercial (pharmacotherapy and clinical) trials. The partnership will extend the reach and impact of existing NIHR infrastructure and research expertise across the Midlands, into local areas of high need but low research activity. We will utilise our strengths and resource to address disparities across the region.

Geographic and demographic diversity across the Midlands enables the partnership to address inequalities in access and delivery of research for a wide range of communities locally. The remit of the partnership will however be wider than this, aiming to build relationships and create satellite centres for research inside and outside the Midlands, supported by collaboration with the NIHR DART and Clinical Research Network speciality group membership. See figure 2 for the network of UK wide expert collaborators who have agreed to support and provide expertise to this partnership. Target areas could include those with high levels of deprivation such as Hull and Liverpool, low research activity Leicestershire and those with high prevalence of obesity-related liver disease, for example North Lincolnshire and Glasgow.

We will utilise 18 months to establish the Midlands Liver Research Alliance working with core partners and extend collaboration opportunities inside and outside the Midlands addressing NIHR research priorities highlighted in the commission brief around NAFLD (reducing health inequalities; prevention and self-management; evaluation of new treatments [e.g. pharmacotherapy]).

Aims and objectives

The central aim is to establish a cross-sector, multi-disciplinary research partnership based in the Midlands with national expert collaborators (figure 2) to address obesity-related liver disease and associated health inequalities. The partnership will utilise expertise, resource and extend the impact of existing NIHR infrastructure (figure 1).

Objectives;

- Cultivate a sustainable public and stakeholder engagement network focusing on hard-to-reach and underserved populations
- Identify and define obesity-related liver disease research priorities
- Establish partners to scope and facilitate the development of a core set of patient-reported outcomes
- Create a network of obesity-related liver disease satellite research sites to provide increased research capacity, capability and knowledge mobilisation in areas of need
- Generate an effective research implementation framework into clinical practice
- Offer training to develop obesity-related liver disease clinical and allied health professional research specialists and provide training around cultural competencies and hard to reach populations

- Develop cross-infrastructure mentoring and mobilisation of research best practice

Partnership activities

Three partnership workstreams will include;

- 1) PPIE and stakeholder inclusivity and engagement
- 2) Research strategy, priority setting and methodology
- 3) Partnership capacity and capability mapping.

PPIE and stakeholder inclusivity and engagement

We will establish a public and stakeholder engagement strategy utilising existing (local advisory group networks), newly established (liver and/or obesity charities) and novel engagement networks. The engagement strategy will be developed early in the partnership, with a focus on reaching 'seldom-heard groups' raising research awareness and offering training for PPIE representatives. The strategy will be underpinned by three work packages. The work package design has been informed by individuals with lived experience of NAFLD.

Advisory group: An obesity related liver disease partnership advisory group will be established in the early phase of the partnership, identified via multiple channels (see PPI involvement plan) to ensure representation from multiple varied communities, and the inclusion of underrepresented groups. The advisory group will meet throughout the partnership, the number of groups and meeting method will be determined in partnership discussions at set-up to ensure accessibility and representation. The advisory group will input into research co-design and all relevant partnership activities throughout.

Campaigns: The partnership will develop NAFLD risk, awareness and care campaigns. We will work to raise public awareness in ethnically diverse communities; areas with high levels of obesity, high deprivation; and areas with low/no research output. The Centre for Ethnic Health Research will support training programmes to raise awareness around cultural competency. An awareness raising workshop and working group will include patients, public, researchers, stakeholders (e.g. charities) and healthcare professionals. We will create a campaign, implementation plan, and supporting materials. PPIE representatives will be key to developing accessible public facing material. From Leicester BRCs previous PPI work we know language, tone and visual stimuli are key to public facing resources especially in obesity and associated disease. The campaign could include, online forums, which offer wide reach and impact, locally and nationally. Also, community public events to raise awareness of obesity-related liver disease and research in community settings (including faith centres), and raising awareness with healthcare professionals through targeting campaigns in primary and secondary care.

Advocacy: This programme of work will align research priorities and outcomes, by undertaking a complimentary journey towards co-production of research questions. A listening and consensus approach will be undertaken with non-academic stakeholders, PPIE representatives, individuals with lived experience, and experts in obesity related liver disease to facilitate the framing of research questions and co-design of research methodology. Existing research priorities for obesity related liver disease and NAFLD identified by James Lind Alliance 2018 and the National Institute for Health Research (reducing health inequalities; prevention and self-management; evaluation of new treatments including pharmacotherapy) which align with the partnerships expertise will provide context and initiate conversations. Facilitated discussions will balance rational and experimental aims with person-centred outcomes to ensure direction and clarity. This will lead to generating new ideas, form new themes of work, and discern the consensus ultimately confirming the partnership research objectives.

Research priority setting, strategy and methodology

Partnership research objectives agreed in conjunction with the advocacy public and stakeholder engagement work will lead onto detailed funding proposals developed through a multi-disciplinary collaborative approach.

The establishment and development of priority research questions will be framed by a combined, core (Midlands) and national, multi-disciplinary collaboration of experts in NAFLD, obesity, pharmacotherapy, lifestyle medicine and trial methodology, in conjunction with the partnership advisory group. Research theme/priority leads will be identified based on subject speciality and working groups established; methodologists and liver research specialists will act as expert consultants. Research naïve healthcare professionals and non-specialist researchers will be encouraged to join working groups, mentored through the collaborative development process. A step-by-step research plan will be developed for each theme/priority. This will ensure a systematic approach to conducting timely PPIE and philosophically underpinned research with high quality results, dissemination and implementation plans.

Alongside this, we will explore links between other NHIR liver research partnerships to discuss their priorities and scope collaboration to plan the development of a Core Outcomes Measures in Effectiveness Trial (COMET) in obesity-related metabolic liver disease. We will develop a COMET analysis working group to progress discussions. This initiative aims to facilitate the development and application of 'core outcome sets', which are an agreed standard set of outcomes that should be measured and reported in all clinical trials in specific areas of health, or healthcare. The development of core outcome sets, and their utilisation within trials, enables more direct comparison of outcomes between studies, and pooling of data for secondary analyses and the final reporting of the core outcome sets study⁵². A COMET working group workshop will map the method of developing the core outcome sets, consider its scope, relevant stakeholders, and the process. A recent COMET analysis published for effectiveness trials investigating NASH⁵³, did not specifically consider the importance of obesity, and its associated physical and psychological consequences, when assessing the effectiveness of an intervention for people with chronic liver disease. For instance, obesity is strongly associated with impaired physical function^{54, 55}, quality of life⁵⁶ and mental health (anxiety, depression, stress)⁵⁷. Moreover, obesity, and related metabolic sequel, contribute to established health problems in NAFLD, including sarcopenia⁵⁸, fatigue⁵⁹ and impaired health related quality of life⁶⁰. These issues are important end-points to consider alongside hard liver outcomes in NAFLD therapeutic trials, particularly in the eyes of patients.

Partnership capacity and capability mapping

Partners and stakeholders will be brought together through a series of meetings to map the existing infrastructure and expertise across our partnership and national network. Additionally we will describe the partnerships' research and liver health inequalities (identifying areas of high versus no or low research output), and identifying areas of particular need (e.g. high levels of obesity, low socioeconomic status and low participation groups). This will inform subsequent arrangements for training, mentorship and infrastructure development between partnership members and research sites. Potential satellite research sites will be identified to provide increased research capacity and capability, and knowledge mobilisation in areas of need will be discussed and areas proposed. We will engage with health service providers (e.g. Integrated Care Boards), and with collaborators in local and national hepatology and weight management services. Along with satellite research sites and the patient recruitment centres, this will provide us with capacity to run multi-site trials to address research and health inequalities in obesity related liver disease both locally and nationally.

The partnerships inputs, activities, outputs, short medium and long term goals and intended impact are outlined in the attached logic model (Table 1). Upon successful funding timeline development for events and activities will be undertaken to guide the partnership and ensure timely outputs.

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