Review

From O'Shaughnessy to opportunity: innovating Hepatology Trials in the UK

Oliver D Tavabie ,[1] Yvanne Enever,[2] Daniel Green,[3] Helen Crisp,[4] Emmanouil Tsochatzis,[5] Amir Gander,[5] Dina Mansour ,[6] Vanessa Hebditch,[7] Julie Adams,[7] Adam Ashbourn,[8] Christopher Mysko,[9] Richard Allen,[8] Laura Kent,[10] James B Maurice ,[11] Ankur Srivastava,[11] Abhishek Chauhan,[12] Tom Johnston,[13] Janet Ruane,[8] Rebecca Varni,[8] Caroline Fletcher,[8] Cyril Sieberhagen,[14] Gordon Hay,[15] Giovanna Bretland,[14] Maggie Corrigan,[14] Francesco Ferraro,[14] Riley McMahon,[8] Trudie Burge,[11] Harry Ferguson,[8] Louise Jennings,[11] Brian Hogan,[5] Andrew Cook,[16] Rajiv Jalan,[4,5] Gautam Mehta[4,5]

For numbered affiliations see end of article.

Correspondence to
Dr Oliver D Tavabie, Leeds Teaching Hospitals NHS Trust, Leeds, UK; oliver.tavabie@nhs.net
Dr Gautam Mehta; gautam.mehta@ucl.ac.uk

Received 15 March 2024
Accepted 27 June 2024

To cite: Tavabie OD, Enever Y, Green D, *et al*. *Frontline Gastroenterology* Epub ahead of print: [please include Day Month Year]. doi:10.1136/flgastro-2024-102710

ABSTRACT

Developing new treatments that improve outcomes for patients with decompensated cirrhosis remains an unmet area of clinical need. The UK has a rich history of being on the forefront of clinical trials for this patient group. However, there have been challenges in achieving this goal in the past decade, with several negative studies as well as trials struggling to achieve recruitment. This has been further exacerbated by the changed clinical landscape following the COVID-19 pandemic. In response to this, the O'Shaughnessy report was commissioned to identify potential opportunities to improve clinical trial performance in the UK. In this review article, we identify critical areas for the UK hepatology community to collaborate and develop sustainable partnerships for clinical trial delivery which will ensure that outcomes are representative, inclusive and patient-centred.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the last 5 years, recruitment to clinical trials has significantly dropped across the UK with our global ranking falling from 4th to 10th.
⇒ It is well documented that patients with liver disease are underserved and it is notable that certain areas with high disease prevalence have historically been 'research inactive'.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We propose a number of innovations in clinical trial design to improve access to clinical trials for patients, clinicians and investigators alike.
⇒ We highlight the importance of agreeing and implementing standards of care for this patient group, which should not just improve clinical outcomes but reduce heterogeneity in standard of care/placebo cohorts.
⇒ We discuss the potential role of collaboration with industry to improve the delivery of clinical trials.
⇒ We discuss the importance of ensuring the development of the next generation of investigators to ensure sustainability to this model of working.

Randomised controlled clinical trials have the potential to improve lives. At no time has this been more apparent than during the recent COVID-19 pandemic. Ethical approvals and platform-trial protocols were developed in record time and life-saving therapies were available within months.[1] However, in parallel, the 'business as usual' side of clinical trials in the UK has suffered in recent years. As articulated by Lord O'Shaughnessy in his recent report on UK clinical trials,[2] and the response from the UK government,[3] change is urgently needed to reverse this decline in performance. Within this changing landscape

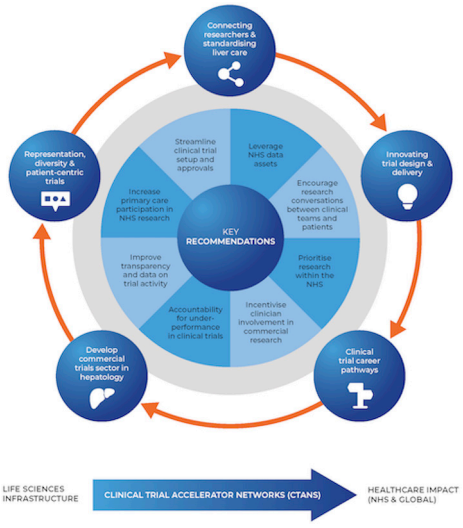

Figure 1 An overview of recommendations and themes from the O'Shaughnessy report. NHS, National Health Service.

of evolution in trial design, streamlining of set-up processes, unmet and growing public health need and a pipeline of therapies in phase II/III trials, there is opportunity for the hepatology community to leverage these changes and improve access to innovative therapies for our patients.

Within the last 5 years, recruitment to commercial clinical trials has fallen by over 40%.[4] Initiation of clinical trials, particularly phase III, has also tumbled with our relative ranking to other countries falling from 4th to 10th globally. Academic-led clinical trials in the UK are largely funded by the National Institute for Health and Care Research (NIHR). Recruitment to these studies has returned close to prepandemic levels, partly due to the NIHR 'Research Reset' programme. However, as a consequence, a number of national studies have closed early, including within liver disease (NIHR award 16/99/02). In response to the decline in commercial trial performance, the O'Shaughnessy report makes several recommendations with the aim of streamlining clinical trial set-up and improving accountability for clinical trial performance (figure 1). Additionally, there were suggestions to address the culture of clinical research within the National Health Service (NHS), including alignment of trial activity alongside routine care and incentivisation of clinical research for staff. These recommendations should be welcomed, particularly as there has never been a more important time to innovate within hepatology research and attract a new generation of researchers to the field. Indeed, aside from providing early access to new therapies, commercial research is of financial benefit to NHS trusts—on average £9000 for each patient recruited, and a further £5800 in drug costs saved per patient.[5]

Historically, the UK has made major contributions to translational liver disease research. The first clinical trial in liver disease was conducted over five decades ago by Dame Sheila Sherlock, and large randomised trials in alcohol-related hepatitis and decompensated cirrhosis have been completed within recent years.[6–8] Despite this, new therapies for alcohol-related hepatitis and decompensated cirrhosis remain lacking, and there are consequently several aspects of trial design and delivery that may be innovated in the postpandemic era. In 2022, NIHR announced funding for a series of 'research partnerships' to amplify the impact from liver disease research in the NHS. This article was informed by a series of public-facing meetings of the UK-Chronic Liver Failure network (UK-CLIF)—a NIHR-funded research partnership focused on liver cirrhosis—attended by hepatologists, patients, carers, researchers, allied health professionals, NHS R&D staff, charity and industry representatives. Five themes discussed, aligned with Lord O'Shaughnessy's recommendations, are outlined below.

REPRESENTATION, DIVERSITY AND PATIENT-CENTRIC TRIALS

To achieve the greatest benefit from clinical trials, the participants recruited must be representative of the target disease population. Where this has not been the case, for example in areas of cardiovascular research, clinical trial benefits have not been realised in real-world practice.[9] Liver disease frequently affects groups that are underserved, through ethnicity, sex or socio-economic factors. The five most deprived areas of England and Wales have a significantly lower median age at death (62 years) for liver disease compared with the least deprived (71 years).[10] Indeed, the geographic variation in prevalence and mortality from liver disease has been widely commented on with social deprivation associated with care provision and clinical outcomes.[11]

Impactful liver disease research in the UK must make efforts to achieve representation from these underserved groups. Currently, most clinical liver research takes place around the major liver centres in the UK, neglecting some areas of high disease prevalence (figure 2). Thus, any potential effort to extend representation should facilitate research from these areas of the country. The creation of open research networks is a deliberate effort to broaden involvement as well as identify barriers and challenges to inclusion of participants from 'hard-to-reach' sectors. The involvement of relevant stakeholders in co-design of the network from healthcare, charity, community organisations and industry is crucial.

Themes identified during public-facing meetings included the need to adapt approaches to engage people from underserved communities, in particular

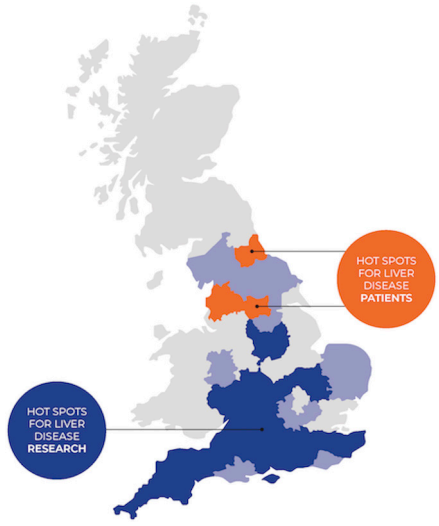

Figure 2 A map demonstrating areas of high disease prevalence for patients with decompensated liver disease compared with areas which have been historically research active.

those with alcohol-related liver disease (ARLD), to improve recruitment and retention to clinical trials. The challenge of conducting trials in this patient group has been vividly described, most recently by the North American TREAT network, although there is limited experience of recruitment strategies for patients with ARLD in the UK.[12] A further important aspect raised by attendees was the need for patient-centric trial protocols with amenable eligibility criteria and visit schedules, including remote data collection processes. These approaches are currently being used in the NIHR-funded AlcoChange trial (ISRCTN 10911773), which will provide important learning for future trials in the UK ARLD population.

CONNECTING RESEARCHERS, PATIENTS, CARERS AND STANDARDISING LIVER CARE

A further theme to emerge from the UK-CLIF meetings was the complexity and administrative burden of the current research landscape, echoing the findings of Lord O'Shaugnessy and others. Aside from the slow and bureaucratic processes, a further point raised was the lack of awareness of open trials among patients, carers and potential investigators in secondary care. The O'Shaughnessy report proposes a roadmap to reducing the regulatory burden on trial set-up, with a goal of 60 days for approvals. However, there is also scope for research networks to increase connectivity between researchers to facilitate this process. Although the NIHR local Clinical Research Networks support potential study sites in the set-up process, additional measures such a 'buddy programmes' between experienced and new investigators and sharing of existing resources for new applications, including ethics forms and patient-facing materials, may increase funding to support research activity in historically low-activity areas. Furthermore, with the lack of non-transplant treatments to improve outcomes for patients with decompensated cirrhosis, there is a need to develop large-scale trials that translate preclinical observations. The additional benefit of the 'buddy programme' would be the development of reciprocal relationships that improve translation of novel therapies, with input from the 'coalface' being critical in determining how they can be implemented in routine care.

Additionally, there is variation in the inpatient management of liver cirrhosis, as noted in the 2013 National Confidential Enquiry into Perioperative Death and termed a 'postcode lottery' by the Lancet Liver Commission.[13 14] For complex interventions, 'standard care' is often employed as the control arm in clinical trials for this patient group; consequently, large variations in care are problematic for sample size and data interpretation. In response, national societies such as the British Society of Gastroenterology and the British Association for the Study of the Liver have produced, and continue to undertake, consensus-building processes to produce guidance and consensus standards for the management of patients with cirrhosis.[15] However, the involvement of research networks in study protocol design will further ensure consensus-based standards of care are effectively implemented in the trial setting.

Moreover, broad representation from healthcare professionals (HCPs), patients and carers within research networks will lead to the development of relevant, patient-focused clinical trial end points through consensus processes, to replace conventionally used surrogate end points. To achieve this, it is necessary that we make research as accessible as possible to those from non-research backgrounds. Currently, UK-CLIF is working with patients and carers to develop research priorities for patients with decompensated cirrhosis in collaboration with the James Lind Alliance (https://www.jla.nihr.ac.uk/priority-setting-partnerships/liver-cirrhosis). An important component of this is capturing lived experience of cirrhosis, which will help us refine the research questions and meaningful end points. This collaboration will enable us to address questions that have the greatest long-term impact.

INNOVATING TRIAL DESIGN AND DELIVERY

Hepatology may have things to learn from other disciplines in the design and delivery of trials. Fuelled by the critical need of the pandemic, recent years have seen utilisation of methodology beyond conventional individually randomised trials. These have included platform designs, Bayesian analysis and use of centrally collected routine data. These processes reduce the need for the setting up of extensive bespoke data collection processes for each trial. The infrastructure required to deliver a large-scale clinical trial is a major contributor to the cost of the study. As used in the COVID-19 RECOVERY trial, a platform design is an approach where a number of interventions can be

compared with each other, or with a control condition, simultaneously. Sharing the infrastructure between multiple research questions offsets these fixed costs of trial delivery. Additionally, it also allows data from control participants to be reused, allowing a greater proportion of patients entering the study to receive the novel intervention and thus making participation more attractive to patients. This trial design is also more efficient, allowing research questions to be answered by randomising fewer patients.

Traditionally, trial design has been 'frequentist', meaning it follows a fixed, predefined plan with specific criteria and predetermined sample sizes. These assumptions are based on the point of view that any outcome is equally likely. A Bayesian design takes into account the investigators' prior belief about what the outcomes are likely to be, and generates a 'likelihood ratio' that can be applied to that prior belief to produce a 'posterior distribution'.[16] This posterior distribution takes account of data that have been collected, and tells the investigator how they should modify their prior beliefs. This has two significant advantages over a frequentist approach, and two significant drawbacks. Because the approach takes into account already existing information, required sample sizes are often smaller. It also allows someone who has a very different prior belief to the investigators to take the likelihood ratio generated by the trial and apply it to their own prior beliefs. This approach has already been used to reanalyse data from the PREDESCI trial of non-selective beta-blockers in cirrhosis.[17] The two major drawbacks of this approach are that not everyone may agree on the prior probabilities, although this can be addressed by individuals using the likelihood ratio with their own priors. A more pressing issue is the scarcity of statisticians skilled in Bayesian approaches compared with those proficient in frequentist methods.

Lord O'Shaughnessy also highlights the considerable data assets within the NHS, and the potential opportunities from integrating electronic patient records and data storage systems within the research pipeline. For example, it should be possible to interrogate NHS and other clinical systems to ask questions such as, "where can I find females with diabetes and cirrhosis aged between 30 and 45?" This capability would enable the opening of study sites in locations with high disease prevalence. Similarly, it should be possible to collect a vast range of clinical outcome measures through these systems. Undoubtedly, the role for artificial intelligence (AI) is going to grow and support the delivery of clinical research. However, the irony of the situation is that potential participants cannot currently be approached, without them already having given consent to be approached. Improvements in data access are in progress; £200 million of funding was committed to improve data infrastructure for NHS England in 2022. Furthermore, the establishment of NHS DigiTrials aims to address questions of trial feasibility using anonymised NHS data, with current pilot efforts focused on recruiting trial participants and using outcome data.[18] However, integrating AI experts with HCPs from different backgrounds, patients and carers will likely increase the potential impact that AI can have on improving patient outcomes and can be delivered by networks such as UK-CLIF.

CLINICAL TRIAL CAREER PATHWAYS

To deliver the vision of Lord O'Shaughnessy to make the NHS a world-leading platform for clinical trials, the next generation of HCPs must be trained and resourced accordingly. In the report, a Clinical Trials Career Path is specifically recommended to be integrated into the NHS Long-Term Workforce Plan. The delivery of clinical trials has traditionally been by medical professionals, but in recent years nurses and allied heath professionals have also come to the fore in trial leadership, development and delivery.[19] This trend is welcomed as data support improved clinical outcomes and better staff retention through broader HCP involvement. However, there are clear challenges in acquiring the necessary skills and experience to develop the next generation of researchers within an overstretched NHS, including the reforms in training following 'Shape of Training'. The NIHR have fellowships tailored to support HCPs in translational research, as well as a specific gastroenterology and hepatology Clinical Research Programme for medical trainees who wish to gain further experience in clinical trials. However, more training opportunities are required, and from this perspective there is clear value in integrating trainees within cross-sectoral research networks. The TORCH trainee network in hepatology recently demonstrated this through a pan-UK study on outcomes of decompensated cirrhosis, involving 294 collaborators from 104 hospitals.[11] Thus, although a commitment to academic posts and Continued Professional Development is articulated in the NHS Workforce Plan, broader exposure of trainees to clinical trials, across all HCP specialties, will be necessary if the vision of a world-leading trials environment is to be realised.

DEVELOPMENT OF THE COMMERCIAL TRIALS SECTOR IN HEPATOLOGY

In the realm of commercial trials, significant change is urgently needed to reverse the UK's declining market share in a field where it once held global leadership. This presents a great opportunity for the hepatology community to capitalise on, through leveraging the establishment of research networks and the planned streamlining of commercial trial processes. Although the economic implications of Brexit and a string of negative trials in liver disease have added a layer of uncertainty to

the hepatology commercial trials arena in recent years, the recent news of a positive phase III trial in metabolic dysfunction-associated steatohepatitis has the potential to renew interest in this sector.[20]

One of the aims of the O'Shaughnessy review is to align clinical research with both the Life Sciences Vision outlined by the UK Government in 2021 and the areas of unmet clinical need within the NHS. This alignment aims to achieve an end-to-end research pipeline.[21] In this sense, liver disease is again a prime candidate for investment given the burden of disease in the UK, alongside stated priorities such as neurodegenerative conditions, cancer, cardiovascular disease and mental health. To this end, the government has committed £20 million for the development of Clinical Trial Accelerator Networks (CTANs), which will provide a 'Rolls Royce' clinical trials service in strategic areas, to expedite approval, delivery and impact of clinical research. The vision is for 8–10 CTANs to be commissioned in the near future, as partnerships between the NHS, academia, industry and medical research charities, although it remains unclear in which strategic and geographical areas these CTANs will sit. It is likely that these CTANs will prioritise areas within the current Life Science Vision or of great public health need, and consequently it is for the hepatology community to push the case for a liver disease CTAN at the highest level.

To conclude, the O'Shaughnessy report is a timely reminder of the need to improve the UK's competitiveness in the running of clinical trials for new drugs and devices in liver disease. With liver cirrhosis likely to become the leading cause of working years of life lost within the next decade, the lack of commercial investment in hepatology research could have potentially far-reaching consequences for public health. Rebuilding hepatology trials capacity must be a key priority for the liver community, if patients are to benefit from the shifting landscape of clinical research in the post-COVID-19 era.

Author affiliations
[1]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]PharmExcel Ltd, London, UK
[3]Department of Bioengineering, Imperial College London, London, UK
[4]Division of Medicine, University College London, London, UK
[5]Royal Free London NHS Foundation Trust, London, UK
[6]Gateshead Health NHS Foundation Trust, Gateshead, UK
[7]British Liver Trust, Ringwood, UK
[8]Patient/carer Representative, London, UK
[9]Manchester University NHS Foundation Trust, Manchester, UK
[10]Great Western Hospitals NHS Foundation Trust, Swindon, UK
[11]North Bristol NHS Trust, Bristol, UK
[12]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[13]Taunton and Somerset NHS Foundation Trust, Taunton, UK
[14]Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
[15]Liverpool John Moores University, Liverpool, UK
[16]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK

X Dina Mansour @drdina_mansour and James B Maurice @jamesbmaurice

Acknowledgements We are grateful to all participants of UK-CLIF events.

Contributors ODT, HC, RJ and GM planned the UK-CLIF meetings and facilitated them. ODT, YE, DG, HC, AC and GM wrote the first draft. GM is guarantor of the manuscript. All authors contributed to outcomes from the meeting, reviewed the draft and made critical revisions.

Funding This study was funded by National Institute for Health and Care Research (NIHR155694).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Oliver D Tavabie http://orcid.org/0000-0003-4693-6632
Dina Mansour http://orcid.org/0000-0002-8367-4232
James B Maurice http://orcid.org/0000-0003-1530-5328

REFERENCES

1 Horby P, Lim WS, Emberson JR, *et al*. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;384:693–704.
2 The Department of Health and Social Care. Commercial clinical trials in the UK: the LORD O'Shaughnessy review - final report. 2023. Available: https://www.gov.uk/government/publications/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review-final-report [accessed 20 Dec 2023]
3 The Department of Health and Social Care. Full government response to the LORD O'Shaughnessy review into commercial clinical trials. 2023. Available: https://www.gov.uk/government/publications/government-response-to-the-review-into-commercial-clinical-trials/full-government-response-to-the-lord-oshaughnessy-review-into-commercial-clinical-trials [Accessed 20 Dec 2023].
4 The Association of the British Pharmaceutical Industry. NHS patients losing access to innovative treatments as UK industry clinical trials face collapse. 2022. Available: https://www.abpi.org.uk/media/news/2022/october/nhs-patients-losing-access-to-innovative-treatments-as-uk-industry-clinical-trials-face-collapse [Accessed 20 Dec 2023].
5 NHS England. Managing research finance in the NHS, 2024. Available: https://www.england.nhs.uk/long-read/managing-research-finance-in-the-nhs [Accessed 17 Jun 2024].
6 Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med* 1971;40:159–85.
7 Thursz MR, Richardson P, Allison M, *et al*. Prednisolone or Pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015;372:1619–28.
8 China L, Freemantle N, Forrest E, *et al*. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *N Engl J Med* 2021;384:808–17.
9 Ferdinand KC, Elkayam U, Mancini D, *et al*. Use of isosorbide dinitrate and Hydralazine in African-Americans with heart failure 9 years after the African-American heart failure trial. *Am J Cardiol* 2014;114:151–9.
10 Office for Health Improvement and Disparities. The 2nd atlas of variation in risk factors and Healthcare for liver disease in England. 2017. Available: https://fingertips.phe.org.uk/profile/atlas-of-variation [Accessed 20 Dec 2023].
11 The Trainee Collaborative for Research and Audit in Hepatology UK. Regional Variations in Inpatient Decompensated Cirrhosis Mortality May Be Associated with Access to Specialist Care: Results from a Multicentre Retrospective Study. London, UK,

12 Comerford M, Lourens S, Liangpunsakul S, *et al*. Challenges in patient Enrolment and retention in clinical studies for alcoholic hepatitis: experience of the TREAT consortium. *Alcohol Clin Exp Res* 2017;41:2000–6.
13 National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Alcohol-related liver disease: measuring the units. A review of patients who died with alcohol-related liver disease. 2013. Available: https://www.ncepod.org.uk/2013arld.html [Accessed 20 Dec 2023].
14 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;384:1953–97.
15 Mansour D, Masson S, Shawcross DL, *et al*. British society of gastroenterology best practice guidance: outpatient management of cirrhosis – part 1: compensated cirrhosis. *Frontline Gastroenterol* 2023;14:453–61.
16 Muehlemann N, Zhou T, Mukherjee R, *et al*. A tutorial on modern Bayesian methods in clinical trials. *Ther Innov Regul Sci* 2023;57:402–16.
17 Rowe IA, Villanueva C, Shearer JE, *et al*. Quantifying the benefit of nonselective beta-blockers in the prevention of hepatic decompensation: a Bayesian reanalysis of the PREDESCI trial. *Hepatology* 2023;78:530–9.
18 NHS England. NHS Digitrials, 2023. Available: https://digital.nhs.uk/services/nhs-digitrials [Accessed 20 Dec 2023].
19 Williams FR, Vallance A, Faulkner T, *et al*. Home-based exercise therapy in patients awaiting liver transplantation: protocol for an observational feasibility trial. *BMJ Open* 2018;8:e019298.
20 Harrison SA, Bedossa P, Guy CD, *et al*. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024;390:497–509.
21 The Department for Science. Innovation and technology [Life sciences vision]. 2021. Available: https://www.gov.uk/government/publications/life-sciences-vision [Accessed 20 Dec 2023].