Viewpoint: From O'Shaughnessy to Opportunity - Innovating Hepatology Trials in the UK

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Abstract

Developing new treatments that improve outcomes for patients with decompensated remains an unmet area of clinical need. The United Kingdom (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 this review article, we identify critical areas for the UK hepatology community to collaborate and develop sustainable partnerships for clinical trial delivery, to ensure that outcomes are representative, inclusive and patient-centred.

Key points

- In the last five 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'
- 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

Randomized 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 of evolution in trial design, streamlining of set-up processes, unmet and growing public health need, and a pipeline of therapies in phase 2/3 trials, there is opportunity for the hepatology community to leverage these changes and improve access to innovative therapies for our patients.

Within the last five years, recruitment to commercial clinical trials, in particular, has fallen by over 40%[4]. Initiation of clinical trials, particularly phase 3, 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 pre-pandemic 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 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.

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[5-7]. 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 post-pandemic era. In response, 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 focussed 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[8]. 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)[9]. Indeed, the geographic variation in prevalence and mortality from liver disease has been widely commented upon.

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, and 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, therefore, crucial.

Themes identified during public-facing meetings included the need to adapt approaches to engage people from underserved communities, in particular 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 ARLD patients in the UK[10]. 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 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 amongst 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 (CRNs) 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 research activity in historically low-activity areas.

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[11,12]. 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 (BSG) and the British Association for the Study of the Liver (BASL) have produced, and continue to undertake, consensus-building processes to produce guidance and consensus standards for the management of patients with cirrhosis[13]. 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.

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, rather than setting up 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’, that is, following a fixed, pre-defined, plan with specific criteria and sample sizes in advance. 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’[14]. This posterior distribution takes account of data that has 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 nonselective beta-blockers in cirrhosis[15]. The two major drawbacks of this approach are that not everyone may agree on the prior probabilities, although this can be addressed by each individual using the likelihood ratio on their own priors, and the more pressing issue that there are fewer statisticians skilled with Bayesian approaches than there are frequentist experts.

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 or other clinical systems to ask questions like, “where can I find females with diabetes and cirrhosis aged between 30 and 45?”, and consequently open study sites in locations of high prevalence. Similarly, it should be possible to collect a vast range of clinical outcome measures through these systems. 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. Further, the establishment of NHS DigiTrials is aimed to address questions of trial feasibility using anonymised NHS data, and efforts to recruit trial participants and use outcome data are currently being piloted[16].

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 health care professionals 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 (AHPs) have also come to the fore in trial leadership, development and delivery[17]. This trend is to be welcomed; data supports improved clinical outcomes and better staff retention with broader healthcare professional (HCP) involvement. However, there are clear challenges in acquiring the necessary skills and experience to develop the next generation of researchers within a stretched NHS. 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 of decompensated cirrhosis outcomes involving 294 collaborators from 104 hospitals[18]. 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: It is within the area of commercial trials where change is most needed to reverse the UK's falling market share in a field where it was previously a global leader. And, it is here that there is great opportunity for the hepatology community, through leveraging the formation 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 3 trial in metabolic dysfunction-associated steatohepatitis has the potential to renew interest in this sector.

One of the intentions 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, with the specific aim of achieving an end-to-end research pipeline. 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 joint ventures 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, a lack of commercial investment in hepatology research has 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 era.

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