DETAILED RESEARCH PLAN FOR PARTICIPATE-B

1. Introduction and Case for Support

Hepatitis B virus (HBV) infection is a substantial international public health problem [1]. There is an estimated burden of over 300 million cases of chronic infection worldwide, leading to approaching a million deaths each year as a result of liver cirrhosis and hepatocellular carcinoma (HCC). Despite this burden of disease, HBV has been neglected by infrastructure, resource, advocacy and investment. Clinical and public health interventions lag far behind those for other comparable public health threats such as HIV, TB and malaria [2]. The World Health Organisation (WHO) has endorsed ambitious targets, under the umbrella of international Sustainable Development Goals, for the elimination of HBV as a public health threat, which include specific targets for reducing incidence and prevalence, and a 65% reduction in mortality by 2030. WHO European action plan targets include focus on enhanced diagnosis, starting treatment in those who are eligible, and achieving viral suppression on treatment [3]. Most countries are not on track with these targets [4]. The WHO has recommended a need to raise awareness, promote partnerships and mobilise resources, to formulate evidence-based policy and data for action, improve health equity, prevent transmission, underlining an urgent drive scale up screening, care and treatment services [5].

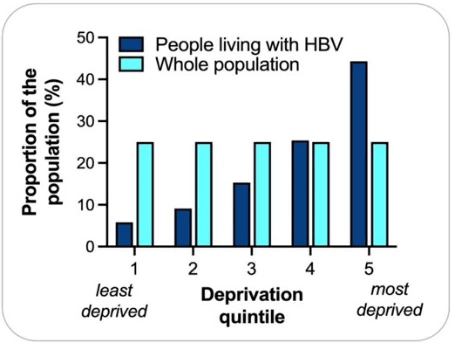

Fig 1: Townsend deprivation quintile breakdown in 8039 adults with chronic hepatitis B virus (HBV) infection identified from the QResearch primary care database (representing 35 million GP records across England) versus the general population [6].

The epidemiology of HBV infection in the UK is not well established. Recent estimates suggest the UK prevalence of CHB is between 0.3-0.7% [7]. However, uniform screening has not been consistently rolled out, and there are significant differences between settings, so these estimates may significantly under-estimate true prevalence, particularly for certain populations.

There is increasing evidence that deprived and marginalised populations are disproportionately affected by HBV infection and associated liver disease, with an increasing prevalence in lower socioeconomic groups (Fig 1). HBV prevalence is also higher in populations who suffer existing health inequities, including migrants and asylum-seekers, the LGBTQ+ community, those experiencing homelessness and substance use disorders, and prison populations, for whom HBV screening and links to stable long-term clinical care are not systematically provided. These communities may be side-lined by clinical services, and individuals feel disengaged and lost in the healthcare system.

In this application, we propose the development of a network of diverse stakeholders, representing clinicians, non-governmental organisations, researchers, and patients, and the establishment of new partnerships with industry, funders, health economists and policy makers. This group will set out to investigate and characterise barriers to care for people living with HBV infection in the UK, in order to develop evidence-based approaches to inform diagnosis, linkage to care, and continuity of clinical services. By providing evidence that supports pathways to diagnosis and continuity of clinical care, in the long term we will provide evidence to facilitate:

- Improved individual health, with access to surveillance and antiviral treatment for those who are eligible, based on national clinical guidelines [8];

- A public health benefit in reducing transmission, by vaccinating partners and households, and treating individuals with high level viraemia;
- Enhanced education and awareness, tackling stigma and discrimination;
- Opportunities for engagement in research, including clinical trials, as new HBV agents are rolled out, such that new research is more representative and equitable [9].

We seek to link our programme's agenda to six domains of healthcare quality [10], developing pathways to clinical care that are safe, effective, patient-centred, timely, efficient, and equitable, with a particular focus on marginalised populations for whom there are complex barriers and challenges.

2. Proposed activities

This funding will support the development of an active interdisciplinary network, leading to the development of a funding bid for implementation research to support the development of HBV services in the UK, with a special focus on under-served groups.

Specific activities will include stakeholder meetings, focus group meetings with patients and the public hosted on-line or in person, and collection/review of preliminary data (gathered through quality improvement and audit activity in NHS Trusts, and/or with informed consent from people engaging with the inclusion health team). We will host a webinar series to collect opinions, stories and experiences. The team will explore the role for eHealth approaches, using smartphone technology and/or apps to provide a consistent linkage to care. We will develop educational resources to boost awareness and provide information, using infographics and diverse languages to make material widely accessible to a diverse audience. The partnership will support the development of new relationships, which will include formalising links with industry, bringing in connections to new NHS sites to expand the diversity of patient populations we represent, and forming collaborations with other disciplines including health economists and social scientists. A preliminary connection to Médecins du Monde will be strengthened, through activities that allow us to learn from their experience and scope their capacity and roles for involvement in future research.

Our partnership will address a set of themes representing known barriers to HBV diagnosis and care, based on our body of existing work in this field, which include lack of education/awareness, language barriers, migrancy and high mobility of populations, stigma and discrimination, provision of antiviral treatment (or lack thereof), and access to clinical services. These domains will be reviewed during the course of the project to refine our approach, determine priorities, and develop specific strategies to tackle barriers. We will develop resources for use in future implementation research programmes, using an iterative approach to reviewing materials that include questionnaires and frameworks for interviews, and exploring the use of an app and/or website to facilitate connections between clinical services and patients. Strategies will be explored through presentation to wider audiences of healthcare providers, industry and academics in regional and national clinical meetings, including the BASL special interest group.

Activities will be reviewed and informed by expert partners in the form of the British Liver Trust and Hepatitis B Foundation, who will provide connections to a wide national and international body of experience, and the opportunities to generate feedback by sharing materials, resources and research proposals with their patient forums. Educational meetings will allow us to engage with a wide audience and provide training to a new cadre of junior clinicians and researchers. Preliminary networking activities have the support of seed funding from a Crick Partnership Award (Matthews) to establish an educational and research network 'HBV FOCUS', which will support us in convening two preliminary meetings ahead of the start date of this funding.

3. Patients/service users/carers/public as stakeholders

In this partnership development programme, we will set out to form a HBV network which provides opportunities for connections and engagement with people living with HBV, and their families and carers, in different settings and with different needs. We are proposing to engage patients as part of our research network, such that their experience is directly integrated into development of future research proposals. This builds on our existing work in which patient voices were represented in developing a position statement for our 'HBV Voice' movement [11]. Through this preliminary activity, we have already established a small but strong body of patient representatives who are engaged, motivated and have ownership in ongoing development of the programme.

Foundations for a future study will be established through connections with clinical teams. This includes healthcare workers working in our hospital-based services in Birmingham and London, and community services led through the UCL Inclusion Health team, through which people living with HBV infection are reviewed in primary care centres or visiting them in their place of residence (including at home, in hostels and in prison). As the network develops, we will expand this activity to other centres. Our professional roles provide us with a national network of connections, for example through BASL (Elsharkawy), BASHH (Flanagan), Inclusion Health networks (Story), and the NIHR Health Informatics Collaborative (Matthews). Review of anonymised routinely-collected data from our clinical services will be undertaken to develop an enhanced understanding of patient populations and characteristics.

This activity will allow us to develop a protocol for subsequent larger scale research, with the establishment of inclusion/exclusion criteria (specifically to ensure that certain groups are not excluded without justification), and to refine our approaches to recruitment and consent to ensure they are practicable, accessible and equitable.

We will develop participant education, information and consent materials, working with feedback from our research network in an iterative process to determine the preferred platforms for service users to access information (e.g. on-line, smartphones, hard copy), and to ensure that the material is widely accessible and appropriate. These findings will also help us to determine optimum approaches to sharing information about study progress and findings with participants and with wider audiences. We will use the network to gather information about the relevant languages that need to be represented, such that we can prioritise translation to reach the relevant populations. We will not offer payments, rewards or recognition for those contributing to the network, but have included a budget to cover travel costs.

4. Data and statistical analysis, including health economics evaluation

Our teams have expertise in handling quantitative and qualitative data generated through a range of laboratory and clinical research, and in service provision and evaluation (e.g. [12–14]). The development of the partnership will provide us with opportunities to plan approaches that integrate statistical advice (e.g. through biostatistics and translation teams at the Crick) in developing implementation projects. This will include refining power calculations, data management plans and statistical analysis plans (approaches to interim analyses, missingness, sensitivity analyses), to support a full research protocol.

Developing and formalising collaborations with health economists is an important part of our planned strategy, and one of our aims for the lifetime of this award, in order to support and strengthen future implementation research. Our group already has some experience in health economics research (e.g. [13,15,16] and we therefore have a network of connections to explore, as well as approaching new collaborators in this field.

5. Scalability and translation

The aim of establishing this partnership is to strengthen and optimise our ability to undertake ambitious implementation research at scale across the UK, and provide evidence and frameworks for service delivery that are flexible, such that they can be adapted to diverse settings, accounting for the needs of different populations. In planning and scaling up our network of collaborators, we will invite representation from a range of healthcare settings, including those that have not been research-active to date. We will consider demographics of local populations (for example, breakdown by age, ethnicity, and sociodemographic status), and will review the needs of urban vs. rural service provision, and consider requirements for primary, secondary and tertiary settings. Incorporating diverse settings in our network will therefore provide us with the best possible reach and representation when developing and evaluating health service interventions.

6. Socioeconomic position and inequalities

Our network sets out to provide a framework through which we can reach populations most at risk of HBV infection and its complications, recognising that the burden falls disproportionately in under-served and socioeconomically deprived populations (Fig 1), with the aim of developing pathways to clinical care that tackle and reduce health inequities.

By collating feedback and experience from across our network, we will assess characteristics that stratify health opportunities and outcomes using the PROGRESS-Plus acronym: Place of residence; Race/ethnicity/culture/language; Occupation; Gender/sex; Religion; Education; Socioeconomic status; Social capital, and ‘Plus’ characteristics, referring to attributes that may be further associated with discrimination (e.g. age, disability, living circumstances, time-course of clinical care). As we develop a full funding bid, this means that participants can be offered the same opportunities to take part in research regardless of their clinical or demographic status and PROGRESS characteristics. In developing our network and designing protocols for a subsequent research study, we will apply the toolkit for increasing participation of ethnic minorities in health and care research [9], the INCLUDE ethnicity framework [17] and the NIHR Race Equality Framework [18].

7. Dissemination, outputs (success criteria) and anticipated impact

The output goals for this partnership are as follows:
(i) To develop a new network with clinical and research links across the UK representing different population settings, such that we can engage and represent diverse populations living with HBV infection;
(ii) To establish pathways through which we can inform guidelines, service development and policy;
(iii) To develop new connections with a multidisciplinary community of stakeholders including engagement with patients and the public, peer support networks, health economists, social scientists, industry, non-government organisations;
(iv) To develop and submit an ambitious implementation research programme to scale-up HBV services for under-served communities, in a model that can be tested and adapted for different settings across the UK.

We will disseminate information and outputs through the following routes:
(i) Use of our developing network to share information through regular progress meetings, such that key outputs can be channelled more widely to relevant stakeholders at intervals during the course of the project. We will capitalise on the wide networks already established by the British Liver Trust and Hepatitis B Foundation, and draw on their expertise in reaching relevant audiences.
(ii) We will generate outputs that are formatted for wide reach and appeal, for example developing infographics, and using social media platforms including Twitter, Instagram and TikTok which appeal to different age groups and demographics, with translation into different languages.

(iii) We will use seminars, conferences and events to share progress and raise awareness, capitalising on our group's links to national/international meetings that include infection, hepatology, public health, and sexual health and engaging with opinion leaders and champions. Forward planning will allow us to identify relevant opportunities during the lifespan of the project to capitalise on events generating maximum reach.
(iv) We will liaise with the communications and public engagement teams in our institutions, including NHS Trusts, and the Crick, to reach diverse audiences with relevant outputs.
(v) Relevant outputs will be shared in the form of publications, which may include peer-reviewed papers, research protocols, datasets, opinion articles, media or blog-posts.

We will use the funding period to develop and optimise strategies for communication with future study participants, including leaflets, institutional or study-specific websites, and social media.

Further funding or support that will be required

The aim of our partnership is to provide the groundwork for at least one substantial funding application within 12 months of the project end-date, with an aspiration to apply for NIHR funding for an implementation research project. During the development of the research partnership, we will also explore other avenues for funding support, including reaching out to established connections with industry (for example, Matthews already works in partnership with GSK), and expanding on local institutional funding awards (e.g. Matthews funding from Crick Partnership Award Scheme).

9. Project / research timetable

A GANTT chart is provided separately, setting out specific timelines for development of the network, establishing collaborations, focus groups, and intended outputs including a funding bid.

10. Project management

The study steering committee for this project will comprise the PI and the named co-investigators. Meetings will be convened at least quarterly on-line, with a minimum of four attendees in order to be quorate. Independent meetings will be planned to develop relationships with new partners and to seek feedback from relevant stakeholders, with patient and public involvement. We will also hold at least two face-to-face meetings (also including other stakeholders and a wider group of contributors) during the life-time of the project. The network will consider the requirement for a Data Management Executive Committee (DMEC) to support any subsequent research that is planned.

Milestones for the project will be established at the outset, to allow monitoring of progress against defined targets. This will include a schedule for appointing personnel, project meetings, planning of applications for funding and ethics, submissions of material to relevant national and international conferences, aligned with the GANTT chart (see point 9).

11. Ethics and governance

Formal ethics approval is not required for the development of a research partnership. However, during the timeframe of this award, we will work towards development and submission of an ethics application required for the next phase of implementation research, via the National Research Ethics Service and local review by ethics committees representing participating centres. Any plans for data collected during this first phase of activities will be prospectively submitted for review by local clinical governance teams and registered as part of audit or quality improvement activities. Our activities will all comply with the UK Framework for Health and Social Care research.

This programme of activity will not generate patient-identifiable data. Any clinical data that are relevant to informing the scope and activities of the project will be completely anonymised before sharing with the partnership team. All those handling any data originating in the clinical domain will be up to date in Good Clinical Practice training. Project data will be held in secure clinical/research environments with restricted access and firewall protection, and subjected to regular back-up, in accordance with the governance stipulations of host NHS and research organisations.

12. Expertise of Project Team

Dr Ahmed Elsharkawy is the lead for this programme. He is a research-active clinical Hepatologist based in Birmingham and Chair for the British Association for Study of the Liver (BASL) HBV special interest group. He has established strong links with the Hepatitis B Foundation (the leading organisation for HBV patients in the US), and is also a member of the HBV Collaborative Forum that is advising regulators on the design of patient-focused clinical trials in HBV. He is also the Chair of the Hepatitis C External Research Advisory Group which is studying the impact of the successful peer delivered models in the hepatitis C national elimination programme in England. He is a member of HSA's National Strategy Group on Viral Hepatitis and has strong links with national public health leaders in the field of viral hepatitis.

Prof Philippa Matthews is a group leader at the Francis Crick Institute and a consultant in clinical infection. She leads a programme focused on HBV elimination including laboratory research, analysis of 'big data' to address epidemiological questions, and translational research [19]. She is co-lead for the NIHR Health Informatics Collaborative (HIC) Viral Hepatitis theme, collating data from secondary care to address translational research questions [20]. She brings experience from a public engagement programme which has connected widely with patients and the public [21], sharing patient stories through high profile news features [22] and participating in a crowdsourcing event which gathered feedback from the global HBV community [23]. She has experience in developing policy as part of an expert group for the World Health Organisation advising on drug resistance in viral hepatitis, and in study design through collaborations with the MRC Clinical Trials Unit.

Prof Al Story leads the Inclusion Health programme in London, working at the interface between public health, clinical service provision and research activity, seeking to advance service delivery for vulnerable and marginalised populations [13, 24–26]. Prof Story has led the development of ambitious, high impact programmes in HIV, TB and HCV both in the UK and internationally, delivering major policy advances. He thus brings a wealth of valuable experience and insights of relevance to scaling up HBV care. He brings connections to a network of policy makers, funders and a diverse team of clinical and public health practitioners.

Dr Stuart Flanagan is a consultant in sexual health at Central and North West London NHS Trust (CNWL), and lead for viral hepatitis, bringing crucial experience in management of clinical services. He has expertise in the management of infectious diseases (including HBV) in the community and has pioneered on developing the role of HBV peers in the management of patients. He chairs the national BASHH group representing HIV, providing a national network of connections, and experience in communication, education and representation. His doctoral research was focused on how to increase diagnosis of viral hepatitis in primary care and his expertise in this field will be of particular value to understanding the healthcare context that many individuals with HBV experience.

Dr Saket Singhal is a consultant Hepatologist in the West of Birmingham with extensive clinical experience in the management of HBV in a predominantly deprived South Asian population. Sandwell is consistently shown to be an area of the country with disproportionately bad liver outcomes due in part to high levels of deprivation. Dr Singhal, therefore, brings experience of the challenges of engaging members of this community in HBV care but also has established patient links which will be invaluable in project design. Furthermore, he has participated in research investigating the prevalence of HBV in South Asian populations.

British Liver Trust (BLT) - Elsharkawy and Matthews have already developed dialogue with the BLT, with the aim of developing a UK-based Hepatitis B advocacy group. This work is ongoing, with a new strategy policy being developed before the end of 2022. This will see the BLT become the lead patient organisation for CHB in the UK, setting foundations that will lead us into the development of a more ambitious long-term proposal. The BLT provides a network of connections and expertise in working with patients affected by liver disease, supporting representation and advocacy, generating educational materials, working with the media, and lobbying for policy change. They also provide the secretariat for the All Party Parliamentary Group on liver disease.

Peer Support Worker - within this funding application, we will identify and appoint a new CHB specific peer support worker (employed by CNWL), bringing direct input from a person with lived experience of the infection to the project team. This individual will engage with individuals and communities affected by CHB, thus providing new connections, involving the patient community in development of research questions relevant to implementation of care pathways, and road-testing methodologies to help refine those proposals that are worked up for the second part of the NIHR call. CNWL will provide support and training for peer support workers, alongside an existing well-developed team of support workers, so that they can integrate quickly into the team and can generate high quality pilot data that will support future proposals, while having their own needs recognised and addressed within the service.

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