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Keywords:	liver, chronic liver disease, research priorities

TOP RESEARCH PRIORITIES IN LIVER AND GALLBLADDER DISORDERS IN THE UNITED KINGDOM

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ABSTRACT

Objectives: There is a mismatch between research questions considered important by patients, carers, and healthcare professionals and the research performed in many fields of medicine. The Non-Alcohol-Related Liver and gallbladder disorders Priority setting partnership (NARLIP) was established to identify the top research priorities in the prevention, diagnostic, and treatment of gallbladder disorders and liver disorders not covered by the James-Lind Alliance (JLA) Alcohol-related liver disease (ARLD) Priority Setting Partnership.

Design: The methods broadly followed the principles of the JLA guidebook. The one major deviation from the JLA methodology was the final step of identifying priorities: instead of prioritisation by group discussions at a consensus workshop involving stakeholders, the prioritisation was achieved by a modified Delphi consensus process.

Results: A total of 428 unique valid diagnostic or treatment research questions were identified. A literature review established that none of these questions were considered 'answered' i.e. high quality systematic reviews suggest that further research is not required on the topic. The Delphi panel achieved consensus (at least 80% Delphi panel members agreed) that a research question was a top research priority for six questions. Four additional research questions with highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

Conclusions: A priority setting process involving patients, carers and healthcare professionals has been used to identify the top ten priority areas for research related to liver and gallbladder disorders. Basic, translational, clinical, and public health research are required to address these uncertainties.

Keywords: liver, chronic liver disease

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ARTICLE SUMMARY

Strengths and limitations

- A research prioritisation process involving clinicians, patients and carer, and public representatives was performed in the field of liver and gallbladder disorders. This will help to address the mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in the field of liver and gallbladder disorders.
- A Delphi consensus method was performed. This prevented dominance of 'loud voices', a problematic issue with small and large group discussions.
- Because of the predominance of people with chronic liver disease on the Delphi panel, many of the top research priorities related to chronic liver diseases.

INTRODUCTION

Failure to address treatment uncertainties by research can lead to significant suffering and deaths [1]. It is important that research in any field of medicine takes into account the shared interests of patients, carers and clinicians [2]. However, there is a mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in many fields of medicine [3 4]. The James Lind Alliance (JLA) exists to help ensure a patient-centred process and enables the limited research resources to be utilised in addressing the research questions that are considered important jointly by patients, carers, and healthcare professionals [2] ('top research priorities'). This is achieved by forming 'Priority Setting Partnerships' (PSPs) between patients, carers, and healthcare professionals [2].

There has only been one formal research prioritisation process involving patients, carers, and healthcare professionals in the field of liver and gallbladder disorders [5]. However, the scope of that PSP was limited to alcohol-related liver disorders [5]. The Non-Alcohol-Related Liver and

gallbladder disorders Priority setting partnership (NARLIP) was established to address the prevention, diagnostic, and treatment uncertainties related to the majority of liver disorders which were not covered by the JLA PSP on alcohol-related liver diseases (ARLD) [5] and to include gallbladder disease.

The aims and objectives of the NARLIP were to work with patients, their carers, and healthcare professionals treating them ('stakeholders') to identify uncertainties about the diagnostic tests and effects of prevention and treatments for non-alcohol related liver and gallbladder disorders, to agree by consensus a prioritised list of those uncertainties for research, to publicise the results and process, and to take the results to research commissioning bodies to be considered for funding and researchers to encourage them to submit grant applications addressing these uncertainties.

METHODS

The methods broadly followed the principles of the JLA guidebook.[6] The broad steps involved the following and are summarised in Figure 1.

1. Formation of the partnership: organisations and individuals representing people affected by non-alcohol related liver or gallbladder disorders, their carers, and healthcare professionals treating people with non-alcohol related liver and gallbladder disorders. A partnership was formed between KG representing University College London and the British Liver Trust initially, but following reorganisation in the British Liver Trust, PSC Support [7] became the leading patient organisation partner of this process. A steering committee was formed. The members of the steering committee who participated in the complete process were KG, MW, BRD, CF, BF, AM, RM, SM, IS, and ET.
2. Establishment of the scope: the steering committee members discussed and decided that the scope should include adult and paediatric liver and gallbladder disorders which required

medical and surgical treatments. The protocol was registered with James-Lind Alliance Priority Setting Partnership.

3. Identifying potential research questions: research questions were collected through online surveys and searching UK Database of Uncertainties about the Effects of Treatments (UK DUETs), research recommendations in high quality systematic reviews and clinical guidelines, and registers of ongoing research.
4. Refining research questions: the research questions identified in the above step were reviewed and where necessary combined to result in a set of unique research questions. Research questions were considered 'answered' when recent high-quality systematic reviews (based on low risk of bias studies) concluded that further research was not required. Removal of such 'answered' research questions was planned. The remaining questions were 'uncertainties'.
5. Interim prioritisation: To shortlist the set of questions to manageable levels for the final prioritisation process, the members of the steering committee ranked the uncertainties after stratifying the questions as medical and surgical questions. The members of the steering committee agreed that the interim prioritisation list should consist of 75% medical questions and 25% surgical questions. This decision was an arbitrary decision made by the steering committee based on the rationale that majority of individuals with liver and gallbladder disorders are treated medically but a minority require surgery which have a major impact on patients' lives.
6. Final prioritisation by consensus: A modified Delphi consensus method was followed to identify the top priorities using methods described by Jones et al [8]. The steps in the modified Delphi consensus method were as follows.
    a. A Delphi panel consisting of patients, their carers, and healthcare professionals treating them was formed. A total of 42 people expressed interest in joining the

Delphi panel and 33 panel members completed all three rounds. Details of the Delphi panel composition and drop-outs are reported in the results section.

b. A total of three rounds were conducted.

c. Delphi panel members scored the short-listed questions in the interim prioritisation process on a scale of 1 to 9 with 1 being considered least important and 9 being considered most important. Scores of 1 to 3 were categorised as 'less important', 4 to 6 as 'moderately important', and 7 to 9 as 'highly important'. Panel members were requested to score the questions according to the importance of the question to them/the persons that they represent or treat and could leave questions that they were unable to score empty. Each Delphi panel member could add a maximum of two questions in the first round to ensure that the questions most important to the Delphi panel members were included in the prioritisation process even if they were not identified in the earlier steps. In the subsequent rounds, the panel members were shown the summary scores and their previous score for each question. They were able to retain or change their score in each of the rounds after the first round. For calculation of the summary scores and the proportion considering a question 'highly important', non-responses were excluded.

d. Consensus about a specific research question being a top research priority was reached when 80% or more Delphi panel members considered the research question as highly important (allocated scores between 7 and 9).

e. When fewer than 10 research priorities were obtained by consensus, the remaining priorities were completed by uncertainties based on the highest proportions of panel members agreeing that the research question was highly important (scores between 7 and 9).

f. There was no restriction on the Delphi panel to consult others while scoring the questions. However, only one final response on the set of questions was accepted from each Delphi panel member.

When there were no recent high-quality systematic reviews on the research question, we have recommended high-quality systematic reviews. When recent high-quality systematic reviews recommended high-quality research, we have recommended randomised controlled trials for prevention and treatment, as such studies carry the lowest risk of bias if conducted well; we would have recommended well conducted diagnostic test accuracy studies for diagnostic uncertainties. All online surveys were completed using Google Forms designed by KG. The Delphi process was completed using Microsoft Excel and email.

Ethical approval was not deemed necessary because no personal identifiable information was being collected, and the questions were being asked of healthcare professionals, patients and their carers were not considered sensitive questions. In addition, we had full support of patient organisations with involvement of patient representatives throughout the whole process rather than patients visiting the hospitals.

Patient and Public involvement

Patients and public were involved in all aspects of this project: they were part of the steering committee and were involved in the definition of the scope, methodology used for the prioritisation process, identification of further patients and public representatives, participation in the Delphi panel, interpretation, and critical revisions of the draft report. They will be involved in the dissemination of the findings through patient websites, patient forums, and to research funders.

RESULTS

Identification and refining of research uncertainties

A total of 126 patients, carers, and those at risk of developing non-alcohol related liver and gallbladder disorders, and 13 healthcare professionals participated in the first survey which was conducted between July and December 2015. This survey resulted in a total of 209 unique research questions. In addition, 219 unique questions were identified from searching the UK DUETs, Pubmed, and ClinicalTrials.gov on 2nd January 2016. A total of 428 unique valid (i.e. falling within the remit of this priority setting partnership) research questions (247 medical-related and 181 surgery-related) were identified from these sources. None of the research questions had been answered by recent high-quality systematic reviews based on low risk of bias studies which concluded that further research was not required. Therefore, all the 428 research questions were considered research 'uncertainties'. The complete list of 428 unique valid uncertainties in no particular order is available in Online Supplement Appendix 1. This has been converted to the population, intervention, control, and outcomes (PICO) format whenever possible.

Interim priorities

To identify a shortlist of questions (from the list of 429 questions) that were to be considered for the next step, a total of 48 research priorities (36 medical questions and 12 surgical questions) were identified on the basis of being selected by at least one patient or carer and healthcare professional of the steering committee (24 questions) and obtaining the highest ranks among the members of the steering committee (additional 24 questions). The list of 48 questions identified as interim priorities in no particular order is available in Online Supplement Appendix 2.

Final priorities

A total of 42 people expressed interest in joining the Delphi panel and 33 panel members completed all three rounds. Five people dropped out before they returned the scores of the first round, three between first and second rounds, and one between the second and third rounds. Of the 33 panel

members who completed all the three rounds, 17 were healthcare professionals and 16 were patients, carers, and general public. Of the 17 healthcare professionals, six were hepatologists, four were surgeons, two were hepatology nurses, and the remaining were general practitioner (GP), HPB surgery (hepato-pancreato biliary) nurse, organ preservation biologist, dietician, and pharmacist (one each). Of the 16 patients, carers, and general public, there was representation from general public and various liver diseases including autoimmune diseases such as primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis, viral hepatitis, metabolic diseases such as non-alcohol related fatty liver disease, and other diseases such as hepatocellular carcinoma and polycystic liver disease. There was also representation of liver transplanted patients in the Delphi panel. In total, 23 panel members were from England, seven were from Scotland, and three were from Wales. There were no panel members from Northern Ireland despite attempts to include panel members from Northern Ireland.

A total of 22 additional questions were added by the Delphi panel members in the first round of the Delphi process. The Delphi panel achieved consensus that an uncertainty was a top research priority for six research questions. Four additional research questions with the highest proportion of Delphi panel members scoring the question as highly important (scores between 7 and 9) were added to constitute the top 10 research priorities. The list of the top 10 research priorities (in the order of proportion who agreed that the uncertainty is a very important research priority) is available is Table 1. All the top 10 research priorities were prevention and treatment uncertainties, and none were diagnostic test uncertainties.

Table 1 Treatment uncertainties for which consensus that the uncertainty is a research priority was reached

Treatment uncertainty (Research question)	Proportion who rated this	Median (interqua

	question as highly important in the final round	rtile range) in the final round
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	93.5%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	93.3%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	90.3%	9(8,9)
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	90.3%	8(7,9)
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	81.8%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	80.6%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	76.7%	8(6.75,9)
Prior to liver transplantation, is it better to transport the	74.2%	7(6,9)

donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?		
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	74.2%	7(6,8)
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	72.4%	7(6,9)

A summary of the availability of systematic review of randomised controlled trials on the topic of the individual questions, randomised controlled trials on the topic not included in the systematic review (if one exists), and the outcomes evaluated in these RCTs are listed in Table 2. Table 2 also contains a suggestion for the next research steps. The list of the existing trials was compiled by searching ClinicalTrials.gov on 7th April 2018. The references to the trials not included in the systematic reviews is available in Online Supplement Appendix 3. As seen in Table 2, a well-designed RCT is the next step for eight of these top 10 research questions. This is because it appears that the outcomes in those trials will not address the outcomes listed in the research questions.

Table 2 Next step to address the top 10 research priorities based on current best evidence (summary)

Treatment uncertainty (Research question)	High-quality systematic	RCTs not included in the systematic review[a, c]	Patient-oriented outcomes assessed in	Next step

	review [a,b]		trials not included in the systematic review[d]	
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[9]	8 trials	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatments
What are the best treatments that cure or delay the progression (worsening) of	[10]	9 trials	None of the trials include	High-quality

primary sclerosing cholangitis (PSC)?			survival, HRQoL as outcomes[e]	RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	[11] (includes only pharmacological interventions)	More than 10 published trials on lifestyle interventions and more than 20 trials on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> 44 trials	Lifestyle interventions and nutritional supplementation Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver	High-quality systematic reviews on lifestyle interventions (one review) and nutritional supplementation to cure or delay the progression of NAFLD and high-quality RCTs on

			disease (11 trials), mortality (2 trials), cirrhosis (2 trials), cardiovascular events (2 trials)[e]	pharmacological interventions with clinical outcomes
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[12] (covers only maintenance immunosuppression)	Induction immunosuppression More than 20 published trials Maintenance immunosuppression 4 trials	Induction immunosuppression Not applicable as there is no high quality systematic review Maintenance immunosuppression Graft	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance

			survival (1 trial) Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	immunosuppression with important clinical outcomes
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	None	None	-	High-quality RCTs on education to prevent NAFLD
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	15 trials	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH			
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or	None	5 trials	Overall survival (4 trials), graft	Await results of the RCTs

preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?			survival (5 trials), health-related quality of life (2 trials)	(all expected to complete by the end of 2019) and perform a high quality systematic review.
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[13]	24 trials	Health-related quality of life (5 trials), relief of symptoms (5 trials)[e]	High-quality RCTs with clinical outcomes
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above)			

	reported on liver fibrosis.

a Numbers indicate the reference number.

b Further well-designed randomised controlled trials using clinical outcomes were recommended by all these systematic reviews.

c Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

The complete list of questions in the Delphi process, the proportion of respondents who considered a research question as very important and the summary scores in each Delphi round is available in Online Supplement Appendix 4.

DISCUSSION

This is the first priority setting partnership on non-alcohol related liver and gallbladder disorders. This included a wide range of disease processes and a total of 428 unique research questions that met the scope of this priority setting partnership were identified. All the research questions were considered unanswered as there had been no high quality systematic reviews which indicated that no further research is required, i.e. all the research questions were uncertainties. Consensus that an

uncertainty was a very important research priority was reached for six research questions. Four additional research questions with the highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

As evident from the online supplement Appendix 1, longevity of life and health-related quality of life are two major outcomes that appear important to patients, their carers, and healthcare professionals. However, even when there are ongoing trials, it appears that the outcomes in those trials will not address the outcomes listed in eight of the top 10 research questions (Table 2). Therefore, the next step in addressing these uncertainties is the design and conduct of randomised controlled trials. Such randomised controlled trials may involve qualitative studies to determine the design and should compare the treatments that improve the longevity of life and/or health-related quality of life.

It should be noted that uncertainties 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?' and 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?' are related to each other. Although NAFLD includes NASH, most of the panel members felt that the research questions related to NAFLD and NASH should be kept separate uncertainties. While the same systematic review can cover both the uncertainties, the primary research study designed to address these two questions differ in terms of the setting, the outcomes used, and the period of follow-up. Any primary research that tries to answer these two questions in a single randomised controlled trial will be inefficient.

Similarly, for the uncertainties 'what are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)' and 'are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?', a single randomised controlled trial will be inefficient and the preference of most of the panel members was to keep these uncertainties as separate uncertainties.

There are several limitations to our priority setting process. The first one is deviation from the original protocol. To select the final top priorities, the initial plan was to arrive at consensus by open small group and large group discussions of patients, carers, and healthcare professionals as suggested by the standard James-Lind Alliance process [6], which provides an opportunity for a knowledge exchange of viewpoints and experience. However, part of the steering committee with experience in a similar priority setting partnership felt that open discussions resulted in 'loud voices' being given more importance resulting in an unrepresentative list of top priorities. While this can be mitigated by facilitated group discussions by neutral JLA facilitators to ensure that all voices were heard in the discussions, this was considered by the steering committee as an important source of bias based on their prior experience in participating in open discussions. The steering committee therefore decided to follow the Delphi-consensus method which is one of the major consensus methods[8]. The advantages of Delphi-consensus method over open discussions include anonymity of the response and the equal weight given to the opinions of all members [8]. In addition, they are less costly to conduct without any limitation by geographical location compared to other methods of consensus[8] because of the lack of necessity to travel and take time off regular work. However, there is considerable variability in the previous performance of Delphi processes with regards to the number of rounds and the criteria for achieving consensus [14]. Arriving at consensus depends upon people revising their scores based on the other's scores. Our initial plan was to extend the Delphi to four rounds if consensus on 10 top research priorities was not reached in three rounds. However, there was minimal change in scores between the rounds for most questions (Online Supplement Appendix 3) and the Delphi process was completed in three rounds. Consensus on a top research priority was achieved for six questions only. However, the proportion of Delphi panel members ranking a question as highly important was greater than 70% for the remaining four questions added to the list of top research priorities. Previous Delphi consensus processes have used various cut-off points for defining consensus: greater than 70% agreement among panel members is well within the definition of consensus used in previous Delphi consensus processes [14].

The other major limitation of our priority setting process is the representativeness of the people who completed the survey and took part in the Delphi process. The online survey was shared among clinicians and members of general and disease-specific patient organisations. Most questions resulting from the online survey relate to chronic liver disease (in particular, autoimmune liver diseases), perhaps reflecting the high motivation to support research from those groups. The Delphi panel also had a high representation of people related to chronic liver disease (in particular, autoimmune liver diseases) as patients, carers, or healthcare professionals. Whilst people affected by different liver and gallbladder disorders were actively sought through both general and disease-specific patient support groups and organisations, only a few responded and completed all three rounds of the Delphi process. The potential bias towards prioritising chronic liver diseases is evident as nine of the top 10 research priorities relate to chronic liver diseases (four relate to autoimmune liver diseases, three related to non-alcohol related fatty liver disease, two related to liver transplantation). It was surprising that the uncertainties related to the treatment of chronic viral diseases such as chronic hepatitis B and chronic hepatitis C were not identified within the top 10 research priorities. This may be because of the perception by the some of the panel members that the research questions related to the treatment of chronic hepatitis C were answered with the advent of directly acting antivirals (personal communication). The reason for non-prioritisation of chronic hepatitis B is not entirely clear. This may be because chronic hepatitis B may not have been considered as important as other chronic liver diseases or under-representation of chronic hepatitis B in the panel.

Cancer-related questions, childhood-related liver diseases, and other benign disorders did not end up in the top research priorities (except for the treatment of very early hepatocellular carcinoma, which is managed by hepatologists and surgeons) probably for the reasons described above. We recommend that separate prioritisation processes are carried out for people with gallstones, a condition that affects approximately 5% to 25% of the population [15], for people with primary and secondary liver cancer, and childhood liver disorders where significant uncertainties

remain on the effectiveness of different treatments in decreasing mortality and improving health-related quality of life.

As well as the above limitation, we are aware of the inherent limitations of using solely technology to carry out the Delphi exercise. These are limitations that can potentially lead to bias in any consensus-building method including that of face-to-face consensus methods normally used in a JLA PSP.

One solution which might address the limitations of this priority setting process and the standard JLA process may be to collect information routinely from patients visiting hospitals using paper forms and conduct online meetings (video conferencing and presentation) before the final round of the Delphi (or the standard face-to-face priority setting workshop used by the JLA. Some JLA PSPs do use methods such as face-to face interviews and group discussions rather than solely online surveys). By collecting information on paper forms and conducting the meetings in hospitals, it is possible to engage with people who do not have access to or are not familiar with computers. It is also possible to engage with people who have concerns regarding data confidentiality with the use of computers or social media by collecting information using paper forms. Ethical and confidentiality issues will need to be considered prior to engaging patients attending hospital in the research prioritisation process.

Another limitation of our priority setting process is the drop-outs during the Delphi process. While some of the drop-outs may be related to the ability to complete online surveys and use Microsoft Excel, some patient representatives or clinicians may have dropped out because they did not find any research question to be of direct relevance to them. Other reasons include lack of understanding of the conditions, feeling that the process was too complicated, feeling that the process would not work, and the time commitment for the process. This is because of the broad scope of this research prioritisation process and may be overcome by choosing a narrower focus

while defining the scope of the prioritisation process, and by better explanation of the disease processes through presentations.

It should also be recognised that the Delphi panel was constituted of representatives from England, Scotland, and Wales. Therefore, the findings are applicable in only these countries. However, the findings are likely to be applicable throughout the NHS and in other European and Western countries with a similar spectrum of chronic liver diseases and similar treatment options available.

In summary, there are significant uncertainties in the management of liver and gallbladder disorders. Further high-quality research is necessary to address these uncertainties which may require programmes of basic, translational, clinical, and public health research. For issues with diverse and unproven treatment options, randomised controlled trials may be the only mechanism for identifying the most effective treatment and the treatments that represent good value for money for the NHS. Such randomised controlled trials should assess the effect of different treatments in improving longevity of life and/or health-related quality of life.

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CONTRIBUTION OF AUTHORS

Kurinchi Gurusamy – conceptualisation, healthcare professional and methodological lead of steering committee, Delphi panel member, analysis, author of the manuscript.

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CONFLICTS OF INTEREST

The decisions made by healthcare professionals involved in the research prioritisation process might have been influenced by their professional interests, in addition to their own, or family member's experience of health conditions. Decisions made by patients and carers in the research prioritisation process might have been influenced by their particular experiences, health needs and interests.

DATA SHARING AGREEMENT

All data is available in the manuscript or in the supplementary file.

FIGURE 1

Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.

[a]The protocol was registered with James-Lind Alliance Priority Setting Partnership

[b]The final prioritisation was achieved by modified Delphi consensus method.

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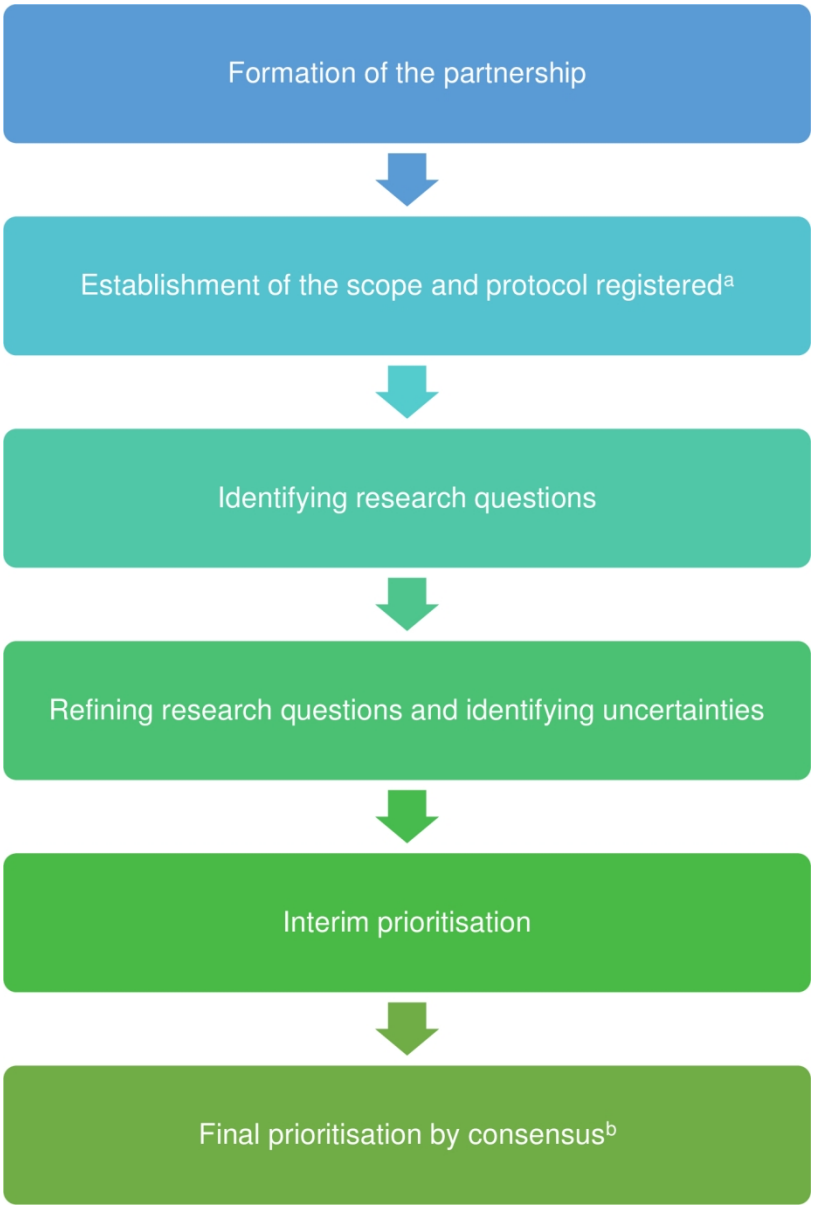

Figure 1: Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.
aThe protocol was registered with James-Lind Alliance Priority Setting Partnership
bThe final prioritisation was achieved by modified Delphi consensus method.

119x177mm (300 x 300 DPI)

Appendix 1 List of all research questions

Patient/population	Intervention	Control	Outcomes
People with obesity	Lifestyle: diet	No intervention	1. Liver transplantation 2. Improvement in BMI. 3. Improved liver function
People with liver disease	Nurse-led care	Standard care	Ability to self-manage
People with asymptomatic chronic liver disease	Education of people	No intervention	1. Improvement in life style. 2. Fatty liver disease
People with NASH (non-alcoholic steatohepatitis)	Different medical treatments	No intervention	1. Halting disease progression. 2. Reversing disease progression. 3. Slowing disease progression. 4. Cure
People with primary sclerosing cholangitis	Treatment for primary sclerosing cholangitis	No intervention	1. Mortality 2. HRQoL (health-related quality of life)

			3. Fewer symptoms - pain, itching, fatigue 4. improved liver function 5. Cure 6. Time to liver transplantation 7. Improvement (no further details) 8. Decreased hospital admission 9. Disease progression 10. Remission from PSC 11. Cancer 12. Requirement for liver transplant.
People with liver disease	Methods to improve compliance to treatment	Not applicable	1. HRQoL 2. Mortality
General population	Screening: early identification of people at risk of liver disease	No screening	1. HRQoL 2. Mortality

People at risk of liver disease	Diagnosis: early identification of people with liver disease	Not applicable	1. HRQoL 2. Mortality 3. Prevention of liver disease 4. Slowing progression of liver disease 5. Reducing requirement for liver transplantation 6. Adverse events of medications
People with primary sclerosing cholangitis and who have had a liver transplant and still have ulcerative colitis even after a sub total colectomy	Symptomatic treatment for primary sclerosing cholangitis	Not applicable	1. HRQoL. 2. Decrease in symptoms (breathlessness and fatigue). 3. Mortality. 4. Decrease in medication. 5. Cure. 6. Decreased progression of primary sclerosing cholangitis.

			7. Improvement in symptoms (unspecified).
People at risk of liver disease (overweight or obese)	Diagnosis: Accurate non-invasive method for diagnosis of chronic liver disease	Not applicable	1. Death 2. Need for liver transplant 3. Requirement for hospital admission. 4. Demonstrating equivalence to biopsy 5. Demonstrating good reproducibility
People at risk of liver disease (overweight or obese)	Screening methods to diagnose liver disease (including history and diagnostic tests)	Not applicable	1. Proportion of people at risk of liver disease 2. Proportion of people at risk who have asymptomatic liver fibrosis 3. Early diagnosis and treatment
People with polycystic liver disease	Treatment for polycystic disease	Not applicable	1. Decrease symptoms 2. Increase quality of

			life 3. Decrease size of cyst or preventing cysts to enlarge 4. Increased longevity 5. Requirement for liver transplant.
People with autoimmune hepatitis	Treatments for autoimmune hepatitis.	Not applicable	1. HRQoL (including ability to carry out normal activities, study, work). 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Treatment related side-effects (unspecified). 8. Brittle teeth

			(treatment-related). 9. More effective treatment unspecified. 10. Complete recovery (unspecified). 11. Mortality. 12. Measure feeling well (unsepcified) 13. Fewer flare ups 14. Less joint pain. 15. Disability 16. Liver damage requiring hospital admission 17. Quicker recovery 18. More monitoring of patients 19. Symptom control. 20. Side-effects
People with autoimmune hepatitis	Standardised protocol care	Standard care	1. HRQoL. 2. Fatigue. 3. Osteoporosis

			(treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related).
People with autoimmune hepatitis	Treatment of fatigue/joint pain related to autoimmune hepatitis.	Not applicable	1. HRQoL. 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Joint pain. 8. Symptoms (unspecified).
People with autoimmune hepatitis	Nurse-led care	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.

People with autoimmune hepatitis	Education of healthcare professionals and patients	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.
People with autoimmune hepatitis	Lifestyle: diet	Standard care	1. Treatment related adverse events. 2. Requirements for liver transplantation. 3. NHS (National Health Service, UK) costs 4. HRQoL 5. Mortality. 6. Free from immunosuppressive therapies. 7. Fatigue. 8. Weight.
People with autoimmune hepatitis	Education of people	Standard care	Faster reduction in strong medications. Need for liver transplantation.
People with autoimmune hepatitis	Cannabis + standard care	Standard care	1. Reduction in immunosuppressants.

			2. Fatigue. 3. Treatment related side effects such as serious infections, anxiety, depression, cancer, physical side effects.
General population (> 40 years or >50 years or middle-aged people, particularly overweight/obese and/or have type 2 diabetes and/or a family history of chronic liver disease)	Screening for liver disease by GP using routine blood tests/other methods	Standard care	1. Earlier diagnosis and treatment. 2. Preventing liver disease progressing to cirrhosis. 3. More cost effective for NHS. 4. Preventing the complications of chronic liver disease such as hepatocellular carcinoma and varices.
People with autoimmune hepatitis	Prednisolone	No intervention	1. Obesity. 2. Osteoporosis. 3. Insomnia. 4. Hypertension.

People with genetic markers associated with autoimmune hepatitis.	Methods for prophylaxis	No intervention	Prevention of autoimmune hepatitis
People with autoimmune hepatitis	Lifestyle: optimal physical exercise	Not applicable	1. Weight 2. Fatigue
People with autoimmune hepatitis (stable)	Nurse-led care	Standard care	1. Fatigue
People with suspected autoimmune hepatitis	Methods to make a quicker diagnosis	Not applicable	1. Earlier diagnosis
People with NASH, diabetes, and gastroparesis	Treatments for breathlessness and pain	Not applicable	1. Breathlessness and pain.
People with NASH cirrhosis, diabetes, and anaemia	Treatments	Not applicable	HRQoL
People with NASH cirrhosis, diabetes, and anaemia	Education of people	Standard care	Better knowledge
General population	Education of people	Standard care	Better knowledge
People with NASH cirrhosis, diabetes, and anaemia	Non-pharmacological treatments to decrease pain and depression	Pharmacological interventions or no intervention	1. Pain 2. Depression
People with suspected autoimmune diseases with potential to cause acute liver failure	Diagnosis of autoimmune diseases that cause acute liver failure	Not applicable	Identification of specific autoimmune diseases

People with autoimmune diseases with potential to cause acute liver failure	Prophylactic treatments	Not applicable	Prevent acute liver failure
People with primary sclerosing cholangitis	Lifestyle: diet (including alcohol consumption) and physical exercise	Not applicable	1. Reduction in symptoms 2. Overall health benefits (unspecified) 3. Ability to return to useful occupation. 4. Reduce medication. 5. Reduce need for annual investigations.
People with primary sclerosing cholangitis	Azathioprine	Other interventions	Treatment related adverse events
People with autoimmune hepatitis	Non-pharmacological treatments to treat autoimmune hepatitis	Pharmacological interventions or no intervention	1. Reduction in symptoms 2. HRQoL (including the ability to do everyday tasks/ back into education or employment)

People with primary sclerosing cholangitis	Itching receptor blockers	No intervention/ other interventions	Reduction in itching
People with primary sclerosing cholangitis with and without Vitamin D deficiency	Vitamin D supplements	Standard care	1. Stop the progress of the disease. 2. Fewer flare ups of inflammatory bowel disease and primary sclerosing cholangitis. 3. Improve HRQoL 4. Less depression
People with primary sclerosing cholangitis and autoimmune hepatitis	Ursodeoxycholic acid	No intervention/ other interventions	Reducing symptoms
People at risk of primary sclerosing cholangitis and autoimmune hepatitis	Prophylactic treatments	No intervention	Prevention of the condition
People with autoimmune hepatitis	Non-steroidal interventions	Steroids	Adverse events
People at risk of autoimmune liver diseases	Prophylactic treatments	Not applicable	Reduction in those getting advanced liver disorders

People with autoimmune liver diseases (20 to 30 years old)	Treatments	Not applicable	1. Reduction in those getting advanced liver disorders. 2. Stabilisation of disorder. 3. Reduction in liver cancer rates.
People with autoimmune liver diseases (> 30 years)	Screening: Early diagnosis of liver cancer	No screening	Early diagnosis of liver cancer
People with NASH and stroke	Nurse-led care	Standard care	1. Recovery time 2. Amount of recovery that is made
People with haemochromatosis	Lifestyle: iron avoidance diet	Traditional phlebotomy	Reduction in iron levels
People with haemochromatosis	Acceleration of phlebotomy	Traditional phlebotomy	Reduction in iron levels
People with NAFLD	Nurse-led care	Standard care	1. Faster recovery. 2. Symptom relief (unspecified). 3. Prevention of more serious complications. 4. Patient education

			on diet and exercise to lose weight. 5. Preventing progression into NASH and cirrhosis. 6. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 7. Prevent heart attacks and strokes.
People with NAFLD	Treatments for pain	Not applicable	Reducing pain
People with NAFLD	Treatments for itching	Not applicable	Reduction in itching
People at risk of liver disease (overweight or obese)	Education of healthcare professionals about NAFLD	Standard care	1. Prevention of cirrhosis. 2. Prevention of other related liver complications. 3. Earlier diagnosis and treatment of liver diseases. 4. Increased knowledge.
Midwives and healthcare professionals coming into	Education of healthcare	Standard care	1. Prevention of cirrhosis.

contact with children and young adults	professionals about liver disease		2. Prevention of other related liver complications.
People with chronic hepatitis C	Newer treatments	Older interventions	1. Treatment-related complications 2. Ability to perform usual activities such as work, study, housework. 3. Severe liver damage requiring hospital admission. 4. Decreased anxiety.
New-borns	Screening test for biliary atresia	No screening	Earlier diagnosis and treatment
Children who have undergone liver transplantation	Immunosuppressive regimens	Not applicable	Adverse events
People with liver-related disorders	Treatment for itching	Not applicable	Reduction or eradication of itching
People with primary biliary cholangitis	Education of people	Standard care	Knowledge
People with positive AMA (antimitochondrial antibody) M2	Prophylactic treatments	Not applicable	1. Prevention of primary biliary cholangitis.

			2. Reversion to a negative AMA M2 before cirrhosis develops.
People with positive AMA M2	Standardised protocol care by GP	Standard care	1. Prevention of primary biliary cholangitis. 2. Reversion to a negative AMA M2 before cirrhosis develops.
People with liver disease	Stem cell therapy	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work) 3. Prolonging periods of remission 4. Reducing symptoms
People with liver disease	Bio-artificial livers	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities

			including study and work)
People with autoimmune hepatitis	Targeted therapy against autoimmunity	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work)
People with primary biliary cholangitis not responding to ursodeoxycholic acid	Different treatments	Not applicable	1. Cure 2. Slowing of disease 3. Improved quality of life with respect to fatigue.
People with primary biliary cholangitis	Antiviral treatment	No intervention/ other interventions	1. Improvement in health (unspecified) 2. Mortality
People with primary biliary cholangitis	Treatment for itching and fatigue	Not applicable	1. HRQoL. 2. Anxiety. 3. Itching. 4. Fatigue. 5. Cure 6. Slowing of disease 7. Symptom relief
People with primary biliary cholangitis	Greater patient involvement	Standard care	1. HRQoL. 2. Anxiety.

People with liver and gallbladder disorders	Nurse-led care	Standard care	1. Symptoms. 2. Pain relief. 3. Quicker investigative measures.
People with pain after cholecystectomy (especially elderly and living alone)	Hospital based investigations to find the cause of pain, treatment of the cause of pain and discharged after pain relief	Symptomatic outpatient intervention	Pain relief
People with chronic hepatitis C	Ribavirin	No intervention/ other interventions	Osteoporosis
People with chronic hepatitis C taking ribavirin	Prophylactic treatments for osteoporosis	No prophylactic intervention	Osteoporosis
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about childhood liver disorders	Standard care	1. Knowledge 2. Better treatment of patients with primary biliary cholangitis
People with liver disease	Education of people	Standard care	1. Patient knowledge. 2. Visits to the

			hospital. 3. More patient responsibility
People with symptomatic primary sclerosing cholangitis	Different treatments	Not applicable	1. Cure of disease. 2. Delays progression of disease.
People with primary sclerosing cholangitis	Intervention to reverse liver damage	Not applicable	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation.
People with primary sclerosing cholangitis	Intervention to treat fatigue	Not applicable	1. HRQoL. 2. Fatigue.
People with primary sclerosing cholangitis	Intervention to treat itching	Not applicable	1. HRQoL. 2. Itching.
People with primary sclerosing cholangitis	Specialist interest doctor	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Symptom relief.
People at risk of oesophageal varices	Non-invasive assessment of oesophageal varices	Invasive assessment of oesophageal varices	Reduce bleeding oesophageal varices

People at risk of chronic liver disease	Alternative to biopsy for assessment of cirrhosis	Liver biopsy	Assessment of whole liver
People at risk of primary sclerosing cholangitis (PSC)	Early diagnosis of primary sclerosing cholangitis Alternate to liver biopsy	Not applicable	Not stated
People with primary sclerosing cholangitis with normal or relatively normal liver function tests	Alternative to UKELD (United Kingdom Model for End-Stage Liver Disease) scores for prioritisation for liver transplantation	UKELD	1. More accurate assessment of transplant need for transplant amongst PSC patients. 2. Reduction in numbers of 'low score' PSC patients becoming too ill for transplant, or not being offered a transplant once 'listed'.
People with positive AMA M2 with normal liver function tests	Ursodeoxycholic acid	No intervention	Slowing progression of primary biliary cholangitis

People with suspected primary sclerosing cholangitis	Nurse-led care	Standard care	Earlier diagnosis and treatment
People with liver failure of unknown reason	Investigations to find the cause of liver failure of unknown origin	Not applicable	More knowledge.
People with Gilbert's syndrome	Treatment of fatigue related to Gilbert's syndrome	Not applicable	1. HRQoL. 2. Chronic fatigue. 3. Depression
People with NAFLD (non-alcoholic fatty liver disease)	Breathing exercises	Standard care	1. Faster recovery. 2. Symptom relief 3. Prevention of more serious complications
People with NASH cirrhosis	Treatment of symptoms	Not applicable	Improvement of symptoms
People at risk of liver disease	Screening for autoimmune diseases	No screening	Earlier diagnosis and treatment
People with autoimmune hepatitis	Treatment of symptoms	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups.

			4. Less joint pain. 5. Disability.
People with autoimmune hepatitis	Methods to decrease stress	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups. 4. Less joint pain. 5. Disability.
People with liver disease	Counselling for tremors and confusion	No counselling	Coping with symptoms
People with NAFLD	Staging of liver disease	Not applicable	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Metformin	No intervention	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Standardised protocol for diagnosis and treatment of NAFLD	Standard care	1. Mortality. 2. Reversal of liver damage
People with osteoarthritis	Anti-inflammatory drugs	Other interventions	Cirrhosis
People with diabetes	Adequate control of diabetes	Lack of adequate control of diabetes	1. NASH. 2. Cirrhosis.

People at risk of NAFLD	Screening: Early identification of causes	Standard care	Prevention of liver disease
People with NAFLD	Treatments	Not applicable	1. Cure 2. Prevention of liver disease 3. Disease progression 4. HRQoL
People with upper abdominal pain	Screening: Early scan with ultrasound, blood tests, and urine tests	Standard care	1. Early identification of liver and gallbladder diseases 2. Appropriate advice/treatment
People with NAFLD	Lifestyle: diet and exercise	Standard care	1. HRQoL
People with NAFLD	Specialist interest doctor	Standard care	1. HRQoL
People at risk of liver disease	Prophylactic interventions	Not applicable	1. Prevention of liver disease
People at risk of NAFLD	Prophylactic treatments	Not applicable	1. Prevention of NAFLD 2. Decrease NAFLD
People with NASH fibrosis	Lifestyle: exercise	Standard care	None stated

People with cryptogenic liver cirrhosis	Investigations to find the cause of cryptogenic cirrhosis	Not applicable	1. Reduction in liver disease diagnosis of the percentage regarded as cryptogenic. 2. Establishment of relevant treatment pathways. 3. Reduction in numbers of liver transplant required by earlier intervention using non-invasive treatment regimes.
People with cirrhosis	Community-led psychological support (on lifestyle: diet and exerise, stress, work-life balance, and general well-being)	Standard care	1. Reduction of symptoms such as nausea, fatigue. 2. Improved nutrition and healthier weights. 3. Improved HRQoL 4. Improved sense of wellbeing 5. Successful work

			and job retention 6. Good sense of self determination/empowerment and motivation 7. Improved clinical markers (unspecified)
Newborns	Screening for metabolic liver diseases	No screening	1. Early treatment for people with metabolic liver disease (including dietary advice) 2. Mortality. 3. HRQoL. 4. Prevent type 2 diabetes
People with autoimmune hepatitis	Telephone-based care	Standard care	1. Reduction in time spent in outpatients 2. Less spent on car-parking at hospitals
People with NASH and diabetes	Liver transplantation	Standard care	1. Mortality

People with primary biliary cholangitis (newly diagnosed)	Adequate drinking water	Standard care	1. HRQoL. 2. Liver function tests.
People with primary sclerosing cholangitis	Treatment targeted against deformation of bile duct	Standard care	1. Time to end-stage liver disease.
People with bile duct cancer	Treatment targeted against deformation of bile duct	Standard care	Not stated
People with gallbladder sludge with digestive symptoms	Avoiding surgery	Standard care	1. Symptom relief
People with NAFLD	Education of healthcare professionals	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.
People with NAFLD	Education of general public	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.

People with NAFLD	Methods to make an accurate diagnosis (including liver function tests)	Not applicable	Not stated
People with NAFLD (overweight)	Interventions to lose weight	Not applicable	Weight loss
People with liver disease (newly diagnosed)	Mental health support	Not applicable	Mental health
Children with multiple autoimmune disorders related to liver	Genetic testing of telomere lengths	Other tests/ no tests	Not stated
Children with multiple autoimmune disorders related to liver	Stem cell therapy	Standard care	Reduction in all conditions with only one drug with little side effects
People with primary biliary cholangitis (especially younger age group)	Treatments based on tools for predicting prognosis	Standard care	Better care for people with high risk of progression
People with chronic hepatitis C	Lifestyle: diet	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge.

			4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with chronic hepatitis C	Education of healthcare professionals (about diet)	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge. 4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain

			and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with NAFLD	Education of healthcare professionals (around support to patients on weight control, diet, exercise and life style)	Standard care	1. Preventing progression into NASH and cirrhosis. 2. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 3. Prevent heart attacks and strokes.
Family members of people with primary biliary cholangitis	Screening of family members for primary biliary cholangitis	No screening	1. Establishing the genetic link for primary biliary cholangitis. 2. Earlier identification of primary biliary cholangitis who may have PBC or be at risk. 3. Cost-savings.

People with positive AMA M2 with normal liver function tests	Screening for cirrhosis using biopsy	No screening	Accurate diagnosis of primary biliary cholangitis.
People with primary biliary cholangitis	Screening for other autoimmune conditions associated with primary biliary cholangitis and complications related to primary biliary cholangitis	No screening	1. HRQoL. 2. Costs.
People with autoimmune liver disease	Treatment of fatigue and others symptoms	Not applicable	Remission
People with primary sclerosing cholangitis	Standardised protocol for follow-up of patients with primary sclerosing cholangitis	Standard care	1. Reduce need for annual investigations. 2. Costs.
People with other autoimmune disease	Screening for liver disease	No screening	1. Decreasing risk of severe liver damage and admission to hospital 2. Reducing the need for liver transplants 3. Decreasing the risk of liver cancer

			4. Mortality 5. HRQoL
People with NAFLD	Pathway for managing end of life care	Standard care	1. Patient and carer satisfaction 2. Patient HRQoL 3. Symptom relief.
People with decompensated liver disease	Lifestyle: nutritional treatment	Not applicable	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Measuring energy requirements with indirect calorimeters	Current UK guidance on requirements (Parenteral & Enteral Nutrition Group) (high energy requirements)	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with hepatic encephalopathy	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved

			nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Lifestyle: exercise	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Standardised nutritional assessment of patients and outcomes in nutritional intervention trials	Non-standardised assessment	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.

			5. Better conduct of future trials.
People with NAFLD	Methods to increase self care	Not applicable	Reducing symptoms
People with NAFLD	Methods to decrease shortness of breath	Not applicable	Reducing symptoms
People with liver disease	Interventions to decrease fatigue	Not applicable	Fatigue
Healthcare professionals dealing with people with cirrhosis	Education of healthcare professionals about cirrhosis (complications and benefits and harms of treatment)	Standard care	Better advice to patients by health professionals regarding complications and benefits and harms of different treatments
People with primary biliary cholangitis	Ursodeoxycholic acid (including optimal dose)	No intervention/ other interventions	1. Liver function tests. 2. Minimal effective dose of ursodeoxycholic acid. 3. Good sleep.
People with liver cancer and ascites	Different interventions	Not applicable	HRQoL

People with primary sclerosing cholangitis	Screening for cancer	No screening	1. Benefits 2. Earlier diagnosis of bile duct cancer 3. Mortality
People with primary or metastatic liver cancer	Nurse-led care (follow-up clinic)	Doctor-led follow-up	1. Patient satisfaction 2. Timely surveillance
People with cirrhosis	Life-style: nutritional advice	Not applicable	1. Fatigue 2. Muscle wasting
People with polycystic liver disease	Surgery	Non-surgical management	1. Recurrence 2. HRQoL
People with gallstones	Avoiding surgery	Surgery	1. Requirement for surgery 2. Costs to NHS
People at risk of NASH	Nurse-led care	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Screening for NASH using Fibroscan	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality

People at risk of NASH	Support group focussed on diet and exercise	No intervention	1. Prevention of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Emotional support group for carers	No intervention	HRQoL
People with NASH	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.
People with NASH	Lifestyle: diet	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.

People with NASH	Different interventions to decrease anxiety and depression	Standard care	Anxiety and depression
People with NASH	Research design using support group	Standard research design	Help towards better research
General population	Life style: diet and exercise	No intervention	HRQoL
General population	Education of people (patient information leaflet at GP surgeries)	No intervention	1. Prevention of NASH. 2. HRQoL.
General population	Screening: for liver disease	No intervention	1. Early diagnosis of liver disease 2. Mortality 3. HRQoL 4. Requirement for liver transplantation 5. Costs 6. Requirement for hospital admission for severe liver damage 7. Primary liver cancer
Primary school children	Lifestyle: nutritional and dietary advice	No intervention	1. Adherence to healthy diet and

			exercise to sustain healthy life style.
People undergoing liver resection	Best method to assess function and volume of remnant liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Best method to assess cardiopulmonary function?	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pre-operative education	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Simulation and training of surgeons	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Growth factors to optimise muscle and fat content	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for weight loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein embolisation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Reducing systemic inflammation using steroids	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Open liver resection	Laparoscopic liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Tumour visualisation and localisation of the tumour	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy during operation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Use of magnifying surgical loupes during liver surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) during surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Transection techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Vascular occlusion techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Cardiopulmonary and pharmacological interventions for decreasing blood loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Use of peritoneal drains	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	ALPPS procedure (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy (post-operative)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pain control protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Early mobilisation protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Early oral intake protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) post-operatively	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Radioembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	External beam radiotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Screening for cancer	No screening	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Systemic chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with early or very early hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with intermediate hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Tamoxifen	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Tyrosine kinase inhibitors	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Neoadjuvant and adjuvant therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Interferon	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatocellular carcinoma	Surgical resection	Liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Anterior approach	Conventional liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative lamivudine with or without adefovir dipivoxil	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with advanced biliary tract carcinoma	gemcitabine-based chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable cholangiocarcinoma	Endoscopic treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Pharmacological interventions for	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

	reducing ischaemia reperfusion injury		
People undergoing liver transplantation for hepatitis B infection	Antibiotic prophylaxis	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Hepatitis B immune globulin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Prostaglandins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to prevent hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to treat hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Immunosuppressive regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Venovenous bypass	No intervention	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of biliary reconstruction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of preventing bacterial sepsis and wound complications after liver transplantation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Techniques of flushing and reperfusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Abdominal drainage	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Piggy-back	Conventional liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods to decrease blood loss and transfusion requirements	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Antiviral prophylaxis for prevention of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Antiviral treatment of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Lamivudine or adefovir dipivoxil	No intervention/other interventions including immunoglobulin	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Nutritional interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Celsior solution	UW solution	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for reducing ischaemia reperfusion injury	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Fibrin-based haemostatic agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for colorectal liver metastases	Neoadjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Resection	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Interventions for reducing blood loss	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Methods of decreasing infection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic node positive colorectal liver metastases	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for resectable neuroendocrine tumours	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection or ablation of colorectal liver metastases	Hepatic artery adjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Laparoscopic liver resection	Open liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Nonabsorbable disaccharides	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Benzodiazepine receptor antagonists	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Antibiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Dopamine agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Rifaximin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Acetyl-L-carnitine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatic encephalopathy	Probiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Naloxone	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	L-ornithine-L-aspartate	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Herbal medicines	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Weight reduction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Transarterial (chemo)embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Microwave coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with liver metastases	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable neuroendocrine liver metastases	Palliative cytoreductive surgery	Other palliative interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Hepatic arterial infusion	Systemic chemotherapy	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Electro-coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Percutaneous ethanol injection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Chemotherapy for downstaging	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Selective internal radiation therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with gallbladder polyp	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder dyskinesia	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of cystic duct occlusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for acute cholecystitis	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Mini-incision cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Mini-incision cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Abdominal wall lift	Pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for biliary colic	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Intra-peritoneal saline instillation	No instillation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of intraperitoneal local anaesthetic instillation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of local anaesthetic wound infiltration	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Three-dimensional imaging	Two-dimensional imaging	1. Mortality. 2. HRQoL. 3. Complications.
People with asymptomatic gallstones	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing open cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Robotic assistant	Human assistant	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of gallbladder dissection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Low pressure pneumoperitoneum	Standard pressure pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Education of patients	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Miniports	Standard ports	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Number of ports	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Pharmacological interventions for prevention or treatment of postoperative pain	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Glucocorticoids	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People who have undergone endoscopic sphincterotomy for gallstone related complications	Early cholecystectomy	Delayed or no cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Antibiotic prophylaxis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Day surgery	Overnight stay	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing day surgery laparoscopic cholecystectomy	Anaesthetic regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones undergoing laparoscopic cholecystectomy	Per-operative endoscopic sphincterotomy	Pre-operative endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stenosis	Magnetic resonance cholangiopancreatography	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected bile duct stones	Endoscopic ultrasound	Magnetic resonance cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Endoscopic retrograde cholangiopancreatography	Intraoperative cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Liver function tests	Transabdominal ultrasound	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Pre-operative biliary stenting	No stenting	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated amoebic liver abscess	Percutaneous procedure plus metronidazole	Metronidazole alone	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver tumours	Liver resection	No liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Sphincterotomy	No sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with cirrhosis	Colchicine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with blunt liver injury	Non-surgical treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Surgical treatment	Endoscopic intervention	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Lifestyle: Diets for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Pharmacological interventions for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Sphincteroplasty	Sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Non-steroidal anti-inflammatory drugs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis D	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure vaccines	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
General population	Immunisation against Hepatitis A	No immunisation	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure immunoglobulins	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary stent	Ursodeoxycholic acid to prevent stent occlusion	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Healthcare professionals	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

Pregnant women with Hepatitis B	Immunoglobulins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Newborns of HBSAg (hepatitis B surface antigen) positive mothers	Immunisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Asymptomatic Hepatitis B carriers	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Acupuncture	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
General population	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Lamivudine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with HIV infection	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People who have received Hepatitis B vaccination	Booster dose	No booster dose	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with renal failure	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and peripheral neuropathy	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People in haemodialysis units	Isolation to prevent Hepatitis C transmission	No isolation	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and HIV	Antiviral treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis C	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Caesarean section	Vaginal delivery	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C with vasculitis	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Staging of liver disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Biphosphonates	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Hormonal replacement therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with bleeding oesophageal varices	People with portosystemic shunt	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatorenal syndrome	Terlipressin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatorenal syndrome	Transjugular intrahepatic portosystemic shunts	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing common bile duct exploration	T-tube	No T-tube	1. Mortality. 2. HRQoL. 3. Complications.
People with acute calculous cholecystitis (high risk)	Percutaneous cholecystostomy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Enhanced recovery protocols	Standard intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Perfusion techniques in donor	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
New-borns and infants receiving parenteral nutrition and jaundice	Pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

New-borns and infants receiving parenteral nutrition and jaundice	Alternate interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with sickle cell disease and intrahepatic cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Human recombinant activated factor VII	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Vitamin K	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Antifibrinolytic amino acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Antioxidant supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Vitamin D supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Lifestyle: Nutritional support	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with adverse events related to chemoarterial embolisation for primary liver cancer	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated hepatic hydatid cysts	Percutaneous needle aspiration, injection, and re-aspiration with benzimidazole	Percutaneous needle aspiration, injection, and re-aspiration without benzimidazole	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder cancer	Chemotherapy	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with acute or acute-on-chronic liver failure	Granulocyte-colony stimulating factor	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Early laparoscopic cholecystectomy following endoscopic sphincterotomy	Delayed laparoscopic cholecystectomy following endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.

People with gallstones and common-bile duct stones	Model of service delivery	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Routine intraoperative cholangiography	selective cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstone pancreatitis	Early cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Non-pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary obstruction due to cholangiocarcinoma	Endoscopic bipolar radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile leak	Magnetic resonance cholangiopancreatography	Endoscopic retrograde cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with cholangitis	Antibiotics	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected focal liver lesions	Imaging modalities to distinguish focal liver lesions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver cancer who have undergone surgery	Optimal follow-up regimen to detect early recurrence	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver and bile duct resection	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallbladder polyp	Imaging modalities to confirm diagnosis of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder polyp	Imaging modalities to distinguish nature of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallstones	Methods to confirm diagnosis of gallstone	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected acute cholecystitis	Methods to confirm diagnosis of acute cholecystitis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected gallbladder dyskinesia	Methods to confirm gallbladder dyskinesia	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected Sphincter of Oddi dysfunction	Methods to confirm Sphincter of Oddi dysfunction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for liver cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Imaging modalities to confirm that cancer is limited to liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Bridging ablative therapies	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Goal-directed therapy	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Direct access surgery (without seeing a specialist)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver and gallbladder conditions	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Pharmacological interventions	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Psychological counselling	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People with biliary stricture	Different diagnostic tests	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Routine magnetic resonance cholangio pancreatography	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver and gallbladder disorders	Methods to improve understanding of evidence	Not applicable	1.Improved knowledge. 2. Better involvement in decision making.
People undergoing liver transplantation	Routine fat-assessment in donor livers	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD and obesity	Routine anti-obesity surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with severe polycystic liver disease	Pharmacological interventions to improve functional volume	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Interventions to achieve palliation	Not applicable	1. Palliation.

People with liver disease	Interventions to achieve symptom control	Not applicable	Symptom control
People with liver disease	Interventions to improve quality of life	Not applicable	Quality of life
Healthcare professionals dealing with people with primary sclerosing cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with Crohn's disease	Methods for screening for primary sclerosing cholangitis	Not applicable	Diagnosis of primary sclerosing cholangitis
People with NAFLD	Patient education	Standard care	1. Greater knowledge.
Healthcare professionals dealing with people with polycystic liver disease	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with polycystic liver disease	Early liver transplantation	Standard care	1. Quality of life. 2. Reducing symptoms. 3. Reducing pain.
People with autoimmune hepatitis	Interventions that affect T cells	No intervention	1. Cure. 2. Improve quality of life

People at risk of liver disease	Screening	Not applicable	Early diagnosis and treatment
People with polycystic liver disease	Monitoring polycystic liver disease	Not applicable	
People with polycystic kidney disease	Diagnosis polycystic liver disease	Not applicable	
People with liver disease	Methods to improve early appropriate treatment	Not applicable	Early diagnosis and treatment
People with polycystic kidney disease	Methods to prevent symptomatic polycystic liver disease	Not applicable	1. Quality of life. 2. Liver function.
People undergoing liver transplantation	Various treatments	Not applicable	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work 6. Improvement of symptoms
People with polycystic liver disease	Diet (specifically soy proteins which contain oestrogen	Standard diet	1. Decrease size of cyst or preventing cysts to enlarge. 2. Decrease symptoms

People with NAFLD	Various treatments	Not applicable	1. Impact on health (no further details) 2. Progression to liver failure
People with suspected NAFLD	Diagnosis	Not applicable	1. Early diagnosis
People with gallstones	Various treatments	Not applicable	1. Impact on health (no further details)
People with polycystic liver disease	Genetic treatments	Standard therapy	1. Reduce symptoms. 2. Decrease occurrence and size of cysts. 3. Increased longevity
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People undergoing treatment for ulcerative colitis	Various treatments	Not applicable	1. Adverse events related to liver
People with cholangiocarcinoma	Liver transplantation	Standard therapy	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People undergoing liver transplantation	Machine perfusion of donor organ	Cold storage	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver cancer	Novel treatments (irreversible electropolation, high intensity focused ultrasound)		1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with hepatocellular carcinoma	Liver resection	Liver transplantation	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with colorectal liver metastases	Ablation	Surgery	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Ischaemic preconditioning	No IPC	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Remote ischaemic preconditioning	No RIPC	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Goal-directed therapy	standard fluid treatment	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with compensated liver cirrhosis	Treatments (in particular statins)	Other interventions	1. Decompensation 2. Survival 3. Side effects 4. Quality of life.
People with chronic liver disease/ liver failure	Stem cell therapy	Standard therapy	1. Graft and patient survival 2. QoL. 3. Morbidity compared to conventional transplantation 4. Patient reported outcomes

People with Wilson's disease (and other rare non-alcohol liver related diseases)	Various treatments	Not applicable	Not stated
People with suspected autoimmune hepatitis	Diagnosis of autoimmune diseases	Not applicable	1. Costs of management

Appendix 2 List of unanswered research questions ('uncertainties') prioritised during the interim prioritisation

1. What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?
2. Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?
3. Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?
4. Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?
5. What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?
6. What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?
7. Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?

8. Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?
9. Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?
10. What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?
11. Should the methods used to assess nutrition of patients in liver disease be standardised?
12. Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?
13. Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?
14. What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?
15. Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?
16. What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?
17. What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?
18. Do statins (or other treatments) delay liver failure in people with advanced liver disease?
19. What are the best treatments that provide temporary symptom relief in people with advanced liver disease?
20. Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?

21. What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?
22. Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?
23. What are the best nutritional interventions in people undergoing liver transplantation?
24. What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?
25. Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?
26. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?
27. Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?
28. What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?
29. Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?
30. Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?
31. Is surgery (in the form of removal of gallbladder) required in people with gallstones?
32. Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis (NASH) receive additional education about the condition?
33. What is the best immunosuppressive regimen in adults undergoing liver transplantation?

34. Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangiopancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?
35. How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly follows medical advice) in people with liver disease?
36. What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?
37. What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?
38. Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?
39. What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?
40. Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or without chemotherapy drugs) effective in the treatment of people with liver metastases?
41. Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete hormones and nervous system) undergo liver resection?
42. What are the best methods available to decrease blood loss during liver resection?
43. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?
44. What are the best treatments for people with polycystic liver disease?
45. Should the healthcare professionals dealing with childhood liver diseases be provided additional education about childhood liver diseases compared to standard education where childhood diseases are learnt as part of overall education?

46. What is the best immunosuppressive regimen in children undergoing liver transplantation?
47. Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?
48. What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent reinfection with chronic hepatitis B virus (HBV) infection?

Appendix 3 Next step to address the top 10 uncertainty based on current best evidence (detailed)

Treatment uncertainty (Research question)	High-quality systematic review[a]	Research recommendations of systematic review	RCTs not included in the systematic review[a,b,c]	Patient-oriented outcomes assessed in trials not included in the systematic review[d]	Next step
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[1]	High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period (approximately five years) are needed.	NCT02169765 NCT02704130 NCT02728193 NCT02243384 NCT00844454 NCT01918683 NCT01570075 NCT01351194	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatments

What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	[2]	An urgent need exists to identify an effective medical treatment for primary sclerosing cholangitis through well-designed RCTs with adequate follow-up that aim to identify differences in outcomes important to people with primary sclerosing cholangitis.	NCT03394781 NCT02605213 NCT02943460 NCT02704364 NCT01688024 NCT02177136 NCT01672853 NCT03035058 NCT03333928	None of the trials include survival, HRQoL as outcomes[e]	High-quality RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of non-	[3] (includes only pharmacological interventions)	Further well-designed randomised clinical trials with sufficiently	More than 10 published trials on lifestyle interventions and more than 20 trials	Lifestyle interventions and nutritional supplementation	High-quality systematic reviews on lifestyle interventions (one review) and nutritional

alcohol-related fatty liver disease (NAFLD)?		large sample sizes are necessary.	on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> NCT02605616 NCT01002547 NCT02927314 NCT03291249 NCT03166735 NCT03486899 NCT03061721 NCT02784444 NCT02077374 NCT03486912	Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver disease (11 trials), mortality (2 trials), cirrhosis (2 trials), cardiovascular events (2 trials)[e]	supplementation to cure or delay the progression of NAFLD and high-quality RCTs on pharmacological interventions with clinical outcomes

			NCT02854605 NCT01963845 NCT03437720 NCT02684591 NCT02787304 NCT02466516 NCT02633956 NCT03008070 NCT03205150 NCT02923154 NCT02913105 NCT01899859 NCT02548351 NCT03053063 NCT03053050 NCT02413372		

			NCT02443116 NCT01464801 NCT03449446 NCT02912260 NCT02856555 NCT02704403 NCT01617772 NCT02217475 NCT01406704 NCT03248882 NCT01051219 NCT02316717 NCT02970942 NCT03439254 NCT02574325 NCT01703260		

			NCT01260246 NCT02960204		
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[4] (covers only maintenance immunosuppression)	Future randomised clinical trials should be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid postrandomisation dropouts or planned cross-overs; and use clinically important outcomes such as	<u>Induction immunosuppression</u> More than 20 published trials <u>Maintenance immunosuppression</u> NCT01998789 NCT01230502 NCT02909335 NCT00286871	<u>Induction immunosuppression</u> Not applicable as there is no high quality systematic review <u>Maintenance immunosuppression</u> Graft survival (1 trial) Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance immunosuppression with important clinical outcomes

		mortality, graft loss, renal impairment, chronic kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups. Moreover, such trials ought to be designed in such a way as to ensure low risk of bias and low risks of random errors.			
Should general public be educated about non-alcohol-related	None	-	None	-	High-quality RCTs on education to prevent NAFLD

fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?					
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	-	[5-7] NCT02050646 NCT02463331 NCT00608894 NCT02900443 NCT02239562 NCT01170351 NCT03217422 NCT01661842 NCT00687180 NCT01980745 NCT02878863	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes

			NCT02936596		
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH				
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine	None	-	NCT02775162 NCT03124641 NCT02940600 NCT02584283 NCT01317342	Overall survival (4 trials), graft survival (5 trials), health-related quality of life (2 trials)	Await results of the RCTs (all expected to complete by the end of 2019) and perform a high quality systematic review.

perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?					
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[8]	Further well-designed randomised clinical trials are necessary. Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the	NCT02937012 NCT01473524 NCT02823353 NCT02135536 NCT01614405 NCT02609048 NCT00746486 NCT02955602 NCT03226067	Health-related quality of life (5 trials), relief of symptoms (5 trials)[e]	High-quality RCTs with clinical outcomes

		clinic rather than in highly selected participants; employ blinding; avoid post-randomisation dropouts or planned cross-overs; should have sufficient follow-up period (e.g. five or 10 years or more); and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated	NCT03112681 NCT01904058 NCT02943447 NCT03124108 NCT03345589 NCT03092765 NCT03394924 NCT02516605 NCT03253276 NCT02965911 NCT01899703 NCT01654731 NCT02308111 NCT00125281 NCT02701166		

		cirrhosis, and liver transplantation. Alternatively, very large groups of participants should be randomised to facilitate shorter trial duration.			
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above) reported on liver fibrosis.				

a Numbers indicate the reference number.

b Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

c NCT followed by a number indicates trial registration number

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

Appendix 4 Scores obtained by each question in the different Delphi rounds

Questions[a]	**Delphi 1: Proportion who rated this question as highly important**	**Delphi 1: Median (IQR)**	**Delphi 2: Proportion who rated this question as highly important**	**Delphi 2: Median (IQR)**	**Delphi 3: Proportion who rated this question as highly important**	**Delphi 3: Median (IQR)**	**Consensus reached in Delphi 3?[b]**

1.What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	78.8%	8(7,9)	83.9%	8(7,9)	93.3%	8(7,9)	Yes
2.Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?	44.4%	6(5,7)	35.3%	6(5,7)	33.3%	6(5,7)	No
3.Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?	46.9%	6(5,9)	50.0%	6.5(5.75,8)	44.8%	6(6,7.5)	No
4.Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	59.4%	7.5(5,8.75)	70.0%	7.5(6,9)	72.4%	7(6,9)	Yes
5.What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	76.5%	8(6.75,9)	87.5%	8.5(7,9)	90.3%	9(8,9)	Yes
6.What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?	48.5%	6(5,7.5)	48.4%	6(5,7)	50.0%	6.5(5,7)	No

7.Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?	48.6%	6(5,8)	54.5%	7(5.5,8)	56.3%	7(6,8)	No
8.Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?	37.1%	6(4,7)	39.4%	6(4,7)	37.5%	6(4.25,7.75)	No
9.Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?	38.2%	6(4,8)	46.9%	6(4,8)	48.4%	6(5,8)	No
10.What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	76.5%	8(6.75,9)	87.5%	8(7,9)	93.5%	8(7,9)	Yes
11.Should the methods used to assess nutrition of patients in liver disease be standardised?	57.1%	7(5,9)	54.5%	7(5,8)	59.4%	7(5,8)	No
12.Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?	48.6%	6(4,8)	44.1%	6(4,7.25)	48.5%	6(5,7)	No

13.Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	72.2%	7.5(6,9)	73.5%	8(6,9)	81.8%	8(7,9)	Yes
14.What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?	48.5%	6(4.5,7)	48.4%	6(5,7)	50.0%	6.5(5,7)	No
15.Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?	19.4%	5(4,6)	20.0%	5(4,6)	20.7%	5(4,6)	No
16.What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?	37.1%	5(4,8)	27.3%	6(4,7)	28.1%	5(4,7)	No
17.What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	67.6%	8(5,8.25)	71.0%	8(6,9)	76.7%	8(6.75,9)	Yes

18.Do statins (or other treatments) delay liver failure in people with advanced liver disease?	45.7%	6(5,7)	39.4%	6(6,7)	43.8%	6(6,7)	No
19.What are the best treatments that provide temporary symptom relief in people with advanced liver disease?	50.0%	6.5(5,7.75)	52.9%	7(5.75,7.25)	54.5%	7(6,7)	No
20.Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?	64.7%	7(5,8)	68.8%	7(5.25,8)	67.7%	7(5,8)	No
21.What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	75.8%	7(6.5,9)	81.3%	7.5(7,9)	80.6%	8(7,9)	Yes
22.Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?	53.1%	7(5,8)	60.0%	7(5,8)	58.6%	7(5,8)	No
23.What are the best nutritional interventions in people undergoing liver transplantation?	52.8%	7(5,8)	51.5%	7(5,8)	53.1%	7(5,8)	No

24.What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?	61.8%	7(6,8)	65.6%	7(6,8)	64.5%	7(6,8)	No
25.Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	54.5%	7(5,9)	68.8%	7(6,8.75)	74.2%	7(6,9)	Yes
26.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?	42.4%	6(2,8)	40.0%	5.5(2,7)	37.9%	5(2,7)	No
27.Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?	51.4%	7(4,8)	58.8%	7(4,7.25)	57.6%	7(4,8)	No
28.What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	61.8%	7(5.75,8)	68.8%	7(6,8)	74.2%	7(6,8)	Yes

29.Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?	38.2%	5(4,8)	31.3%	5(4,7)	25.8%	5(4,7)	No
30.Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?	35.5%	5(4,7)	22.6%	5(4,6)	20.0%	5(4,6)	No
31.Is surgery (in the form of removal of gallbladder) required in people with gallstones?	24.2%	5(4,6.5)	30.0%	5(4,7)	24.1%	5(4.5,6.5)	No
32.Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis (NASH) receive additional education about the condition?	52.9%	7(4,8)	56.3%	7(4.25,8)	54.8%	7(5,8)	No
33.What is the best immunosuppressive regimen in adults undergoing liver transplantation?	73.5%	7(6,9)	84.4%	8(7,9)	90.3%	8(7,9)	Yes
34.Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangio pancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?	36.7%	5(4,7)	30.0%	5(4,7)	20.7%	5(4,6)	No

35.How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly follows medical advice) in people with liver disease?	67.6%	7(5,8)	69.7%	7(5,8)	71.9%	7(5,8)	Yes
36.What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?	51.6%	7(5,8)	56.7%	7(5,8)	55.2%	7(6,8)	No
37.What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?	50.0%	6.5(5,7)	43.8%	6(5,7)	41.9%	6(5,7)	No
38.Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?	54.3%	7(5,8)	51.5%	7(4.5,8)	53.1%	7(5,7.75)	No
39.What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?	38.7%	6(4,7)	31.0%	6(4.5,7)	27.6%	6(5,7)	No
40.Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or	40.6%	6(4,8)	34.4%	6(4,7)	32.3%	6(5,7)	No

without chemotherapy drugs) effective in the treatment of people with liver metastases?							
41.Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete hormones and nervous system) undergo liver resection?	36.7%	6(4,7.25)	40.0%	6(4.75,7.25)	37.9%	6(5.5,7)	No
42.What are the best methods available to decrease blood loss during liver resection?	43.8%	6(5,7.75)	48.4%	6(5,8)	46.7%	6(5,7.25)	No
43.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?	51.6%	7(4,8)	46.7%	6(4.75,7.25)	48.3%	6(5,7.5)	No
44.What are the best treatments for people with polycystic liver disease?	39.3%	6(4,8)	34.5%	6(4,8)	35.7%	6(5,7)	No
45.Should the healthcare professionals dealing with childhood liver diseases be provided additional education about childhood liver	35.5%	5(3,8)	37.9%	5(3.5,7.5)	37.9%	5(4.5,7.5)	No

diseases compared to standard education where childhood diseases are learnt as part of overall education?							
46.What is the best immunosuppressive regimen in children undergoing liver transplantation?	65.6%	8(4.25,9)	67.7%	8(6,9)	70.0%	8(6,9)	Yes
47.Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?	31.0%	6(4,7)	26.7%	5.5(4,7)	27.6%	6(5,7)	No
48.What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent reinfection with chronic hepatitis B virus (HBV) infection?	46.9%	6(3.5,7)	36.7%	6(3,7)	37.9%	6(5,7)	No
49.Are there alternatives to steroids in treating people with autoimmune hepatitis (AIH)?	-	-	51.9%	7(5,8)	50.0%	6.5(5,8)	No
50.What impact does the home situation have on recovery from chronic liver disease and its treatment?	-	-	34.5%	5(3.5,7.5)	32.1%	5(4,7)	No

51.Does cure of hepatitis C provide benefits to the patient outside reduction in liver related complications?	-	-	29.2%	5.5(3.25,7)	30.4%	6(4,7)	No
52.How fast does liver fibrosis (scarring) actually progress in non-alcoholic liver disease patients and does this predict overall outcome?	-	-	62.1%	7(6,8)	64.3%	7.5(6,8)	No
53.Should direct-acting antiviral treatments therapies be made more easily accessible to GPs and drug service clinics for treatment of hepatitis C virus?	-	-	50.0%	6.5(3.5,7)	52.2%	7(5,7)	No
54.Should patients diagnosed with liver fibrosis/cirrhosis related to NAFLD (non-alcoholic fatty liver disease) be offered more intensive nutritional support or dietician review?	-	-	60.7%	7(5,8)	63.0%	7(5,8)	No
55.Why have there been no alternatives to surgery in the form of new drug treatments for gall bladder disease & biliary sludge?	-	-	29.2%	4.5(1.25,7)	26.1%	4(2,7)	No

56.Why is there no proper evidence-based research on nutrition as a way of managing gall bladder disease/biliary sludge?	-	-	36.0%	5(1.5,7)	33.3%	5(2,7)	No
57.Why is there such variability in the natural progression of people with primary sclerosing cholangitis: some are very sick and require a transplant whereas others can remain relatively healthy for a long period?	-	-	56.0%	7(6,7)	54.2%	7(6,7)	No
58.What are the warning signals that primary sclerosing cholangitis will be aggressive or cancerous?	-	-	57.7%	7(5.75,8.25)	60.0%	7(5.5,8)	No
59.Does information on the impact of the complication on the people's quality of life improve the patient's informed decision-making process about treatment of liver and gallbladder diseases?	-	-	46.4%	6(4,7)	44.4%	6(4,7)	No
60.Will clinical pathways developed with patients and healthcare professionals having an equal say result in greater patient satisfaction and health in people with liver and gallbladder diseases?	-	-	44.8%	6(4.5,8)	46.4%	6(4.25,8)	No

61.Should high school teenagers be educated about the risks of hepatitis C?	-	-	53.8%	7(3.75,8)	57.7%	7(4.75,7.25)	No
62.How can patients with end stage liver failure be better prepared for end of life. How can the healthcare professionals supporting them be better prepared to provide that support?	-	-	65.5%	7(6,8)	67.9%	7(6,8)	No
63.Is aggressive control of inflammation on colonic inflammatory bowel disease in primary sclerosing cholangitis associated with improved liver outcomes?	-	-	48.0%	6(5,7)	50.0%	6.5(5.25,7)	No
64.What is the best way to survey for cholangiocarcinoma in primary sclerosing cholangitis?	-	-	61.5%	7(5.75,8)	60.0%	7(6,8)	No
65.Should the criteria for polycystic liver disease and transplantation be changed to take into account the size the liver cysts can grow and the additional pressures on all the internal organs?	-	-	29.2%	4.5(2,7)	30.4%	6(3,7)	No

66.Does control of colitis at the time of liver transplant reduce the risk of recurrent primary sclerosing cholangitis?	-	-	36.0%	6(5,7)	33.3%	6(5,7)	No
67.Are people with liver disease likely to develop other conditions, if so, what other conditions?	-	-	42.9%	6(3.25,7)	46.4%	6(3.25,7.75)	No
68.Do people with liver disease have a reduced life expectancy?	-	-	30.0%	5.5(3,8)	34.5%	6(3,8)	No
69.Should transjugular intrahepatic portosystemic shunt (TIPS) be used earlier in management of variceal haemorrhage?	-	-	51.9%	7(5,7)	55.6%	7(6,7)	No
70.Should abnormal alanine transaminase (ALT) reference ranges be revised downwards in line with ACG (American College of Gastroenterology) guidance?	-	-	36.0%	6(5,7)	37.5%	6(5,7)	No

a Questions from 49 to 70 were collected during the first round of Delphi.

b Consensus was reached when at least 80% of Delphi-panel members scored between 7 and 9 for the specific question.

Abbreviation: IQR = interquartile range

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TOP RESEARCH PRIORITIES IN LIVER AND GALLBLADDER DISORDERS IN THE UNITED KINGDOM

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TOP RESEARCH PRIORITIES IN LIVER AND GALLBLADDER DISORDERS IN THE UNITED KINGDOM

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ABSTRACT

Objectives: There is a mismatch between research questions considered important by patients, carers, and healthcare professionals and the research performed in many fields of medicine. The Non-Alcohol-Related Liver and gallbladder disorders Priority setting partnership (NARLIP) was established to identify the top research priorities in the prevention, diagnostic, and treatment of gallbladder disorders and liver disorders not covered by the James-Lind Alliance (JLA) Alcohol-related liver disease (ARLD) Priority Setting Partnership.

Design: The methods broadly followed the principles of the JLA guidebook. The one major deviation from the JLA methodology was the final step of identifying priorities: instead of prioritisation by group discussions at a consensus workshop involving stakeholders, the prioritisation was achieved by a modified Delphi consensus process.

Results: A total of 428 unique valid diagnostic or treatment research questions were identified. A literature review established that none of these questions were considered 'answered' i.e. high quality systematic reviews suggest that further research is not required on the topic. The Delphi panel achieved consensus (at least 80% Delphi panel members agreed) that a research question was a top research priority for six questions. Four additional research questions with highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

Conclusions: A priority setting process involving patients, carers and healthcare professionals has been used to identify the top ten priority areas for research related to liver and gallbladder disorders. Basic, translational, clinical, and public health research are required to address these uncertainties.

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ARTICLE SUMMARY

Strengths and limitations

- A research prioritisation process involving clinicians, patients and carer, and public representatives was performed in the field of liver and gallbladder disorders. This will help to address the mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in the field of liver and gallbladder disorders.
- A Delphi consensus method was performed. This prevented dominance of 'loud voices', a problematic issue with small and large group discussions.
- Because of the predominance of people with chronic liver disease on the Delphi panel, many of the top research priorities related to chronic liver diseases.

INTRODUCTION

Failure to address treatment uncertainties by research can lead to significant suffering and deaths [1]. It is important that research in any field of medicine takes into account the shared interests of patients, carers and clinicians [2]. However, there is a mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in many fields of medicine [3 4]. The James Lind Alliance (JLA) exists to help ensure a patient-centred process and enables the limited research resources to be utilised in addressing the research questions that are considered important jointly by patients, carers, and healthcare professionals [2] ('top research priorities'). This is achieved by forming 'Priority Setting Partnerships'

(PSPs) between patients, carers, and healthcare professionals [2]. Formal prioritisation of research topics jointly by patients and healthcare professionals can lead to increased research on the topic [5 6].

There has only been one formal research prioritisation process involving patients, carers, and healthcare professionals in the field of liver and gallbladder disorders [7]. However, the scope of that PSP was limited to alcohol-related liver disorders [7]. The Non-Alcohol-Related Liver and gallbladder disorders Priority setting partnership (NARLIP) was established to address the prevention, diagnostic, and treatment uncertainties related to the majority of liver disorders which were not covered by the JLA PSP on alcohol-related liver diseases (ARLD) [7] and to include gallbladder disease.

The aims and objectives of the NARLIP were to work with patients, their carers, and healthcare professionals treating them ('stakeholders') to identify uncertainties about the diagnostic tests and effects of prevention and treatments for non-alcohol related liver and gallbladder disorders, to agree by consensus a prioritised list of those uncertainties for research, to publicise the results and process, and to take the results to research commissioning bodies to be considered for funding and researchers to encourage them to submit grant applications addressing these uncertainties.

METHODS

The methods broadly followed the principles of the JLA guidebook.[8] The broad steps involved the following and are summarised in Figure 1.

1. Formation of the partnership: organisations and individuals representing people affected by non-alcohol related liver or gallbladder disorders, their carers, and healthcare professionals treating people with non-alcohol related liver and gallbladder disorders. A partnership was formed between KG representing University College London and the British Liver Trust initially, but following reorganisation in the British Liver Trust, PSC Support [9] became the

leading patient organisation partner of this process. A steering committee was formed. The members of the steering committee who participated in the complete process were KG, MW, BRD, CF, BF, AM, RM, SM, IS, and ET.

2. Establishment of the scope: the steering committee members discussed and decided that the scope should include adult and paediatric liver and gallbladder disorders which required medical and surgical treatments. The protocol was registered with James-Lind Alliance Priority Setting Partnership.
3. Identifying potential research questions: research questions were collected through online surveys and searching UK Database of Uncertainties about the Effects of Treatments (UK DUETs), research recommendations in high quality systematic reviews and clinical guidelines, and registers of ongoing research.
4. Refining research questions: the research questions identified in the above step were reviewed and where necessary combined to result in a set of unique research questions. Research questions were considered 'answered' when recent high-quality systematic reviews (based on low risk of bias studies) concluded that further research was not required. Removal of such 'answered' research questions was planned. The remaining questions were 'uncertainties'.
5. Interim prioritisation: To shortlist the set of questions to manageable levels for the final prioritisation process, the members of the steering committee ranked the uncertainties after stratifying the questions as medical and surgical questions. The members of the steering committee agreed that the interim prioritisation list should consist of 75% medical questions and 25% surgical questions. This decision was an arbitrary decision made by the steering committee based on the rationale that majority of individuals with liver and gallbladder disorders are treated medically but a minority require surgery which have a major impact on patients' lives.

6. Final prioritisation by consensus: A modified Delphi consensus method was followed to identify the top priorities using methods described by Jones et al [10]. The Delphi was performed electronically using Excel for managing the process. The steps in the modified Delphi consensus method were as follows.

    a. A Delphi panel consisting of patients, their carers, and healthcare professionals treating them was formed. The Delphi panel was formed by using 'snowballing' sampling methods and by contacting people through emails, online liver patient forums (British Liver Trust Health Unlocked forum), and newsletters. A total of 42 people expressed interest in joining the Delphi panel and 33 panel members completed all three rounds. Details of the Delphi panel composition and drop-outs are reported in the results section.

    b. A total of three rounds were conducted.

    c. Delphi panel members scored the short-listed questions in the interim prioritisation process on a scale of 1 to 9 with 1 being considered least important and 9 being considered most important. Scores of 1 to 3 were categorised as 'less important', 4 to 6 as 'moderately important', and 7 to 9 as 'highly important'. Panel members were requested to score the questions according to the importance of the question to them/the persons that they represent or treat and could leave questions that they were unable to score empty. Each Delphi panel member could add a maximum of two questions in the first round to ensure that the questions most important to the Delphi panel members were included in the prioritisation process even if they were not identified in the earlier steps. In the subsequent rounds, the panel members were shown the summary scores and their previous score for each question. They were able to retain or change their score in each of the rounds after the first round. For calculation of the summary scores and the proportion considering a question 'highly important', non-responses were excluded.

d. Consensus about a specific research question being a top research priority was reached when 80% or more Delphi panel members considered the research question as highly important (allocated scores between 7 and 9).

e. When fewer than 10 research priorities were obtained by consensus, the remaining priorities were completed by uncertainties based on the highest proportions of panel members agreeing that the research question was highly important (scores between 7 and 9).

f. There was no restriction on the Delphi panel to consult others while scoring the questions. However, only one final response on the set of questions was accepted from each Delphi panel member.

When there were no recent high-quality systematic reviews on the research question, we have recommended high-quality systematic reviews. When recent high-quality systematic reviews recommended high-quality research, we have recommended randomised controlled trials for prevention and treatment, as such studies carry the lowest risk of bias if conducted well; we would have recommended well conducted diagnostic test accuracy studies for diagnostic uncertainties. All online surveys were completed using Google Forms designed by KG. The Delphi process was completed using Microsoft Excel and email.

Ethical approval was not deemed necessary because no personal identifiable information was being collected, and the questions were being asked of healthcare professionals, patients and their carers were not considered sensitive questions. In addition, we had full support of patient organisations with involvement of patient representatives throughout the whole process rather than patients visiting the hospitals.

Patient and Public involvement

Patients and public were involved in all aspects of this project: they were part of the steering committee and were involved in the definition of the scope, methodology used for the prioritisation process, identification of further patients and public representatives, participation in the Delphi panel, interpretation, and critical revisions of the draft report. They will be involved in the dissemination of the findings through patient websites, patient forums, and to research funders.

RESULTS

Identification and refining of research uncertainties

A total of 126 patients, carers, and those at risk of developing non-alcohol related liver and gallbladder disorders, and 13 healthcare professionals participated in the first survey which was conducted between July and December 2015. This survey resulted in a total of 209 unique research questions. In addition, 219 unique questions were identified from searching the UK DUETs, Pubmed, and ClinicalTrials.gov on 2nd January 2016. A total of 428 unique valid (i.e. falling within the remit of this priority setting partnership) research questions (247 medical-related and 181 surgery-related) were identified from these sources. None of the research questions had been answered by recent high-quality systematic reviews based on low risk of bias studies which concluded that further research was not required. Therefore, all the 428 research questions were considered research 'uncertainties'. The complete list of 428 unique valid uncertainties in no particular order is available in Online Supplement Appendix 1. This has been converted to the population, intervention, control, and outcomes (PICO) format whenever possible.

Interim priorities

To identify a shortlist of questions (from the list of 429 questions) that were to be considered for the next step, a total of 48 research priorities (36 medical questions and 12 surgical questions) were identified on the basis of being selected by at least one patient or carer and healthcare professional of the steering committee (24 questions) and obtaining the highest ranks among the members of the steering committee (additional 24 questions). The list of 48 questions identified as interim priorities in no particular order is available in Online Supplement Appendix 2.

Final priorities

A total of 42 people expressed interest in joining the Delphi panel and 33 panel members completed all three rounds. Five people dropped out before they returned the scores of the first round (all patients, carers, and general public), three between first and second rounds (all healthcare professionals), and one between the second and third rounds (healthcare professional). Of the 33 panel members who completed all the three rounds, 17 were healthcare professionals and 16 were patients, carers, and general public. Of the 17 healthcare professionals, six were hepatologists, four were surgeons, two were hepatology nurses, and the remaining were general practitioner (GP), HPB surgery (hepato-pancreato biliary) nurse, organ preservation biologist, dietician, and pharmacist (one each). Of the 16 patients, carers, and general public, there was representation from general public and various liver diseases including autoimmune diseases such as primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis, viral hepatitis, metabolic diseases such as non-alcohol related fatty liver disease, and other diseases such as hepatocellular carcinoma and polycystic liver disease. There was also representation of liver transplanted patients in the Delphi panel. In total, 23 panel members were from England, seven were from Scotland, and three were from Wales. There were no panel members from Northern Ireland despite attempts to include panel members from Northern Ireland.

A total of 22 additional questions were added by the Delphi panel members in the first round of the Delphi process. The Delphi panel achieved consensus that an uncertainty was a top research priority for six research questions. Four additional research questions with the highest proportion of Delphi panel members scoring the question as highly important (scores between 7 and 9) were added to constitute the top 10 research priorities. The list of the top 10 research priorities (in the order of proportion who agreed that the uncertainty is a very important research priority) is available is Table 1. All the top 10 research priorities were prevention and treatment uncertainties, and none were diagnostic test uncertainties. None of the panel members thought the first two questions as least important (scores of 1 to 3). For the remaining 8 questions, 3% to 6.5% of people considered the questions to be least important (scores of 1 to 3).

Table 1 Treatment uncertainties for which consensus that the uncertainty is a research priority was reached

Treatment uncertainty (Research question)	Proportion who rated this question as highly important in the final round	Median (interquartile range) in the final round
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	93.5%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	93.3%	8(7,9)

What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	90.3%	9(8,9)
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	90.3%	8(7,9)
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	81.8%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	80.6%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	76.7%	8(6.75,9)
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	74.2%	7(6,9)
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	74.2%	7(6,8)

Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	72.4%	7(6,9)

A summary of the availability of systematic review of randomised controlled trials on the topic of the individual questions, randomised controlled trials on the topic not included in the systematic review (if one exists), and the outcomes evaluated in these RCTs are listed in Table 2. Table 2 also contains a suggestion for the next research steps. The list of the existing trials was compiled by searching ClinicalTrials.gov on 7th April 2018. The references to the trials not included in the systematic reviews is available in Online Supplement Appendix 3. As seen in Table 2, a well-designed RCT is the next step for eight of these top 10 research questions. This is because it appears that the outcomes in those trials will not address the outcomes listed in the research questions.

Table 2 Next step to address the top 10 research priorities based on current best evidence (summary)

Treatment uncertainty (Research question)	High-quality systematic review[a,b]	RCTs not included in the systematic review[a, c]	Patient-oriented outcomes assessed in trials not included in the systematic review[d]	Next step

What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[11]	8 trials	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatments
What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	[12]	9 trials	None of the trials include survival, HRQoL as outcomes[e]	High-quality RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of	[13] (includ	More than 10 published trials	Lifestyle intervention	High-quality

non-alcohol-related fatty liver disease (NAFLD)?	es only pharmacological interventions)	on lifestyle interventions and more than 20 trials on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> 44 trials	s and nutritional supplementation Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver disease (11 trials), mortality (2 trials),	systematic reviews on lifestyle interventions (one review) and nutritional supplementation to cure or delay the progression of NAFLD and high-quality RCTs on pharmacological interventions with

			cirrhosis (2 trials), cardiovascular events (2 trials)[e]	clinical outcomes
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[14] (covers only maintenance immunosuppression)	Induction immunosuppression More than 20 published trials Maintenance immunosuppression 4 trials	Induction immunosuppression Not applicable as there is no high quality systematic review Maintenance immunosuppression Graft survival (1 trial)	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance immunosuppression with

			Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	important clinical outcomes
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	None	None	-	High-quality RCTs on education to prevent NAFLD
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	15 trials	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH			

Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	None	5 trials	Overall survival (4 trials), graft survival (5 trials), health-related quality of life (2 trials)	Await results of the RCTs (all expected to complete by the end of 2019) and perform a high quality systematic review.
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[15]	24 trials	Health-related quality of life (5 trials), relief of symptoms (5 trials)[e]	High-quality RCTs with clinical outcomes
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the			

	outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above) reported on liver fibrosis.

a Numbers indicate the reference number.

b Further well-designed randomised controlled trials using clinical outcomes were recommended by all these systematic reviews.

c Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

The complete list of questions in the Delphi process, the proportion of respondents who considered a research question as very important and the summary scores in each Delphi round is available in Online Supplement Appendix 4.

DISCUSSION

This is the first priority setting partnership on non-alcohol related liver and gallbladder disorders. This included a wide range of disease processes and a total of 428 unique research questions that met the scope of this priority setting partnership were identified. All the research questions were considered unanswered as there had been no high quality systematic reviews which indicated that no further research is required, i.e. all the research questions were uncertainties. Consensus that an uncertainty was a very important research priority was reached for six research questions. Four additional research questions with the highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

As evident from the online supplement Appendix 1, longevity of life and health-related quality of life are two major outcomes that appear important to patients, their carers, and healthcare professionals. However, even when there are ongoing trials, it appears that the outcomes in those trials will not address the outcomes listed in eight of the top 10 research questions (Table 2). Therefore, the next step in addressing these uncertainties is the design and conduct of randomised controlled trials. Such randomised controlled trials may involve qualitative studies to determine the design and should compare the treatments that improve the longevity of life and/or health-related quality of life.

It should be noted that uncertainties 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?' and 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?' are related to each other. Although NAFLD includes NASH, most of the panel members felt that the research questions related to NAFLD and NASH should be kept separate uncertainties. While the same systematic review can cover both the uncertainties, the primary research study designed to address these two questions differ in terms of the setting, the outcomes used, and the

period of follow-up. Any primary research that tries to answer these two questions in a single randomised controlled trial will be inefficient.

Similarly, for the uncertainties 'what are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)' and 'are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?', a single randomised controlled trial will be inefficient and the preference of most of the panel members was to keep these uncertainties as separate uncertainties.

There are several limitations to our priority setting process. The first one is deviation from the original protocol. To select the final top priorities, the initial plan was to arrive at consensus by open small group and large group discussions of patients, carers, and healthcare professionals as suggested by the standard James-Lind Alliance process [8], which provides an opportunity for a knowledge exchange of viewpoints and experience. However, part of the steering committee with experience in a similar priority setting partnership felt that open discussions resulted in 'loud voices' being given more importance resulting in an unrepresentative list of top priorities. While this can be mitigated by facilitated group discussions by neutral JLA facilitators to ensure that all voices were heard in the discussions, this was considered by the steering committee as an important source of bias based on their prior experience in participating in open discussions. The steering committee therefore decided to follow the Delphi-consensus method which is one of the major consensus methods[10]. The advantages of Delphi-consensus method over open discussions include anonymity of the response and the equal weight given to the opinions of all members [10]. In addition, they are less costly to conduct without any limitation by geographical location compared to other methods of consensus[10] because of the lack of necessity to travel and take time off regular work. However, there is considerable variability in the previous performance of Delphi processes with regards to the number of rounds and the criteria for achieving consensus [16]. Arriving at consensus depends upon people revising their scores based on the other's scores. Our initial plan was to extend the Delphi to four rounds if consensus on 10 top research priorities was not reached in three rounds. However,

there was minimal change in scores between the rounds for most questions (Online Supplement Appendix 3) and the Delphi process was completed in three rounds. Consensus on a top research priority was achieved for six questions only. However, the proportion of Delphi panel members ranking a question as highly important was greater than 70% for the remaining four questions added to the list of top research priorities. Previous Delphi consensus processes have used various cut-off points for defining consensus: greater than 70% agreement among panel members is well within the definition of consensus used in previous Delphi consensus processes [16].

The other major limitation of our priority setting process is the representativeness of the people who completed the survey and took part in the Delphi process. The online survey was shared among clinicians and members of general and disease-specific patient organisations. Most questions resulting from the online survey relate to chronic liver disease (in particular, autoimmune liver diseases), perhaps reflecting the high motivation to support research from those groups. The Delphi panel also had a high representation of people related to chronic liver disease (in particular, autoimmune liver diseases) as patients, carers, or healthcare professionals. Whilst people affected by different liver and gallbladder disorders were actively sought through both general and disease-specific patient support groups and organisations, only a few responded and completed all three rounds of the Delphi process. The potential bias towards prioritising chronic liver diseases is evident as nine of the top 10 research priorities relate to chronic liver diseases (four relate to autoimmune liver diseases, three related to non-alcohol related fatty liver disease, two related to liver transplantation). It was surprising that the uncertainties related to the treatment of chronic viral diseases such as chronic hepatitis B and chronic hepatitis C were not identified within the top 10 research priorities. This may be because of the perception by the some of the panel members that the research questions related to the treatment of chronic hepatitis C were answered with the advent of directly acting antivirals (personal communication). The reason for non-prioritisation of chronic hepatitis B is not entirely clear. This may be because chronic hepatitis B may not have been

considered as important as other chronic liver diseases or under-representation of chronic hepatitis B in the panel.

Cancer-related questions, childhood-related liver diseases, and other benign disorders did not end up in the top research priorities (except for the treatment of very early hepatocellular carcinoma, which is managed by hepatologists and surgeons) probably for the reasons described above. We recommend that separate prioritisation processes are carried out for people with gallstones, a condition that affects approximately 5% to 25% of the population [17], for people with primary and secondary liver cancer, and childhood liver disorders where significant uncertainties remain on the effectiveness of different treatments in decreasing mortality and improving health-related quality of life.

As well as the above limitation, we are aware of the inherent limitations of using solely technology to carry out the Delphi exercise. These are limitations that can potentially lead to bias in any consensus-building method including that of face-to-face consensus methods normally used in a JLA PSP.

One solution which might address the limitations of this priority setting process and the standard JLA process may be to collect information routinely from patients visiting hospitals using paper forms and conduct online meetings (video conferencing and presentation) before the final round of the Delphi (or the standard face-to-face priority setting workshop used by the JLA. Some JLA PSPs do use methods such as face-to face interviews and group discussions rather than solely online surveys). By collecting information on paper forms and conducting the meetings in hospitals, it is possible to engage with people who do not have access to or are not familiar with computers. It is also possible to engage with people who have concerns regarding data confidentiality with the use of computers or social media by collecting information using paper forms. Ethical and confidentiality issues will need to be considered prior to engaging patients attending hospital in the research prioritisation process.

Another limitation of our priority setting process is the drop-outs during the Delphi process. While some of the drop-outs may be related to the ability to complete online surveys and use Microsoft Excel, some patient representatives or clinicians may have dropped out because they did not find any research question to be of direct relevance to them. Other reasons include lack of understanding of the conditions, feeling that the process was too complicated, feeling that the process would not work, and the time commitment for the process. This is because of the broad scope of this research prioritisation process and may be overcome by choosing a narrower focus while defining the scope of the prioritisation process, and by better explanation of the disease processes through presentations.

It should also be recognised that the Delphi panel was constituted of representatives from England, Scotland, and Wales. Therefore, the findings are applicable in only these countries. However, the findings are likely to be applicable throughout the NHS and in other European and Western countries with a similar spectrum of chronic liver diseases and similar treatment options available.

In summary, there are significant uncertainties in the management of liver and gallbladder disorders. Further high-quality research is necessary to address these uncertainties which may require programmes of basic, translational, clinical, and public health research. For issues with diverse and unproven treatment options, randomised controlled trials may be the only mechanism for identifying the most effective treatment and the treatments that represent good value for money for the NHS. Such randomised controlled trials should assess the effect of different treatments in improving longevity of life and/or health-related quality of life.

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CONTRIBUTION OF AUTHORS

Kurinchi Gurusamy – conceptualisation, healthcare professional and methodological lead of steering committee, Delphi panel member, analysis, author of the manuscript.

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Brian Davidson, Claire Frier, Barry Fuller, Angela Madden, Steven Masson, Ivana Safarik, Emmanouil Tsochatzis – Steering committee, Delphi panel member, suggested revisions to the manuscript

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Irfan Ahmed, Maxine Cowlin, John Dillon, Graham Ellicott, Ahmed Elsharkawy, Liz Farrington, Anthony Glachan, Nagappan Kumar, EJ Milne, Simon Rushbrook, Amanda Smith, Lizzie Stafford, Andrew Yeoman – Delphi panel member, suggested revisions to the manuscript

CONFLICTS OF INTEREST

The decisions made by healthcare professionals involved in the research prioritisation process might have been influenced by their professional interests, in addition to their own, or family member's experience of health conditions. Decisions made by patients and carers in the research prioritisation process might have been influenced by their particular experiences, health needs and interests.

DATA SHARING AGREEMENT

All data is available in the manuscript or in the supplementary file.

FIGURE 1

Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.

[a]The protocol was registered with James-Lind Alliance Priority Setting Partnership

[b]The final prioritisation was achieved by modified Delphi consensus method.

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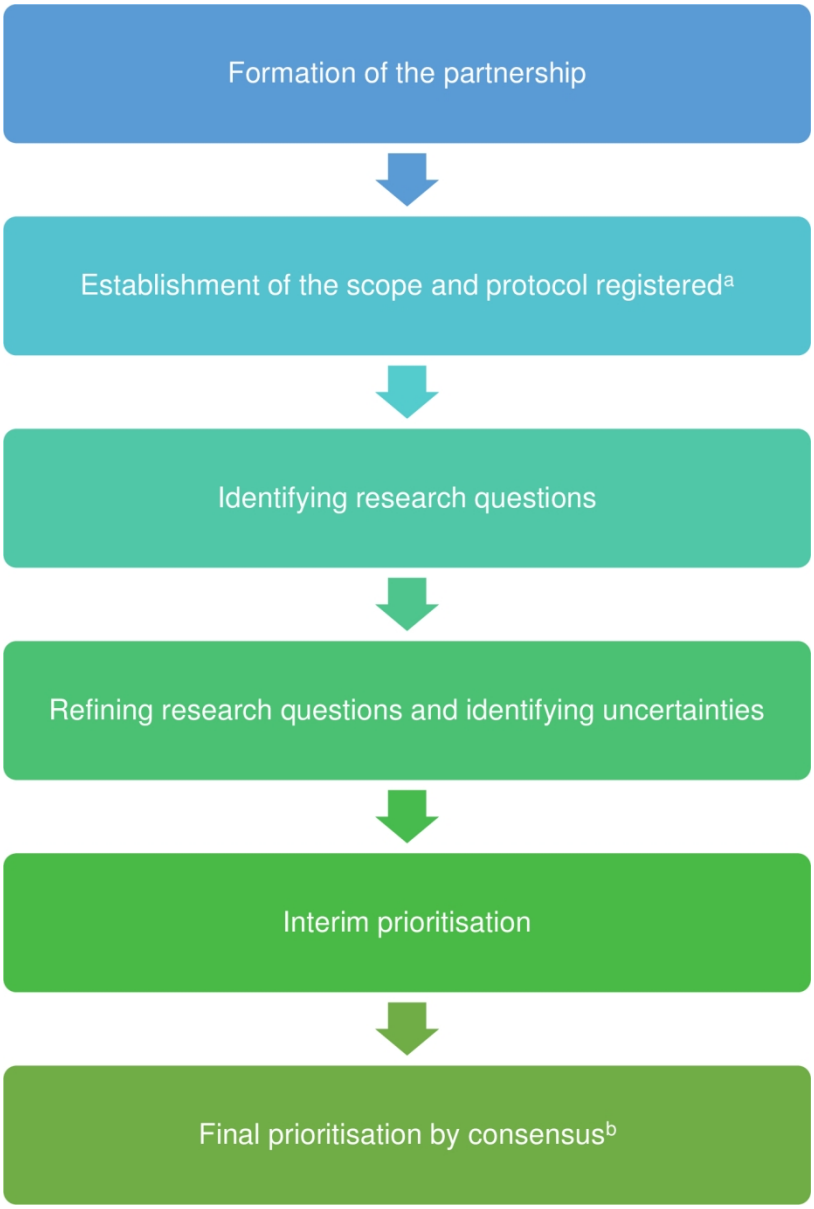

Figure 1: Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.
aThe protocol was registered with James-Lind Alliance Priority Setting Partnership
bThe final prioritisation was achieved by modified Delphi consensus method.

119x177mm (300 x 300 DPI)

Appendix 1 List of all research questions

Patient/population	Intervention	Control	Outcomes
People with obesity	Lifestyle: diet	No intervention	1. Liver transplantation 2. Improvement in BMI. 3. Improved liver function
People with liver disease	Nurse-led care	Standard care	Ability to self-manage
People with asymptomatic chronic liver disease	Education of people	No intervention	1. Improvement in life style. 2. Fatty liver disease
People with NASH (non-alcoholic steatohepatitis)	Different medical treatments	No intervention	1. Halting disease progression. 2. Reversing disease progression. 3. Slowing disease progression. 4. Cure
People with primary sclerosing cholangitis	Treatment for primary sclerosing cholangitis	No intervention	1. Mortality 2. HRQoL (health-related quality of life)

			3. Fewer symptoms - pain, itching, fatigue 4. improved liver function 5. Cure 6. Time to liver transplantation 7. Improvement (no further details) 8. Decreased hospital admission 9. Disease progression 10. Remission from PSC 11. Cancer 12. Requirement for liver transplant.
People with liver disease	Methods to improve compliance to treatment	Not applicable	1. HRQoL 2. Mortality
General population	Screening: early identification of people at risk of liver disease	No screening	1. HRQoL 2. Mortality

People at risk of liver disease	Diagnosis: early identification of people with liver disease	Not applicable	1. HRQoL 2. Mortality 3. Prevention of liver disease 4. Slowing progression of liver disease 5. Reducing requirement for liver transplantation 6. Adverse events of medications
People with primary sclerosing cholangitis and who have had a liver transplant and still have ulcerative colitis even after a sub total colectomy	Symptomatic treatment for primary sclerosing cholangitis	Not applicable	1. HRQoL. 2. Decrease in symptoms (breathlessness and fatigue). 3. Mortality. 4. Decrease in medication. 5. Cure. 6. Decreased progression of primary sclerosing cholangitis.

			7. Improvement in symptoms (unspecified).
People at risk of liver disease (overweight or obese)	Diagnosis: Accurate non-invasive method for diagnosis of chronic liver disease	Not applicable	1. Death 2. Need for liver transplant 3. Requirement for hospital admission. 4. Demonstrating equivalence to biopsy 5. Demonstrating good reproducibility
People at risk of liver disease (overweight or obese)	Screening methods to diagnose liver disease (including history and diagnostic tests)	Not applicable	1. Proportion of people at risk of liver disease 2. Proportion of people at risk who have asymptomatic liver fibrosis 3. Early diagnosis and treatment
People with polycystic liver disease	Treatment for polycystic disease	Not applicable	1. Decrease symptoms 2. Increase quality of

			life 3. Decrease size of cyst or preventing cysts to enlarge 4. Increased longevity 5. Requirement for liver transplant.
People with autoimmune hepatitis	Treatments for autoimmune hepatitis.	Not applicable	1. HRQoL (including ability to carry out normal activities, study, work). 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Treatment related side-effects (unspecified). 8. Brittle teeth

			(treatment-related). 9. More effective treatment unspecified. 10. Complete recovery (unspecified). 11. Mortality. 12. Measure feeling well (unsepcified) 13. Fewer flare ups 14. Less joint pain. 15. Disability 16. Liver damage requiring hospital admission 17. Quicker recovery 18. More monitoring of patients 19. Symptom control. 20. Side-effects
People with autoimmune hepatitis	Standardised protocol care	Standard care	1. HRQoL. 2. Fatigue. 3. Osteoporosis

			(treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related).
People with autoimmune hepatitis	Treatment of fatigue/joint pain related to autoimmune hepatitis.	Not applicable	1. HRQoL. 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Joint pain. 8. Symptoms (unspecified).
People with autoimmune hepatitis	Nurse-led care	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.

People with autoimmune hepatitis	Education of healthcare professionals and patients	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.
People with autoimmune hepatitis	Lifestyle: diet	Standard care	1. Treatment related adverse events. 2. Requirements for liver transplantation. 3. NHS (National Health Service, UK) costs 4. HRQoL 5. Mortality. 6. Free from immunosuppressive therapies. 7. Fatigue. 8. Weight.
People with autoimmune hepatitis	Education of people	Standard care	Faster reduction in strong medications. Need for liver transplantation.
People with autoimmune hepatitis	Cannabis + standard care	Standard care	1. Reduction in immunosuppressants.

			2. Fatigue. 3. Treatment related side effects such as serious infections, anxiety, depression, cancer, physical side effects.
General population (> 40 years or >50 years or middle-aged people, particularly overweight/obese and/or have type 2 diabetes and/or a family history of chronic liver disease)	Screening for liver disease by GP using routine blood tests/other methods	Standard care	1. Earlier diagnosis and treatment. 2. Preventing liver disease progressing to cirrhosis. 3. More cost effective for NHS. 4. Preventing the complications of chronic liver disease such as hepatocellular carcinoma and varices.
People with autoimmune hepatitis	Prednisolone	No intervention	1. Obesity. 2. Osteoporosis. 3. Insomnia. 4. Hypertension.

People with genetic markers associated with autoimmune hepatitis.	Methods for prophylaxis	No intervention	Prevention of autoimmune hepatitis
People with autoimmune hepatitis	Lifestyle: optimal physical exercise	Not applicable	1. Weight 2. Fatigue
People with autoimmune hepatitis (stable)	Nurse-led care	Standard care	1. Fatigue
People with suspected autoimmune hepatitis	Methods to make a quicker diagnosis	Not applicable	1. Earlier diagnosis
People with NASH, diabetes, and gastroparesis	Treatments for breathlessness and pain	Not applicable	1. Breathlessness and pain.
People with NASH cirrhosis, diabetes, and anaemia	Treatments	Not applicable	HRQoL
People with NASH cirrhosis, diabetes, and anaemia	Education of people	Standard care	Better knowledge
General population	Education of people	Standard care	Better knowledge
People with NASH cirrhosis, diabetes, and anaemia	Non-pharmacological treatments to decrease pain and depression	Pharmacological interventions or no intervention	1. Pain 2. Depression
People with suspected autoimmune diseases with potential to cause acute liver failure	Diagnosis of autoimmune diseases that cause acute liver failure	Not applicable	Identification of specific autoimmune diseases

People with autoimmune diseases with potential to cause acute liver failure	Prophylactic treatments	Not applicable	Prevent acute liver failure
People with primary sclerosing cholangitis	Lifestyle: diet (including alcohol consumption) and physical exercise	Not applicable	1. Reduction in symptoms 2. Overall health benefits (unspecified) 3. Ability to return to useful occupation. 4. Reduce medication. 5. Reduce need for annual investigations.
People with primary sclerosing cholangitis	Azathioprine	Other interventions	Treatment related adverse events
People with autoimmune hepatitis	Non-pharmacological treatments to treat autoimmune hepatitis	Pharmacological interventions or no intervention	1. Reduction in symptoms 2. HRQoL (including the ability to do everyday tasks/ back into education or employment)

People with primary sclerosing cholangitis	Itching receptor blockers	No intervention/ other interventions	Reduction in itching
People with primary sclerosing cholangitis with and without Vitamin D deficiency	Vitamin D supplements	Standard care	1. Stop the progress of the disease. 2. Fewer flare ups of inflammatory bowel disease and primary sclerosing cholangitis. 3. Improve HRQoL 4. Less depression
People with primary sclerosing cholangitis and autoimmune hepatitis	Ursodeoxycholic acid	No intervention/ other interventions	Reducing symptoms
People at risk of primary sclerosing cholangitis and autoimmune hepatitis	Prophylactic treatments	No intervention	Prevention of the condition
People with autoimmune hepatitis	Non-steroidal interventions	Steroids	Adverse events
People at risk of autoimmune liver diseases	Prophylactic treatments	Not applicable	Reduction in those getting advanced liver disorders

People with autoimmune liver diseases (20 to 30 years old)	Treatments	Not applicable	1. Reduction in those getting advanced liver disorders. 2. Stabilisation of disorder. 3. Reduction in liver cancer rates.
People with autoimmune liver diseases (> 30 years)	Screening: Early diagnosis of liver cancer	No screening	Early diagnosis of liver cancer
People with NASH and stroke	Nurse-led care	Standard care	1. Recovery time 2. Amount of recovery that is made
People with haemochromatosis	Lifestyle: iron avoidance diet	Traditional phlebotomy	Reduction in iron levels
People with haemochromatosis	Acceleration of phlebotomy	Traditional phlebotomy	Reduction in iron levels
People with NAFLD	Nurse-led care	Standard care	1. Faster recovery. 2. Symptom relief (unspecified). 3. Prevention of more serious complications. 4. Patient education

			on diet and exercise to lose weight. 5. Preventing progression into NASH and cirrhosis. 6. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 7. Prevent heart attacks and strokes.
People with NAFLD	Treatments for pain	Not applicable	Reducing pain
People with NAFLD	Treatments for itching	Not applicable	Reduction in itching
People at risk of liver disease (overweight or obese)	Education of healthcare professionals about NAFLD	Standard care	1. Prevention of cirrhosis. 2. Prevention of other related liver complications. 3. Earlier diagnosis and treatment of liver diseases. 4. Increased knowledge.
Midwives and healthcare professionals coming into	Education of healthcare	Standard care	1. Prevention of cirrhosis.

contact with children and young adults	professionals about liver disease		2. Prevention of other related liver complications.
People with chronic hepatitis C	Newer treatments	Older interventions	1. Treatment-related complications 2. Ability to perform usual activities such as work, study, housework. 3. Severe liver damage requiring hospital admission. 4. Decreased anxiety.
New-borns	Screening test for biliary atresia	No screening	Earlier diagnosis and treatment
Children who have undergone liver transplantation	Immunosuppressive regimens	Not applicable	Adverse events
People with liver-related disorders	Treatment for itching	Not applicable	Reduction or eradication of itching
People with primary biliary cholangitis	Education of people	Standard care	Knowledge
People with positive AMA (antimitochondrial antibody) M2	Prophylactic treatments	Not applicable	1. Prevention of primary biliary cholangitis.

			2. Reversion to a negative AMA M2 before cirrhosis develops.
People with positive AMA M2	Standardised protocol care by GP	Standard care	1. Prevention of primary biliary cholangitis. 2. Reversion to a negative AMA M2 before cirrhosis develops.
People with liver disease	Stem cell therapy	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work) 3. Prolonging periods of remission 4. Reducing symptoms
People with liver disease	Bio-artificial livers	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities

			including study and work)
People with autoimmune hepatitis	Targeted therapy against autoimmunity	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work)
People with primary biliary cholangitis not responding to ursodeoxycholic acid	Different treatments	Not applicable	1. Cure 2. Slowing of disease 3. Improved quality of life with respect to fatigue.
People with primary biliary cholangitis	Antiviral treatment	No intervention/ other interventions	1. Improvement in health (unspecified) 2. Mortality
People with primary biliary cholangitis	Treatment for itching and fatigue	Not applicable	1. HRQoL. 2. Anxiety. 3. Itching. 4. Fatigue. 5. Cure 6. Slowing of disease 7. Symptom relief
People with primary biliary cholangitis	Greater patient involvement	Standard care	1. HRQoL. 2. Anxiety.

People with liver and gallbladder disorders	Nurse-led care	Standard care	1. Symptoms. 2. Pain relief. 3. Quicker investigative measures.
People with pain after cholecystectomy (especially elderly and living alone)	Hospital based investigations to find the cause of pain, treatment of the cause of pain and discharged after pain relief	Symptomatic outpatient intervention	Pain relief
People with chronic hepatitis C	Ribavirin	No intervention/ other interventions	Osteoporosis
People with chronic hepatitis C taking ribavirin	Prophylactic treatments for osteoporosis	No prophylactic intervention	Osteoporosis
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about childhood liver disorders	Standard care	1. Knowledge 2. Better treatment of patients with primary biliary cholangitis
People with liver disease	Education of people	Standard care	1. Patient knowledge. 2. Visits to the

			hospital. 3. More patient responsibility
People with symptomatic primary sclerosing cholangitis	Different treatments	Not applicable	1. Cure of disease. 2. Delays progression of disease.
People with primary sclerosing cholangitis	Intervention to reverse liver damage	Not applicable	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation.
People with primary sclerosing cholangitis	Intervention to treat fatigue	Not applicable	1. HRQoL. 2. Fatigue.
People with primary sclerosing cholangitis	Intervention to treat itching	Not applicable	1. HRQoL. 2. Itching.
People with primary sclerosing cholangitis	Specialist interest doctor	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Symptom relief.
People at risk of oesophageal varices	Non-invasive assessment of oesophageal varices	Invasive assessment of oesophageal varices	Reduce bleeding oesophageal varices

People at risk of chronic liver disease	Alternative to biopsy for assessment of cirrhosis	Liver biopsy	Assessment of whole liver
People at risk of primary sclerosing cholangitis (PSC)	Early diagnosis of primary sclerosing cholangitis Alternate to liver biopsy	Not applicable	Not stated
People with primary sclerosing cholangitis with normal or relatively normal liver function tests	Alternative to UKELD (United Kingdom Model for End-Stage Liver Disease) scores for prioritisation for liver transplantation	UKELD	1. More accurate assessment of transplant need for transplant amongst PSC patients. 2. Reduction in numbers of 'low score' PSC patients becoming too ill for transplant, or not being offered a transplant once 'listed'.
People with positive AMA M2 with normal liver function tests	Ursodeoxycholic acid	No intervention	Slowing progression of primary biliary cholangitis

People with suspected primary sclerosing cholangitis	Nurse-led care	Standard care	Earlier diagnosis and treatment
People with liver failure of unknown reason	Investigations to find the cause of liver failure of unknown origin	Not applicable	More knowledge.
People with Gilbert's syndrome	Treatment of fatigue related to Gilbert's syndrome	Not applicable	1. HRQoL. 2. Chronic fatigue. 3. Depression
People with NAFLD (non-alcoholic fatty liver disease)	Breathing exercises	Standard care	1. Faster recovery. 2. Symptom relief 3. Prevention of more serious complications
People with NASH cirrhosis	Treatment of symptoms	Not applicable	Improvement of symptoms
People at risk of liver disease	Screening for autoimmune diseases	No screening	Earlier diagnosis and treatment
People with autoimmune hepatitis	Treatment of symptoms	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups.

			4. Less joint pain. 5. Disability.
People with autoimmune hepatitis	Methods to decrease stress	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups. 4. Less joint pain. 5. Disability.
People with liver disease	Counselling for tremors and confusion	No counselling	Coping with symptoms
People with NAFLD	Staging of liver disease	Not applicable	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Metformin	No intervention	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Standardised protocol for diagnosis and treatment of NAFLD	Standard care	1. Mortality. 2. Reversal of liver damage
People with osteoarthritis	Anti-inflammatory drugs	Other interventions	Cirrhosis
People with diabetes	Adequate control of diabetes	Lack of adequate control of diabetes	1. NASH. 2. Cirrhosis.

People at risk of NAFLD	Screening: Early identification of causes	Standard care	Prevention of liver disease
People with NAFLD	Treatments	Not applicable	1. Cure 2. Prevention of liver disease 3. Disease progression 4. HRQoL
People with upper abdominal pain	Screening: Early scan with ultrasound, blood tests, and urine tests	Standard care	1. Early identification of liver and gallbladder diseases 2. Appropriate advice/treatment
People with NAFLD	Lifestyle: diet and exercise	Standard care	1. HRQoL
People with NAFLD	Specialist interest doctor	Standard care	1. HRQoL
People at risk of liver disease	Prophylactic interventions	Not applicable	1. Prevention of liver disease
People at risk of NAFLD	Prophylactic treatments	Not applicable	1. Prevention of NAFLD 2. Decrease NAFLD
People with NASH fibrosis	Lifestyle: exercise	Standard care	None stated

People with cryptogenic liver cirrhosis	Investigations to find the cause of cryptogenic cirrhosis	Not applicable	1. Reduction in liver disease diagnosis of the percentage regarded as cryptogenic. 2. Establishment of relevant treatment pathways. 3. Reduction in numbers of liver transplant required by earlier intervention using non-invasive treatment regimes.
People with cirrhosis	Community-led psychological support (on lifestyle: diet and exerise, stress, work-life balance, and general well-being)	Standard care	1. Reduction of symptoms such as nausea, fatigue. 2. Improved nutrition and healthier weights. 3. Improved HRQoL 4. Improved sense of wellbeing 5. Successful work

			and job retention 6. Good sense of self determination/empowerment and motivation 7. Improved clinical markers (unspecified)
Newborns	Screening for metabolic liver diseases	No screening	1. Early treatment for people with metabolic liver disease (including dietary advice) 2. Mortality. 3. HRQoL. 4. Prevent type 2 diabetes
People with autoimmune hepatitis	Telephone-based care	Standard care	1. Reduction in time spent in outpatients 2. Less spent on car-parking at hospitals
People with NASH and diabetes	Liver transplantation	Standard care	1. Mortality

People with primary biliary cholangitis (newly diagnosed)	Adequate drinking water	Standard care	1. HRQoL. 2. Liver function tests.
People with primary sclerosing cholangitis	Treatment targeted against deformation of bile duct	Standard care	1. Time to end-stage liver disease.
People with bile duct cancer	Treatment targeted against deformation of bile duct	Standard care	Not stated
People with gallbladder sludge with digestive symptoms	Avoiding surgery	Standard care	1. Symptom relief
People with NAFLD	Education of healthcare professionals	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.
People with NAFLD	Education of general public	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.

People with NAFLD	Methods to make an accurate diagnosis (including liver function tests)	Not applicable	Not stated
People with NAFLD (overweight)	Interventions to lose weight	Not applicable	Weight loss
People with liver disease (newly diagnosed)	Mental health support	Not applicable	Mental health
Children with multiple autoimmune disorders related to liver	Genetic testing of telomere lengths	Other tests/ no tests	Not stated
Children with multiple autoimmune disorders related to liver	Stem cell therapy	Standard care	Reduction in all conditions with only one drug with little side effects
People with primary biliary cholangitis (especially younger age group)	Treatments based on tools for predicting prognosis	Standard care	Better care for people with high risk of progression
People with chronic hepatitis C	Lifestyle: diet	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge.

			4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with chronic hepatitis C	Education of healthcare professionals (about diet)	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge. 4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain

			and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with NAFLD	Education of healthcare professionals (around support to patients on weight control, diet, exercise and life style)	Standard care	1. Preventing progression into NASH and cirrhosis. 2. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 3. Prevent heart attacks and strokes.
Family members of people with primary biliary cholangitis	Screening of family members for primary biliary cholangitis	No screening	1. Establishing the genetic link for primary biliary cholangitis. 2. Earlier identification of primary biliary cholangitis who may have PBC or be at risk. 3. Cost-savings.

People with positive AMA M2 with normal liver function tests	Screening for cirrhosis using biopsy	No screening	Accurate diagnosis of primary biliary cholangitis.
People with primary biliary cholangitis	Screening for other autoimmune conditions associated with primary biliary cholangitis and complications related to primary biliary cholangitis	No screening	1. HRQoL. 2. Costs.
People with autoimmune liver disease	Treatment of fatigue and others symptoms	Not applicable	Remission
People with primary sclerosing cholangitis	Standardised protocol for follow-up of patients with primary sclerosing cholangitis	Standard care	1. Reduce need for annual investigations. 2. Costs.
People with other autoimmune disease	Screening for liver disease	No screening	1. Decreasing risk of severe liver damage and admission to hospital 2. Reducing the need for liver transplants 3. Decreasing the risk of liver cancer

			4. Mortality 5. HRQoL
People with NAFLD	Pathway for managing end of life care	Standard care	1. Patient and carer satisfaction 2. Patient HRQoL 3. Symptom relief.
People with decompensated liver disease	Lifestyle: nutritional treatment	Not applicable	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Measuring energy requirements with indirect calorimeters	Current UK guidance on requirements (Parenteral & Enteral Nutrition Group) (high energy requirements)	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with hepatic encephalopathy	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved

			nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Lifestyle: exercise	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Standardised nutritional assessment of patients and outcomes in nutritional intervention trials	Non-standardised assessment	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.

			5. Better conduct of future trials.
People with NAFLD	Methods to increase self care	Not applicable	Reducing symptoms
People with NAFLD	Methods to decrease shortness of breath	Not applicable	Reducing symptoms
People with liver disease	Interventions to decrease fatigue	Not applicable	Fatigue
Healthcare professionals dealing with people with cirrhosis	Education of healthcare professionals about cirrhosis (complications and benefits and harms of treatment)	Standard care	Better advice to patients by health professionals regarding complications and benefits and harms of different treatments
People with primary biliary cholangitis	Ursodeoxycholic acid (including optimal dose)	No intervention/ other interventions	1. Liver function tests. 2. Minimal effective dose of ursodeoxycholic acid. 3. Good sleep.
People with liver cancer and ascites	Different interventions	Not applicable	HRQoL

People with primary sclerosing cholangitis	Screening for cancer	No screening	1. Benefits 2. Earlier diagnosis of bile duct cancer 3. Mortality
People with primary or metastatic liver cancer	Nurse-led care (follow-up clinic)	Doctor-led follow-up	1. Patient satisfaction 2. Timely surveillance
People with cirrhosis	Life-style: nutritional advice	Not applicable	1. Fatigue 2. Muscle wasting
People with polycystic liver disease	Surgery	Non-surgical management	1. Recurrence 2. HRQoL
People with gallstones	Avoiding surgery	Surgery	1. Requirement for surgery 2. Costs to NHS
People at risk of NASH	Nurse-led care	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Screening for NASH using Fibroscan	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality

People at risk of NASH	Support group focussed on diet and exercise	No intervention	1. Prevention of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Emotional support group for carers	No intervention	HRQoL
People with NASH	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.
People with NASH	Lifestyle: diet	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.

People with NASH	Different interventions to decrease anxiety and depression	Standard care	Anxiety and depression
People with NASH	Research design using support group	Standard research design	Help towards better research
General population	Life style: diet and exercise	No intervention	HRQoL
General population	Education of people (patient information leaflet at GP surgeries)	No intervention	1. Prevention of NASH. 2. HRQoL.
General population	Screening: for liver disease	No intervention	1. Early diagnosis of liver disease 2. Mortality 3. HRQoL 4. Requirement for liver transplantation 5. Costs 6. Requirement for hospital admission for severe liver damage 7. Primary liver cancer
Primary school children	Lifestyle: nutritional and dietary advice	No intervention	1. Adherence to healthy diet and

			exercise to sustain healthy life style.
People undergoing liver resection	Best method to assess function and volume of remnant liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Best method to assess cardiopulmonary function?	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pre-operative education	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Simulation and training of surgeons	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Growth factors to optimise muscle and fat content	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for weight loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein embolisation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Reducing systemic inflammation using steroids	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Open liver resection	Laparoscopic liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Tumour visualisation and localisation of the tumour	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy during operation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Use of magnifying surgical loupes during liver surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) during surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Transection techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Vascular occlusion techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Cardiopulmonary and pharmacological interventions for decreasing blood loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Use of peritoneal drains	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	ALPPS procedure (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy (post-operative)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pain control protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Early mobilisation protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Early oral intake protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) post-operatively	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Radioembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	External beam radiotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Screening for cancer	No screening	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Systemic chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with early or very early hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with intermediate hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Tamoxifen	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Tyrosine kinase inhibitors	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Neoadjuvant and adjuvant therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Interferon	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatocellular carcinoma	Surgical resection	Liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Anterior approach	Conventional liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative lamivudine with or without adefovir dipivoxil	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with advanced biliary tract carcinoma	gemcitabine-based chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable cholangiocarcinoma	Endoscopic treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Pharmacological interventions for	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

	reducing ischaemia reperfusion injury		
People undergoing liver transplantation for hepatitis B infection	Antibiotic prophylaxis	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Hepatitis B immune globulin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Prostaglandins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to prevent hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to treat hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Immunosuppressive regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Venovenous bypass	No intervention	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of biliary reconstruction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of preventing bacterial sepsis and wound complications after liver transplantation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Techniques of flushing and reperfusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Abdominal drainage	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Piggy-back	Conventional liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods to decrease blood loss and transfusion requirements	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Antiviral prophylaxis for prevention of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Antiviral treatment of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Lamivudine or adefovir dipivoxil	No intervention/other interventions including immunoglobulin	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Nutritional interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Celsior solution	UW solution	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for reducing ischaemia reperfusion injury	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Fibrin-based haemostatic agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for colorectal liver metastases	Neoadjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Resection	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Interventions for reducing blood loss	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Methods of decreasing infection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic node positive colorectal liver metastases	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for resectable neuroendocrine tumours	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection or ablation of colorectal liver metastases	Hepatic artery adjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Laparoscopic liver resection	Open liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Nonabsorbable disaccharides	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Benzodiazepine receptor antagonists	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Antibiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Dopamine agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Rifaximin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Acetyl-L-carnitine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatic encephalopathy	Probiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Naloxone	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	L-ornithine-L-aspartate	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Herbal medicines	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Weight reduction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Transarterial (chemo)embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Microwave coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with liver metastases	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable neuroendocrine liver metastases	Palliative cytoreductive surgery	Other palliative interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Hepatic arterial infusion	Systemic chemotherapy	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Electro-coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Percutaneous ethanol injection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Chemotherapy for downstaging	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Selective internal radiation therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with gallbladder polyp	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder dyskinesia	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of cystic duct occlusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for acute cholecystitis	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Mini-incision cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Mini-incision cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Abdominal wall lift	Pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for biliary colic	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Intra-peritoneal saline instillation	No instillation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of intraperitoneal local anaesthetic instillation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of local anaesthetic wound infiltration	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Three-dimensional imaging	Two-dimensional imaging	1. Mortality. 2. HRQoL. 3. Complications.
People with asymptomatic gallstones	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing open cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Robotic assistant	Human assistant	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of gallbladder dissection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Low pressure pneumoperitoneum	Standard pressure pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Education of patients	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Miniports	Standard ports	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Number of ports	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Pharmacological interventions for prevention or treatment of postoperative pain	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Glucocorticoids	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People who have undergone endoscopic sphincterotomy for gallstone related complications	Early cholecystectomy	Delayed or no cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Antibiotic prophylaxis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Day surgery	Overnight stay	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing day surgery laparoscopic cholecystectomy	Anaesthetic regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones undergoing laparoscopic cholecystectomy	Per-operative endoscopic sphincterotomy	Pre-operative endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stenosis	Magnetic resonance cholangiopancreatography	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected bile duct stones	Endoscopic ultrasound	Magnetic resonance cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Endoscopic retrograde cholangiopancreatography	Intraoperative cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Liver function tests	Transabdominal ultrasound	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Pre-operative biliary stenting	No stenting	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated amoebic liver abscess	Percutaneous procedure plus metronidazole	Metronidazole alone	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver tumours	Liver resection	No liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Sphincterotomy	No sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with cirrhosis	Colchicine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with blunt liver injury	Non-surgical treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Surgical treatment	Endoscopic intervention	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Lifestyle: Diets for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Pharmacological interventions for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Sphincteroplasty	Sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Non-steroidal anti-inflammatory drugs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis D	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure vaccines	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
General population	Immunisation against Hepatitis A	No immunisation	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure immunoglobulins	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary stent	Ursodeoxycholic acid to prevent stent occlusion	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Healthcare professionals	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

Pregnant women with Hepatitis B	Immunoglobulins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Newborns of HBSAg (hepatitis B surface antigen) positive mothers	Immunisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Asymptomatic Hepatitis B carriers	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Acupuncture	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
General population	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Lamivudine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with HIV infection	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People who have received Hepatitis B vaccination	Booster dose	No booster dose	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with renal failure	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and peripheral neuropathy	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People in haemodialysis units	Isolation to prevent Hepatitis C transmission	No isolation	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and HIV	Antiviral treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis C	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Caesarean section	Vaginal delivery	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C with vasculitis	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Staging of liver disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Biphosphonates	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Hormonal replacement therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with bleeding oesophageal varices	People with portosystemic shunt	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatorenal syndrome	Terlipressin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatorenal syndrome	Transjugular intrahepatic portosystemic shunts	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing common bile duct exploration	T-tube	No T-tube	1. Mortality. 2. HRQoL. 3. Complications.
People with acute calculous cholecystitis (high risk)	Percutaneous cholecystostomy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Enhanced recovery protocols	Standard intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Perfusion techniques in donor	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
New-borns and infants receiving parenteral nutrition and jaundice	Pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

New-borns and infants receiving parenteral nutrition and jaundice	Alternate interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with sickle cell disease and intrahepatic cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Human recombinant activated factor VII	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Vitamin K	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Antifibrinolytic amino acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Antioxidant supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Vitamin D supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Lifestyle: Nutritional support	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with adverse events related to chemoarterial embolisation for primary liver cancer	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated hepatic hydatid cysts	Percutaneous needle aspiration, injection, and re-aspiration with benzimidazole	Percutaneous needle aspiration, injection, and re-aspiration without benzimidazole	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder cancer	Chemotherapy	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with acute or acute-on-chronic liver failure	Granulocyte-colony stimulating factor	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Early laparoscopic cholecystectomy following endoscopic sphincterotomy	Delayed laparoscopic cholecystectomy following endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.

People with gallstones and common-bile duct stones	Model of service delivery	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Routine intraoperative cholangiography	selective cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstone pancreatitis	Early cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Non-pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary obstruction due to cholangiocarcinoma	Endoscopic bipolar radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile leak	Magnetic resonance cholangiopancreatography	Endoscopic retrograde cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with cholangitis	Antibiotics	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected focal liver lesions	Imaging modalities to distinguish focal liver lesions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver cancer who have undergone surgery	Optimal follow-up regimen to detect early recurrence	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver and bile duct resection	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallbladder polyp	Imaging modalities to confirm diagnosis of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder polyp	Imaging modalities to distinguish nature of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallstones	Methods to confirm diagnosis of gallstone	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected acute cholecystitis	Methods to confirm diagnosis of acute cholecystitis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected gallbladder dyskinesia	Methods to confirm gallbladder dyskinesia	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected Sphincter of Oddi dysfunction	Methods to confirm Sphincter of Oddi dysfunction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for liver cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Imaging modalities to confirm that cancer is limited to liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Bridging ablative therapies	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Goal-directed therapy	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Direct access surgery (without seeing a specialist)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver and gallbladder conditions	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Pharmacological interventions	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Psychological counselling	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People with biliary stricture	Different diagnostic tests	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Routine magnetic resonance cholangio pancreatography	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver and gallbladder disorders	Methods to improve understanding of evidence	Not applicable	1.Improved knowledge. 2. Better involvement in decision making.
People undergoing liver transplantation	Routine fat-assessment in donor livers	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD and obesity	Routine anti-obesity surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with severe polycystic liver disease	Pharmacological interventions to improve functional volume	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Interventions to achieve palliation	Not applicable	1. Palliation.

People with liver disease	Interventions to achieve symptom control	Not applicable	Symptom control
People with liver disease	Interventions to improve quality of life	Not applicable	Quality of life
Healthcare professionals dealing with people with primary sclerosing cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with Crohn's disease	Methods for screening for primary sclerosing cholangitis	Not applicable	Diagnosis of primary sclerosing cholangitis
People with NAFLD	Patient education	Standard care	1. Greater knowledge.
Healthcare professionals dealing with people with polycystic liver disease	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with polycystic liver disease	Early liver transplantation	Standard care	1. Quality of life. 2. Reducing symptoms. 3. Reducing pain.
People with autoimmune hepatitis	Interventions that affect T cells	No intervention	1. Cure. 2. Improve quality of life

People at risk of liver disease	Screening	Not applicable	Early diagnosis and treatment
People with polycystic liver disease	Monitoring polycystic liver disease	Not applicable	
People with polycystic kidney disease	Diagnosis polycystic liver disease	Not applicable	
People with liver disease	Methods to improve early appropriate treatment	Not applicable	Early diagnosis and treatment
People with polycystic kidney disease	Methods to prevent symptomatic polycystic liver disease	Not applicable	1. Quality of life. 2. Liver function.
People undergoing liver transplantation	Various treatments	Not applicable	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work 6. Improvement of symptoms
People with polycystic liver disease	Diet (specifically soy proteins which contain oestrogen	Standard diet	1. Decrease size of cyst or preventing cysts to enlarge. 2. Decrease symptoms

People with NAFLD	Various treatments	Not applicable	1. Impact on health (no further details) 2. Progression to liver failure
People with suspected NAFLD	Diagnosis	Not applicable	1. Early diagnosis
People with gallstones	Various treatments	Not applicable	1. Impact on health (no further details)
People with polycystic liver disease	Genetic treatments	Standard therapy	1. Reduce symptoms. 2. Decrease occurrence and size of cysts. 3. Increased longevity
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People undergoing treatment for ulcerative colitis	Various treatments	Not applicable	1. Adverse events related to liver
People with cholangiocarcinoma	Liver transplantation	Standard therapy	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People undergoing liver transplantation	Machine perfusion of donor organ	Cold storage	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver cancer	Novel treatments (irreversible electropolation, high intensity focused ultrasound)		1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with hepatocellular carcinoma	Liver resection	Liver transplantation	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with colorectal liver metastases	Ablation	Surgery	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Ischaemic preconditioning	No IPC	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Remote ischaemic preconditioning	No RIPC	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Goal-directed therapy	standard fluid treatment	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with compensated liver cirrhosis	Treatments (in particular statins)	Other interventions	1. Decompensation 2. Survival 3. Side effects 4. Quality of life.
People with chronic liver disease/ liver failure	Stem cell therapy	Standard therapy	1. Graft and patient survival 2. QoL. 3. Morbidity compared to conventional transplantation 4. Patient reported outcomes

People with Wilson's disease (and other rare non-alcohol liver related diseases)	Various treatments	Not applicable	Not stated
People with suspected autoimmune hepatitis	Diagnosis of autoimmune diseases	Not applicable	1. Costs of management

Appendix 2 List of unanswered research questions ('uncertainties') prioritised during the interim prioritisation

1. What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?
2. Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?
3. Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?
4. Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?
5. What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?
6. What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?
7. Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?

8. Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?
9. Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?
10. What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?
11. Should the methods used to assess nutrition of patients in liver disease be standardised?
12. Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?
13. Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?
14. What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?
15. Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?
16. What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?
17. What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?
18. Do statins (or other treatments) delay liver failure in people with advanced liver disease?
19. What are the best treatments that provide temporary symptom relief in people with advanced liver disease?
20. Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?

21. What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?
22. Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?
23. What are the best nutritional interventions in people undergoing liver transplantation?
24. What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?
25. Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?
26. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?
27. Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?
28. What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?
29. Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?
30. Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?
31. Is surgery (in the form of removal of gallbladder) required in people with gallstones?
32. Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis (NASH) receive additional education about the condition?
33. What is the best immunosuppressive regimen in adults undergoing liver transplantation?

34. Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangiopancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?
35. How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly follows medical advice) in people with liver disease?
36. What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?
37. What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?
38. Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?
39. What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?
40. Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or without chemotherapy drugs) effective in the treatment of people with liver metastases?
41. Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete hormones and nervous system) undergo liver resection?
42. What are the best methods available to decrease blood loss during liver resection?
43. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?
44. What are the best treatments for people with polycystic liver disease?
45. Should the healthcare professionals dealing with childhood liver diseases be provided additional education about childhood liver diseases compared to standard education where childhood diseases are learnt as part of overall education?

46. What is the best immunosuppressive regimen in children undergoing liver transplantation?
47. Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?
48. What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent reinfection with chronic hepatitis B virus (HBV) infection?

Appendix 3 Next step to address the top 10 uncertainty based on current best evidence (detailed)

Treatment uncertainty (Research question)	High-quality systematic review[a]	Research recommendations of systematic review	RCTs not included in the systematic review[a,b,c]	Patient-oriented outcomes assessed in trials not included in the systematic review[d]	Next step
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[1]	High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period (approximately five years) are needed.	NCT02169765 NCT02704130 NCT02728193 NCT02243384 NCT00844454 NCT01918683 NCT01570075 NCT01351194	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatments

What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	[2]	An urgent need exists to identify an effective medical treatment for primary sclerosing cholangitis through well-designed RCTs with adequate follow-up that aim to identify differences in outcomes important to people with primary sclerosing cholangitis.	NCT03394781 NCT02605213 NCT02943460 NCT02704364 NCT01688024 NCT02177136 NCT01672853 NCT03035058 NCT03333928	None of the trials include survival, HRQoL as outcomes[e]	High-quality RCTs with clinical outcomes
What are the best treatments that cure or delay the progression (worsening) of non-	[3] (includes only pharmacological interventions)	Further well-designed randomised clinical trials with sufficiently	More than 10 published trials on lifestyle interventions and more than 20 trials	Lifestyle interventions and nutritional supplementation	High-quality systematic reviews on lifestyle interventions (one review) and nutritional

alcohol-related fatty liver disease (NAFLD)?		large sample sizes are necessary.	on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> NCT02605616 NCT01002547 NCT02927314 NCT03291249 NCT03166735 NCT03486899 NCT03061721 NCT02784444 NCT02077374 NCT03486912	Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver disease (11 trials), mortality (2 trials), cirrhosis (2 trials), cardiovascular events (2 trials)[e]	supplementation to cure or delay the progression of NAFLD and high-quality RCTs on pharmacological interventions with clinical outcomes

			NCT02854605 NCT01963845 NCT03437720 NCT02684591 NCT02787304 NCT02466516 NCT02633956 NCT03008070 NCT03205150 NCT02923154 NCT02913105 NCT01899859 NCT02548351 NCT03053063 NCT03053050 NCT02413372		

			NCT02443116 NCT01464801 NCT03449446 NCT02912260 NCT02856555 NCT02704403 NCT01617772 NCT02217475 NCT01406704 NCT03248882 NCT01051219 NCT02316717 NCT02970942 NCT03439254 NCT02574325 NCT01703260		

			NCT01260246 NCT02960204		
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[4] (covers only maintenance immunosuppression)	Future randomised clinical trials should be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid postrandomisation dropouts or planned cross-overs; and use clinically important outcomes such as	<u>Induction immunosuppression</u> More than 20 published trials <u>Maintenance immunosuppression</u> NCT01998789 NCT01230502 NCT02909335 NCT00286871	<u>Induction immunosuppression</u> Not applicable as there is no high quality systematic review <u>Maintenance immunosuppression</u> Graft survival (1 trial) Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance immunosuppression with important clinical outcomes

		mortality, graft loss, renal impairment, chronic kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups. Moreover, such trials ought to be designed in such a way as to ensure low risk of bias and low risks of random errors.			
Should general public be educated about non-alcohol-related	None	-	None	-	High-quality RCTs on education to prevent NAFLD

fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?					
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	-	[5-7] NCT02050646 NCT02463331 NCT00608894 NCT02900443 NCT02239562 NCT01170351 NCT03217422 NCT01661842 NCT00687180 NCT01980745 NCT02878863	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes

			NCT02936596		
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH				
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine	None	-	NCT02775162 NCT03124641 NCT02940600 NCT02584283 NCT01317342	Overall survival (4 trials), graft survival (5 trials), health-related quality of life (2 trials)	Await results of the RCTs (all expected to complete by the end of 2019) and perform a high quality systematic review.

perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?					
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[8]	Further well-designed randomised clinical trials are necessary. Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the	NCT02937012 NCT01473524 NCT02823353 NCT02135536 NCT01614405 NCT02609048 NCT00746486 NCT02955602 NCT03226067	Health-related quality of life (5 trials), relief of symptoms (5 trials)[e]	High-quality RCTs with clinical outcomes

		clinic rather than in highly selected participants; employ blinding; avoid post-randomisation dropouts or planned cross-overs; should have sufficient follow-up period (e.g. five or 10 years or more); and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated	NCT03112681 NCT01904058 NCT02943447 NCT03124108 NCT03345589 NCT03092765 NCT03394924 NCT02516605 NCT03253276 NCT02965911 NCT01899703 NCT01654731 NCT02308111 NCT00125281 NCT02701166		

		cirrhosis, and liver transplantation. Alternatively, very large groups of participants should be randomised to facilitate shorter trial duration.			
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above) reported on liver fibrosis.				

a Numbers indicate the reference number.

b Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

c NCT followed by a number indicates trial registration number

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

Appendix 4 Scores obtained by each question in the different Delphi rounds

Questions[a]	**Delphi 1: Proportion who rated this question as highly important**	**Delphi 1: Median (IQR)**	**Delphi 2: Proportion who rated this question as highly important**	**Delphi 2: Median (IQR)**	**Delphi 3: Proportion who rated this question as highly important**	**Delphi 3: Median (IQR)**	**Consensus reached in Delphi 3?**[b]

1.What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	All: 78.8% HCP: 80.0% PCP: 76.9%	All: 8(7,9) HCP: 8.5(7,9) PCP: 8(6.5,9)	All: 83.9% HCP: 83.3% PCP: 84.6%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	All: 93.3% HCP: 94.1% PCP: 92.3%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	Yes
2.Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?	All: 44.4% HCP: 40.0% PCP: 50.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(4,7.75)	All: 35.3% HCP: 27.8% PCP: 43.8%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7.75)	All: 33.3% HCP: 29.4% PCP: 37.5%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7.75)	No
3.Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?	All: 46.9% HCP: 40.0% PCP: 58.3%	All: 6(5,9) HCP: 6(5,9) PCP: 6(5,9)	All: 50.0% HCP: 38.9% PCP: 66.7%	All: 6.5(5.75,8) HCP: 6(5.75,7.25) PCP: 6.5(5.25,9)	All: 44.8% HCP: 35.3% PCP: 58.3%	All: 6(6,7.5) HCP: 6(5.5,7) PCP: 6(6,9)	No

4.Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	All: 59.4% HCP: 55.0% PCP: 66.7%	All: 7.5(5,8.75) HCP: 7.5(4.25,8) PCP: 7.5(6,9)	All: 70.0% HCP: 61.1% PCP: 83.3%	All: 7.5(6,9) HCP: 7.5(4.75,8.25) PCP: 7.5(7,9)	All: 72.4% HCP: 64.7% PCP: 83.3%	All: 7(6,9) HCP: 7(5,8) PCP: 7(7,9)	No
5.What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	All: 76.5% HCP: 75.0% PCP: 78.6%	All: 8(6.75,9) HCP: 8.5(6.25,9) PCP: 8(6.75,9)	All: 87.5% HCP: 83.3% PCP: 92.9%	All: 8.5(7,9) HCP: 8.5(7,9) PCP: 8.5(7,9)	All: 90.3% HCP: 88.2% PCP: 92.9%	All: 9(8,9) HCP: 9(7.5,9) PCP: 9(7.75,9)	Yes
6.What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?	All: 48.5% HCP: 45.0% PCP: 53.8%	All: 6(5,7.5) HCP: 6(5,7) PCP: 6(5.5,8)	All: 48.4% HCP: 38.9% PCP: 61.5%	All: 6(5,7) HCP: 6(4.75,7) PCP: 6(6,8)	All: 50.0% HCP: 41.2% PCP: 61.5%	All: 6.5(5,7) HCP: 6(4.5,7) PCP: 6.5(6,8)	No

7.Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?	All: 48.6% HCP: 30.0% PCP: 73.3%	All: 6(5,8) HCP: 6(3,7) PCP: 6(6,9)	All: 54.5% HCP: 33.3% PCP: 80.0%	All: 7(5.5,8) HCP: 6(4,7) PCP: 7(7,9)	All: 56.3% HCP: 29.4% PCP: 86.7%	All: 7(6,8) HCP: 6(4,7) PCP: 7(7,9)	No
8.Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?	All: 37.1% HCP: 21.1% PCP: 56.3%	All: 6(4,7) HCP: 4(4,6) PCP: 6(6,9)	All: 39.4% HCP: 23.5% PCP: 56.3%	All: 6(4,7) HCP: 5(4,6.5) PCP: 6(6,9)	All: 37.5% HCP: 18.8% PCP: 56.3%	All: 6(4.25,7.75) HCP: 5(4,6) PCP: 6(6,8.75)	No
9.Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?	All: 38.2% HCP: 25.0% PCP: 57.1%	All: 6(4,8) HCP: 5(4,6.75) PCP: 6(5,9)	All: 46.9% HCP: 27.8% PCP: 71.4%	All: 6(4,8) HCP: 5(4,7) PCP: 6(5,9)	All: 48.4% HCP: 29.4% PCP: 71.4%	All: 6(5,8) HCP: 6(4.5,7) PCP: 6(5,9)	No
10.What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	All: 76.5% HCP: 75.0% PCP: 78.6%	All: 8(6.75,9) HCP: 7(6.25,9)	All: 87.5% HCP: 88.9% PCP: 85.7%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	All: 93.5% HCP: 94.1% PCP: 92.9%	All: 8(7,9) HCP: 8(7,9)	Yes

		PCP: 8(6.75,9)				PCP: 8(7.75,9)	
11.Should the methods used to assess nutrition of patients in liver disease be standardised?	All: 57.1% HCP: 60.0% PCP: 53.3%	All: 7(5,9) HCP: 7(5,8.75) PCP: 7(5,9)	All: 54.5% HCP: 55.6% PCP: 53.3%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,9)	All: 59.4% HCP: 58.8% PCP: 60.0%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,8)	No
12.Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?	All: 48.6% HCP: 38.1% PCP: 62.5%	All: 6(4,8) HCP: 6(3,8) PCP: 6(5.25,7)	All: 44.1% HCP: 27.8% PCP: 62.5%	All: 6(4,7.25) HCP: 6(3.75,7.25) PCP: 6(5.25,7.75)	All: 48.5% HCP: 29.4% PCP: 68.8%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5.25,7)	No
13.Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	All: 72.2% HCP: 75.0% PCP: 68.8%	All: 7.5(6,9) HCP: 8(6.25,9) PCP: 7.5(6,9)	All: 73.5% HCP: 72.2% PCP: 75.0%	All: 8(6,9) HCP: 7.5(5.75,9) PCP: 8(6.25,9)	All: 81.8% HCP: 82.4% PCP: 81.3%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	Yes

14.What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?	All: 48.5% HCP: 35.0% PCP: 69.2%	All: 6(4.5,7) HCP: 6(4,7) PCP: 6(5,7.5)	All: 48.4% HCP: 27.8% PCP: 76.9%	All: 6(5,7) HCP: 6(4,7) PCP: 6(6,8)	All: 50.0% HCP: 29.4% PCP: 76.9%	All: 6.5(5,7) HCP: 6(4.5,7) PCP: 6.5(6.5,8)	No
15.Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?	All: 19.4% HCP: 21.1% PCP: 16.7%	All: 5(4,6) HCP: 5(4,6) PCP: 5(4,6)	All: 20.0% HCP: 16.7% PCP: 25.0%	All: 5(4,6) HCP: 5(3.75,6) PCP: 5(4,6.75)	All: 20.7% HCP: 17.6% PCP: 25.0%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,6.75)	No
16.What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?	All: 37.1% HCP: 35.0% PCP: 40.0%	All: 5(4,8) HCP: 5.5(4,7) PCP: 5(4,8)	All: 27.3% HCP: 22.2% PCP: 33.3%	All: 6(4,7) HCP: 6(4,6.25) PCP: 6(3,8)	All: 28.1% HCP: 23.5% PCP: 33.3%	All: 5(4,7) HCP: 5(5,6.5) PCP: 5(3,7)	No

17.What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	All: 67.6% HCP: 71.4% PCP: 61.5%	All: 8(5,8.25) HCP: 8(5.5,9) PCP: 8(5,8)	All: 71.0% HCP: 77.8% PCP: 61.5%	All: 8(6,9) HCP: 7.5(6.75,9) PCP: 8(5,8.5)	All: 76.7% HCP: 82.4% PCP: 69.2%	All: 8(6.75,9) HCP: 8(7,9) PCP: 8(5,8.5)	No
18.Do statins (or other treatments) delay liver failure in people with advanced liver disease?	All: 45.7% HCP: 36.8% PCP: 56.3%	All: 6(5,7) HCP: 6(4,7) PCP: 6(6,7.75)	All: 39.4% HCP: 35.3% PCP: 43.8%	All: 6(6,7) HCP: 6(3.5,7) PCP: 6(6,7.75)	All: 43.8% HCP: 37.5% PCP: 50.0%	All: 6(6,7) HCP: 6(5.25,7) PCP: 6(6,7.75)	No
19.What are the best treatments that provide temporary symptom relief in people with advanced liver disease?	All: 50.0% HCP: 35.0% PCP: 68.8%	All: 6.5(5,7.75) HCP: 6(5,7) PCP: 6.5(5.25,8.75)	All: 52.9% HCP: 33.3% PCP: 75.0%	All: 7(5.75,7.25) HCP: 6(5,7) PCP: 7(6.25,8)	All: 54.5% HCP: 35.3% PCP: 75.0%	All: 7(6,7) HCP: 6(5,7) PCP: 7(6.25,8)	No

20.Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?	All: 64.7% HCP: 70.0% PCP: 57.1%	All: 7(5,8) HCP: 7(6,8) PCP: 7(5,8)	All: 68.8% HCP: 72.2% PCP: 64.3%	All: 7(5.25,8) HCP: 7(6,8) PCP: 7(5,8)	All: 67.7% HCP: 70.6% PCP: 64.3%	All: 7(5,8) HCP: 7(6,8) PCP: 7(5,8)	No
21.What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	All: 75.8% HCP: 68.4% PCP: 85.7%	All: 7(6.5,9) HCP: 7(6,8) PCP: 7(7,9)	All: 81.3% HCP: 77.8% PCP: 85.7%	All: 7.5(7,9) HCP: 7(6.75,8) PCP: 7.5(7,9)	All: 80.6% HCP: 76.5% PCP: 85.7%	All: 8(7,9) HCP: 7(6.5,8) PCP: 8(7,9)	Yes
22.Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?	All: 53.1% HCP: 36.8% PCP: 76.9%	All: 7(5,8) HCP: 6(5,7) PCP: 7(6.5,8)	All: 60.0% HCP: 47.1% PCP: 76.9%	All: 7(5,8) HCP: 6(5,8) PCP: 7(6.5,8)	All: 58.6% HCP: 43.8% PCP: 76.9%	All: 7(5,8) HCP: 6(5,7.75) PCP: 7(6.5,8)	No
23.What are the best nutritional interventions in people undergoing liver transplantation?	All: 52.8% HCP: 42.9% PCP: 66.7%	All: 7(5,8) HCP: 6(4,8) PCP: 7(5,8)	All: 51.5% HCP: 38.9% PCP: 66.7%	All: 7(5,8) HCP:	All: 53.1% HCP: 41.2% PCP: 66.7%	All: 7(5,8) HCP: 6(5,7) PCP: 7(6,8)	No

				6(4,7.25) PCP: 7(5,8)			
24.What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?	All: 61.8% HCP: 45.0% PCP: 85.7%	All: 7(6,8) HCP: 6(3.25,7) PCP: 7(7,9)	All: 65.6% HCP: 50.0% PCP: 85.7%	All: 7(6,8) HCP: 6.5(3.75,7) PCP: 7(7,9)	All: 64.5% HCP: 47.1% PCP: 85.7%	All: 7(6,8) HCP: 6(4,7) PCP: 7(7,9)	No
25.Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	All: 54.5% HCP: 42.1% PCP: 71.4%	All: 7(5,9) HCP: 6(5,8) PCP: 7(6,9)	All: 68.8% HCP: 61.1% PCP: 78.6%	All: 7(6,8.75) HCP: 7(5,8) PCP: 7(6.75,9)	All: 74.2% HCP: 70.6% PCP: 78.6%	All: 7(6,9) HCP: 7(6,8) PCP: 7(6.75,9)	No

26.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?	All: 42.4% HCP: 42.9% PCP: 41.7%	All: 6(2,8) HCP: 5(1,8) PCP: 6(4.25,7.75)	All: 40.0% HCP: 44.4% PCP: 33.3%	All: 5.5(2,7) HCP: 4.5(1,8) PCP: 5.5(4.25,7)	All: 37.9% HCP: 47.1% PCP: 25.0%	All: 5(2,7) HCP: 5(1,8) PCP: 5(4.25,6.75)	No
27.Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?	All: 51.4% HCP: 52.4% PCP: 50.0%	All: 7(4,8) HCP: 7(4.5,7.5) PCP: 7(3.25,8.75)	All: 58.8% HCP: 50.0% PCP: 68.8%	All: 7(4,7.25) HCP: 6.5(4,7) PCP: 7(4,8.75)	All: 57.6% HCP: 47.1% PCP: 68.8%	All: 7(4,8) HCP: 6(4,7) PCP: 7(4,8)	No
28.What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	All: 61.8% HCP: 60.0% PCP: 64.3%	All: 7(5.75,8) HCP: 7(6,8) PCP: 7(5,8)	All: 68.8% HCP: 66.7% PCP: 71.4%	All: 7(6,8) HCP: 7(5.75,8) PCP: 7(5.75,8.25)	All: 74.2% HCP: 70.6% PCP: 78.6%	All: 7(6,8) HCP: 7(6,8) PCP: 7(6.5,8.25)	No

29.Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?	All: 38.2% HCP: 35.0% PCP: 42.9%	All: 5(4,8) HCP: 4.5(3,7.75) PCP: 5(4,8)	All: 31.3% HCP: 27.8% PCP: 35.7%	All: 5(4,7) HCP: 4(3,7) PCP: 5(4,7.25)	All: 25.8% HCP: 23.5% PCP: 28.6%	All: 5(4,7) HCP: 4(3.5,6.5) PCP: 5(4,7)	No
30.Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?	All: 35.5% HCP: 27.8% PCP: 46.2%	All: 5(4,7) HCP: 5(2.75,7) PCP: 5(4,7.5)	All: 22.6% HCP: 11.1% PCP: 38.5%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,7)	All: 20.0% HCP: 11.8% PCP: 30.8%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,7)	No
31.Is surgery (in the form of removal of gallbladder) required in people with gallstones?	All: 24.2% HCP: 23.8% PCP: 25.0%	All: 5(4,6.5) HCP: 5(4,6.5) PCP: 5(4.25,6.75)	All: 30.0% HCP: 33.3% PCP: 25.0%	All: 5(4,7) HCP: 5(4,7) PCP: 5(3.5,6.75)	All: 24.1% HCP: 29.4% PCP: 16.7%	All: 5(4.5,6.5) HCP: 5(4.5,7) PCP: 5(3.5,6)	No
32.Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis	All: 52.9% HCP: 50.0% PCP: 57.1%	All: 7(4,8) HCP:	All: 56.3% HCP: 50.0% PCP: 64.3%	All: 7(4.25,8) HCP: 6.5(2,7.25)	All: 54.8% HCP: 47.1% PCP: 64.3%	All: 7(5,8) HCP: 6(4,7.5)	No

(NASH) receive additional education about the condition?		6.5(2.5,7.75) PCP: 7(4,9)		PCP: 7(5.75,8.25)		PCP: 7(5.75,8.25)	
33.What is the best immunosuppressive regimen in adults undergoing liver transplantation?	All: 73.5% HCP: 60.0% PCP: 92.9%	All: 7(6,9) HCP: 7(5,8) PCP: 7(7,9)	All: 84.4% HCP: 77.8% PCP: 92.9%	All: 8(7,9) HCP: 7(6.5,8) PCP: 8(7,9)	All: 90.3% HCP: 82.4% PCP: 100.0%	All: 8(7,9) HCP: 8(7,8) PCP: 8(7.75,9)	Yes
34.Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangio pancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?	All: 36.7% HCP: 22.2% PCP: 58.3%	All: 5(4,7) HCP: 4(3.75,6.25) PCP: 5(5,7)	All: 30.0% HCP: 22.2% PCP: 41.7%	All: 5(4,7) HCP: 5(4,6.25) PCP: 5(5,7)	All: 20.7% HCP: 11.8% PCP: 33.3%	All: 5(4,6) HCP: 5(4,6) PCP: 5(5,7)	No
35.How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly	All: 67.6% HCP: 75.0% PCP: 57.1%	All: 7(5,8) HCP: 7(6.25,8)	All: 69.7% HCP: 72.2% PCP: 66.7%	All: 7(5,8) HCP: 7(4.75,8) PCP: 7(5,8)	All: 71.9% HCP: 70.6% PCP: 73.3%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,8)	No

follows medical advice) in people with liver disease?		PCP: 7(4.75,8)					
36.What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?	All: 51.6% HCP: 36.8% PCP: 75.0%	All: 7(5,8) HCP: 6(4,7) PCP: 7(5.5,8.75)	All: 56.7% HCP: 44.4% PCP: 75.0%	All: 7(5,8) HCP: 6(4.75,7) PCP: 7(6.25,8.75)	All: 55.2% HCP: 41.2% PCP: 75.0%	All: 7(6,8) HCP: 6(5.5,7) PCP: 7(6.25,9)	No
37.What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?	All: 50.0% HCP: 45.0% PCP: 57.1%	All: 6.5(5,7) HCP: 6(5,7) PCP: 6.5(5,7.25)	All: 43.8% HCP: 33.3% PCP: 57.1%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,8)	All: 41.9% HCP: 29.4% PCP: 57.1%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,8)	No
38.Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?	All: 54.3% HCP: 45.0% PCP: 66.7%	All: 7(5,8) HCP: 6(4.25,7.75) PCP: 7(5,8)	All: 51.5% HCP: 38.9% PCP: 66.7%	All: 7(4.5,8) HCP: 5(3.5,7.25) PCP: 7(5,8)	All: 53.1% HCP: 35.3% PCP: 73.3%	All: 7(5,7.75) HCP: 5(4,7) PCP: 7(5,8)	No

39.What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?	All: 38.7% HCP: 25.0% PCP: 63.6%	All: 6(4,7) HCP: 5(4,6.75) PCP: 6(6,8)	All: 31.0% HCP: 27.8% PCP: 36.4%	All: 6(4.5,7) HCP: 5(4,7) PCP: 6(6,8)	All: 27.6% HCP: 23.5% PCP: 33.3%	All: 6(5,7) HCP: 5(4.5,6.5) PCP: 6(5.25,7)	No
40.Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or without chemotherapy drugs) effective in the treatment of people with liver metastases?	All: 40.6% HCP: 36.8% PCP: 46.2%	All: 6(4,8) HCP: 6(3,8) PCP: 6(5,8.5)	All: 34.4% HCP: 22.2% PCP: 50.0%	All: 6(4,7) HCP: 5.5(3,6.25) PCP: 6(5,7)	All: 32.3% HCP: 23.5% PCP: 42.9%	All: 6(5,7) HCP: 6(3.5,6.5) PCP: 6(5,7)	No
41.Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete	All: 36.7% HCP: 31.6% PCP: 45.5%	All: 6(4,7.25) HCP: 6(4,7) PCP: 6(5,8)	All: 40.0% HCP: 38.9% PCP: 41.7%	All: 6(4.75,7.25) HCP: 6(4,7) PCP: 6(5.25,8)	All: 37.9% HCP: 41.2% PCP: 33.3%	All: 6(5.5,7) HCP: 6(5,7) PCP: 6(5.25,8)	No

hormones and nervous system) undergo liver resection?							
42.What are the best methods available to decrease blood loss during liver resection?	All: 43.8% HCP: 26.3% PCP: 69.2%	All: 6(5,7.75) HCP: 5(3,7) PCP: 6(6,8)	All: 48.4% HCP: 27.8% PCP: 76.9%	All: 6(5,8) HCP: 5.5(4,7) PCP: 6(6.5,8)	All: 46.7% HCP: 29.4% PCP: 69.2%	All: 6(5,7.25) HCP: 6(5,7) PCP: 6(6,8)	No
43.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?	All: 51.6% HCP: 42.1% PCP: 66.7%	All: 7(4,8) HCP: 6(4,7) PCP: 7(6,8)	All: 46.7% HCP: 38.9% PCP: 58.3%	All: 6(4.75,7.25) HCP: 5.5(4,7) PCP: 6(6,8)	All: 48.3% HCP: 41.2% PCP: 58.3%	All: 6(5,7.5) HCP: 6(4.5,7) PCP: 6(6,8)	No
44.What are the best treatments for people with polycystic liver disease?	All: 39.3% HCP: 17.6% PCP: 72.7%	All: 6(4,8) HCP: 5(4,6) PCP: 6(6,8)	All: 34.5% HCP: 16.7% PCP: 63.6%	All: 6(4,8) HCP: 5(3.75,6) PCP: 6(6,8)	All: 35.7% HCP: 17.6% PCP: 63.6%	All: 6(5,7) HCP: 5(4,6) PCP: 6(6,7)	No
45.Should the HCP dealing with childhood liver diseases be provided additional education about childhood liver diseases	All: 35.5% HCP: 15.0% PCP: 72.7%	All: 5(3,8) HCP:	All: 37.9% HCP: 16.7% PCP: 72.7%	All: 5(3.5,7.5) HCP:	All: 37.9% HCP: 17.6% PCP: 66.7%	All: 5(4.5,7.5) HCP: 5(2,5.5)	No

compared to standard education where childhood diseases are learnt as part of overall education?		5(2,5.75) PCP: 5(5,9)		5(2,5.25) PCP: 5(6,9)		PCP: 5(6,8.75)	
46.What is the best immunosuppressive regimen in children undergoing liver transplantation?	All: 65.6% HCP: 57.9% PCP: 76.9%	All: 8(4.25,9) HCP: 7(4,8) PCP: 8(6,9)	All: 67.7% HCP: 61.1% PCP: 76.9%	All: 8(6,9) HCP: 7.5(4,8) PCP: 8(6.5,9)	All: 70.0% HCP: 64.7% PCP: 76.9%	All: 8(6,9) HCP: 8(5,8) PCP: 8(6.5,9)	No
47.Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?	All: 31.0% HCP: 11.1% PCP: 63.6%	All: 6(4,7) HCP: 5(2.75,6) PCP: 6(5,7)	All: 26.7% HCP: 11.1% PCP: 50.0%	All: 5.5(4,7) HCP: 5(3.75,6) PCP: 5.5(5.25,7.75)	All: 27.6% HCP: 11.8% PCP: 50.0%	All: 6(5,7) HCP: 5(4,6) PCP: 6(5.25,7)	No
48.What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent	All: 46.9% HCP: 40.0% PCP: 58.3%	All: 6(3.5,7) HCP: 6(3,7) PCP: 6(6,8)	All: 36.7% HCP: 22.2% PCP: 58.3%	All: 6(3,7) HCP: 6(2.75,6.25)	All: 37.9% HCP: 23.5% PCP: 58.3%	All: 6(5,7) HCP: 6(4,6.5) PCP: 6(6,7.75)	No

reinfection with chronic hepatitis B virus (HBV) infection?				PCP: 6(6,7.75)			
49.Are there alternatives to steroids in treating people with autoimmune hepatitis (AIH)?	-	-	All: 51.9% HCP: 40.0% PCP: 66.7%	All: 7(5,8) HCP: 6(4,7) PCP: 7(6,9)	All: 50.0% HCP: 35.7% PCP: 66.7%	All: 6.5(5,8) HCP: 5.5(3.75,7) PCP: 6.5(6,9)	No
50.What impact does the home situation have on recovery from chronic liver disease and its treatment?	-	-	All: 34.5% HCP: 13.3% PCP: 57.1%	All: 5(3.5,7.5) HCP: 4(3,6) PCP: 5(5,8)	All: 32.1% HCP: 0.0% PCP: 64.3%	All: 5(4,7) HCP: 4(3,5.25) PCP: 5(5,8)	No
51.Does cure of hepatitis C provide benefits to the patient outside reduction in liver related complications?	-	-	All: 29.2% HCP: 33.3% PCP: 22.2%	All: 5.5(3.25,7) HCP: 5(3,7) PCP: 5.5(4.5,6.5)	All: 30.4% HCP: 35.7% PCP: 22.2%	All: 6(4,7) HCP: 5.5(3,7.25) PCP: 6(4.5,6.5)	No

52.How fast does liver fibrosis (scarring) actually progress in non-alcoholic liver disease patients and does this predict overall outcome?	-	-	All: 62.1% HCP: 40.0% PCP: 85.7%	All: 7(6,8) HCP: 6(5,8) PCP: 7(7,8.25)	All: 64.3% HCP: 42.9% PCP: 85.7%	All: 7.5(6,8) HCP: 6(5,8) PCP: 7.5(7,8.25)	No
53.Should direct-acting antiviral treatments therapies be made more easily accessible to GPs and drug service clinics for treatment of hepatitis C virus?	-	-	All: 50.0% HCP: 46.7% PCP: 55.6%	All: 6.5(3.5,7) HCP: 6(3,7) PCP: 6.5(5.5,8)	All: 52.2% HCP: 50.0% PCP: 55.6%	All: 7(5,7) HCP: 6.5(4.5,7.25) PCP: 7(5.5,8)	No
54.Should patients diagnosed with liver fibrosis/cirrhosis related to NAFLD (non-alcoholic fatty liver disease) be offered more intensive nutritional support or dietician review?	-	-	All: 60.7% HCP: 46.7% PCP: 76.9%	All: 7(5,8) HCP: 6(3,8) PCP: 7(6.5,9)	All: 63.0% HCP: 50.0% PCP: 76.9%	All: 7(5,8) HCP: 7(4.5,8) PCP: 7(6.5,8.5)	No
55.Why have there been no alternatives to surgery in the form of new drug	-	-	All: 29.2% HCP: 20.0% PCP: 44.4%	All: 4.5(1.25,7) HCP: 4(1,6)	All: 26.1% HCP: 21.4% PCP: 33.3%	All: 4(2,7) HCP:	No

treatments for gall bladder disease & biliary sludge?				PCP: 4.5(2,7.5)		4(1.75,5.5) PCP: 4(2,7.5)	
56.Why is there no proper evidence-based research on nutrition as a way of managing gall bladder disease/biliary sludge?	-	-	All: 36.0% HCP: 26.7% PCP: 50.0%	All: 5(1.5,7) HCP: 4(1,7) PCP: 5(2.5,7.5)	All: 33.3% HCP: 28.6% PCP: 40.0%	All: 5(2,7) HCP: 4.5(1.75,7) PCP: 5(2.5,7.5)	No
57.Why is there such variability in the natural progression of people with primary sclerosing cholangitis: some are very sick and require a transplant whereas others can remain relatively healthy for a long period?	-	-	All: 56.0% HCP: 42.9% PCP: 72.7%	All: 7(6,7) HCP: 6(4,7) PCP: 7(6,8)	All: 54.2% HCP: 38.5% PCP: 72.7%	All: 7(6,7) HCP: 6(4,7) PCP: 7(6,8)	No
58.What are the warning signals that primary sclerosing cholangitis will be aggressive or cancerous?	-	-	All: 57.7% HCP: 53.3% PCP: 63.6%	All: 7(5.75,8.25)	All: 60.0% HCP: 50.0% PCP: 72.7%	All: 7(5.5,8) HCP:	No

				HCP: 7(5,8) PCP: 7(6,9)		6.5(4.75,8) PCP: 7(6,9)	
59.Does information on the impact of the complication on the people's quality of life improve the patient's informed decision- making process about treatment of liver and gallbladder diseases?	-	-	All: 46.4% HCP: 40.0% PCP: 53.8%	All: 6(4,7) HCP: 6(4,7) PCP: 6(4.5,8)	All: 44.4% HCP: 35.7% PCP: 53.8%	All: 6(4,7) HCP: 5.5(4,7) PCP: 6(5,8)	No
60.Will clinical pathways developed with patients and HCP having an equal say result in greater patient satisfaction and health in people with liver and gallbladder diseases?	-	-	All: 44.8% HCP: 33.3% PCP: 57.1%	All: 6(4.5,8) HCP: 5(4,8) PCP: 6(5,8)	All: 46.4% HCP: 35.7% PCP: 57.1%	All: 6(4.25,8) HCP: 5(3.75,8) PCP: 6(5.75,8.25)	No
61.Should high school teenagers be educated about the risks of hepatitis C?	-	-	All: 53.8% HCP: 40.0% PCP: 72.7%	All: 7(3.75,8) HCP: 5(2,7) PCP: 7(6,9)	All: 57.7% HCP: 42.9% PCP: 75.0%	All: 7(4.75,7.25) HCP: 5.5(2,7)	No

						PCP: 7(6.25,8.75)	
62.How can patients with end stage liver failure be better prepared for end of life. How can the HCP supporting them be better prepared to provide that support?	-	-	All: 65.5% HCP: 46.7% PCP: 85.7%	All: 7(6,8) HCP: 6(5,8) PCP: 7(7,9)	All: 67.9% HCP: 50.0% PCP: 85.7%	All: 7(6,8) HCP: 6.5(4.75,8) PCP: 7(7,9)	No
63.Is aggressive control of inflammation on colonic inflammatory bowel disease in primary sclerosing cholangitis associated with improved liver outcomes?	-	-	All: 48.0% HCP: 46.7% PCP: 50.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(6,8)	All: 50.0% HCP: 42.9% PCP: 60.0%	All: 6.5(5.25,7) HCP: 6(5,7) PCP: 6.5(6,8)	No
64.What is the best way to survey for cholangiocarcinoma in primary sclerosing cholangitis?	-	-	All: 61.5% HCP: 60.0% PCP: 63.6%	All: 7(5.75,8) HCP: 7(5,7) PCP: 7(6,9)	All: 60.0% HCP: 57.1% PCP: 63.6%	All: 7(6,8) HCP: 7(5,7) PCP: 7(6,9)	No
65.Should the criteria for polycystic liver disease and transplantation be changed to take into account the size the liver	-	-	All: 29.2% HCP: 13.3% PCP: 55.6%	All: 4.5(2,7) HCP: 4(2,6)	All: 30.4% HCP: 7.1% PCP: 66.7%	All: 6(3,7) HCP: 4(2,6) PCP: 6(6,7.5)	No

cysts can grow and the additional pressures on all the internal organs?				PCP: 4.5(5.5,7)			
66.Does control of colitis at the time of liver transplant reduce the risk of recurrent primary sclerosing cholangitis?	-	-	All: 36.0% HCP: 33.3% PCP: 40.0%	All: 6(5,7) HCP: 6(4,7) PCP: 6(5,8.25)	All: 33.3% HCP: 28.6% PCP: 40.0%	All: 6(5,7) HCP: 6(3.75,7) PCP: 6(5,8.25)	No
67.Are people with liver disease likely to develop other conditions, if so, what other conditions?	-	-	All: 42.9% HCP: 13.3% PCP: 76.9%	All: 6(3.25,7) HCP: 5(2,6) PCP: 6(6.5,8.5)	All: 46.4% HCP: 14.3% PCP: 78.6%	All: 6(3.25,7.75) HCP: 4.5(2,5.25) PCP: 6(6.75,8.25)	No
68.Do people with liver disease have a reduced life expectancy?	-	-	All: 30.0% HCP: 0.0% PCP: 60.0%	All: 5.5(3,8) HCP: 4(1,5) PCP: 5.5(6,9)	All: 34.5% HCP: 0.0% PCP: 66.7%	All: 6(3,8) HCP: 3.5(1.75,5.25	No

						) PCP: 6(6,9)	
69.Should transjugular intrahepatic portosystemic shunt (TIPS) be used earlier in management of variceal haemorrhage?	-	-	All: 51.9% HCP: 53.3% PCP: 50.0%	All: 7(5,7) HCP: 7(5,8) PCP: 7(5,7)	All: 55.6% HCP: 57.1% PCP: 53.8%	All: 7(6,7) HCP: 7(5.75,8) PCP: 7(5.5,7)	No
70.Should abnormal alanine transaminase (ALT) reference ranges be revised downwards in line with ACG (American College of Gastroenterology) guidance?	-	-	All: 36.0% HCP: 33.3% PCP: 40.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7)	All: 37.5% HCP: 35.7% PCP: 44.4%	All: 6(5,7) HCP: 6(4.5,7.25) PCP: 6(5.875,7)	No

a Questions from 49 to 70 were collected during the first round of Delphi.

b Consensus was reached when at least 80% of Delphi-panel members scored between 7 and 9 for the specific question.

Abbreviations:

HCP = Healthcare professionals

IQR = interquartile range

PCP = Patients, carers, and public

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TOP RESEARCH PRIORITIES IN LIVER AND GALLBLADDER DISORDERS IN THE UNITED KINGDOM

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TOP RESEARCH PRIORITIES IN LIVER AND GALLBLADDER DISORDERS IN THE UNITED KINGDOM

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ABSTRACT

Objectives: There is a mismatch between research questions considered important by patients, carers, and healthcare professionals and the research performed in many fields of medicine. The Non-Alcohol-Related Liver and gallbladder disorders Priority setting partnership (NARLIP) was established to identify the top research priorities in the prevention, diagnostic, and treatment of gallbladder disorders and liver disorders not covered by the James-Lind Alliance (JLA) Alcohol-related liver disease (ARLD) Priority Setting Partnership.

Design: The methods broadly followed the principles of the JLA guidebook. The one major deviation from the JLA methodology was the final step of identifying priorities: instead of prioritisation by group discussions at a consensus workshop involving stakeholders, the prioritisation was achieved by a modified Delphi consensus process.

Results: A total of 428 unique valid diagnostic or treatment research questions were identified. A literature review established that none of these questions were considered 'answered' i.e. high quality systematic reviews suggest that further research is not required on the topic. The Delphi panel achieved consensus (at least 80% Delphi panel members agreed) that a research question was a top research priority for six questions. Four additional research questions with highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

Conclusions: A priority setting process involving patients, carers and healthcare professionals has been used to identify the top ten priority areas for research related to liver and gallbladder disorders. Basic, translational, clinical, and public health research are required to address these uncertainties.

Keywords: liver, chronic liver disease

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ARTICLE SUMMARY

Strengths and limitations

- A research prioritisation process involving clinicians, patients and carer, and public representatives was performed in the field of liver and gallbladder disorders. This will help to address the mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in the field of liver and gallbladder disorders.
- A Delphi consensus method was performed. This prevented dominance of 'loud voices', a problematic issue with small and large group discussions.
- Because of the predominance of people with chronic liver disease on the Delphi panel, many of the top research priorities related to chronic liver diseases.

INTRODUCTION

Failure to address treatment uncertainties by research can lead to significant suffering and deaths [1]. It is important that research in any field of medicine takes into account the shared interests of patients, carers and clinicians [2]. However, there is a mismatch between research questions that are considered important jointly by patients, carers, and healthcare professionals and the research performed in many fields of medicine [3 4]. The James Lind Alliance (JLA) exists to help ensure a patient-centred process and enables the limited research resources to be utilised in addressing the research questions that are considered important jointly by patients, carers, and healthcare professionals [2] ('top research priorities'). This is achieved by forming 'Priority Setting Partnerships'

(PSPs) between patients, carers, and healthcare professionals [2]. Formal prioritisation of research topics jointly by patients and healthcare professionals can lead to increased research on the topic [5 6].

There has only been one formal research prioritisation process involving patients, carers, and healthcare professionals in the field of liver and gallbladder disorders [7]. However, the scope of that PSP was limited to alcohol-related liver disorders [7]. The Non-Alcohol-Related Liver and gallbladder disorders Priority setting partnership (NARLIP) was established to address the prevention, diagnostic, and treatment uncertainties related to the majority of liver disorders which were not covered by the JLA PSP on alcohol-related liver diseases (ARLD) [7] and to include gallbladder disease.

The aims and objectives of the NARLIP were to work with patients, their carers, and healthcare professionals treating them ('stakeholders') to identify uncertainties about the diagnostic tests and effects of prevention and treatments for non-alcohol related liver and gallbladder disorders, to agree by consensus a prioritised list of those uncertainties for research, to publicise the results and process, and to take the results to research commissioning bodies to be considered for funding and researchers to encourage them to submit grant applications addressing these uncertainties.

METHODS

The methods broadly followed the principles of the JLA guidebook.[8] The broad steps involved the following and are summarised in Figure 1.

1. Formation of the partnership: organisations and individuals representing people affected by non-alcohol related liver or gallbladder disorders, their carers, and healthcare professionals treating people with non-alcohol related liver and gallbladder disorders. A partnership was formed between KG representing University College London and the British Liver Trust initially, but following reorganisation in the British Liver Trust, PSC Support [9] became the

leading patient organisation partner of this process. A steering committee was formed. The members of the steering committee who participated in the complete process were KG, MW, BRD, CF, BF, AM, RM, SM, IS, and ET.

2. Establishment of the scope: the steering committee members discussed and decided that the scope should include adult and paediatric liver and gallbladder disorders which required medical and surgical treatments. The protocol was registered with James-Lind Alliance Priority Setting Partnership.
3. Identifying potential research questions: research questions were collected through online surveys and searching UK Database of Uncertainties about the Effects of Treatments (UK DUETs), research recommendations in high quality systematic reviews and clinical guidelines, and registers of ongoing research.
4. Refining research questions: the research questions identified in the above step were reviewed and where necessary combined to result in a set of unique research questions. Research questions were considered 'answered' when recent high-quality systematic reviews (based on low risk of bias studies) concluded that further research was not required. Removal of such 'answered' research questions was planned. The remaining questions were 'uncertainties'.
5. Interim prioritisation: To shortlist the set of questions to manageable levels for the final prioritisation process, the members of the steering committee ranked the uncertainties after stratifying the questions as medical and surgical questions. The members of the steering committee agreed that the interim prioritisation list should consist of 75% medical questions and 25% surgical questions. This decision was an arbitrary decision made by the steering committee based on the rationale that majority of individuals with liver and gallbladder disorders are treated medically but a minority require surgery which have a major impact on patients' lives.

6. Final prioritisation by consensus: A modified Delphi consensus method was followed to identify the top priorities using methods described by Jones et al [10]. The Delphi was performed electronically using Excel for managing the process. The steps in the modified Delphi consensus method were as follows.

    a. A Delphi panel consisting of patients, their carers, and healthcare professionals treating them was formed. The Delphi panel was formed by using 'snowballing' sampling methods and by contacting people through emails, online liver patient forums (British Liver Trust Health Unlocked forum), and newsletters. A total of 42 people expressed interest in joining the Delphi panel and 33 panel members completed all three rounds. Details of the Delphi panel composition and drop-outs are reported in the results section.

    b. A total of three rounds were conducted.

    c. Delphi panel members scored the short-listed questions in the interim prioritisation process on a scale of 1 to 9 with 1 being considered least important and 9 being considered most important. Scores of 1 to 3 were categorised as 'less important', 4 to 6 as 'moderately important', and 7 to 9 as 'highly important'. Panel members were requested to score the questions according to the importance of the question to them/the persons that they represent or treat and could leave questions that they were unable to score empty. Each Delphi panel member could add a maximum of two questions in the first round to ensure that the questions most important to the Delphi panel members were included in the prioritisation process even if they were not identified in the earlier steps. In the subsequent rounds, the panel members were shown the summary scores and their previous score for each question. They were able to retain or change their score in each of the rounds after the first round. For calculation of the summary scores and the proportion considering a question 'highly important', non-responses were excluded.

d. Consensus about a specific research question being a top research priority was reached when 80% or more Delphi panel members considered the research question as highly important (allocated scores between 7 and 9).

e. When fewer than 10 research priorities were obtained by consensus, the remaining priorities were completed by uncertainties based on the highest proportions of panel members agreeing that the research question was highly important (scores between 7 and 9).

f. There was no restriction on the Delphi panel to consult others while scoring the questions. However, only one final response on the set of questions was accepted from each Delphi panel member.

When there were no recent high-quality systematic reviews on the research question, we have recommended high-quality systematic reviews. When recent high-quality systematic reviews recommended high-quality research, we have recommended randomised controlled trials for prevention and treatment, as such studies carry the lowest risk of bias if conducted well; we would have recommended well conducted diagnostic test accuracy studies for diagnostic uncertainties. All online surveys were completed using Google Forms designed by KG. The Delphi process was completed using Microsoft Excel and email.

Ethical approval was not deemed necessary because no personal identifiable information was being collected, and the questions were being asked of healthcare professionals, patients and their carers were not considered sensitive questions. In addition, we had full support of patient organisations with involvement of patient representatives throughout the whole process rather than patients visiting the hospitals.

Patient and Public involvement

Patients and public were involved in all aspects of this project: they were part of the steering committee and were involved in the definition of the scope, methodology used for the prioritisation process, identification of further patients and public representatives, participation in the Delphi panel, interpretation, and critical revisions of the draft report. They will be involved in the dissemination of the findings through patient websites, patient forums, and to research funders.

RESULTS

Identification and refining of research uncertainties

A total of 126 patients, carers, and those at risk of developing non-alcohol related liver and gallbladder disorders, and 13 healthcare professionals participated in the first survey which was conducted between July and December 2015. This survey resulted in a total of 209 unique research questions. In addition, 219 unique questions were identified from searching the UK DUETs, Pubmed, and ClinicalTrials.gov on 2nd January 2016. A total of 428 unique valid (i.e. falling within the remit of this priority setting partnership) research questions (247 medical-related and 181 surgery-related) were identified from these sources. None of the research questions had been answered by recent high-quality systematic reviews based on low risk of bias studies which concluded that further research was not required. Therefore, all the 428 research questions were considered research 'uncertainties'. The complete list of 428 unique valid uncertainties in no particular order is available in Online Supplement Appendix 1. This has been converted to the population, intervention, control, and outcomes (PICO) format whenever possible.

Interim priorities

To identify a shortlist of questions (from the list of 429 questions) that were to be considered for the next step, a total of 48 research priorities (36 medical questions and 12 surgical questions) were identified on the basis of being selected by at least one patient or carer and healthcare professional of the steering committee (24 questions) and obtaining the highest ranks among the members of the steering committee (additional 24 questions). The list of 48 questions identified as interim priorities in no particular order is available in Online Supplement Appendix 2.

Final priorities

A total of 42 people expressed interest in joining the Delphi panel and 33 panel members completed all three rounds. Five people dropped out before they returned the scores of the first round (all patients, carers, and general public), three between first and second rounds (all healthcare professionals), and one between the second and third rounds (healthcare professional). Of the 33 panel members who completed all the three rounds, 17 were healthcare professionals and 16 were patients, carers, and general public. Of the 17 healthcare professionals, six were hepatologists, four were surgeons, two were hepatology nurses, and the remaining were general practitioner (GP), HPB surgery (hepato-pancreato biliary) nurse, organ preservation biologist, dietician, and pharmacist (one each). Of the 16 patients, carers, and general public, there was representation from general public and various liver diseases including autoimmune diseases such as primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis, viral hepatitis, metabolic diseases such as non-alcohol related fatty liver disease, and other diseases such as hepatocellular carcinoma and polycystic liver disease. There was also representation of liver transplanted patients in the Delphi panel. In total, 23 panel members were from England, seven were from Scotland, and three were from Wales. There were no panel members from Northern Ireland despite attempts to include panel members from Northern Ireland.

A total of 22 additional questions were added by the Delphi panel members in the first round of the Delphi process. The Delphi panel achieved consensus that an uncertainty was a top research priority for six research questions. Four additional research questions with the highest proportion of Delphi panel members scoring the question as highly important (scores between 7 and 9) were added to constitute the top 10 research priorities. The list of the top 10 research priorities (in the order of proportion who agreed that the uncertainty is a very important research priority) is available is Table 1. All the top 10 research priorities were prevention and treatment uncertainties, and none were diagnostic test uncertainties. None of the panel members thought the first two questions as least important (scores of 1 to 3). For the remaining 8 questions, 3% to 6.5% of people considered the questions to be least important (scores of 1 to 3).

Table 1 Treatment uncertainties for which consensus that the uncertainty is a research priority was reached

Treatment uncertainty (Research question)	Proportion who rated this question as highly important in the final round	Median (interquartile range) in the final round
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	93.5%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	93.3%	8(7,9)

What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	90.3%	9(8,9)
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	90.3%	8(7,9)
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	81.8%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	80.6%	8(7,9)
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	76.7%	8(6.75,9)
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	74.2%	7(6,9)
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	74.2%	7(6,8)

Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	72.4%	7(6,9)

A summary of the availability of systematic review of randomised controlled trials on the topic of the individual questions, randomised controlled trials on the topic not included in the systematic review (if one exists), and the outcomes evaluated in these RCTs are listed in Table 2. Table 2 also contains a suggestion for the next research steps. The list of the existing trials was compiled by searching ClinicalTrials.gov on 7th April 2018. The references to the trials not included in the systematic reviews is available in Online Supplement Appendix 3. As seen in Table 2, a well-designed RCT is the next step for eight of these top 10 research questions. This is because it appears that the outcomes in those trials will not address the outcomes listed in the research questions.

Table 2 Next step to address the top 10 research priorities based on current best evidence (summary)

Treatment uncertainty (Research question)	High-quality systematic review[a,b]	RCTs not included in the systematic review[a, c]	Patient-oriented outcomes assessed in trials not included in the systematic review[d]	Next step

What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[11]	8 trials	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatment
What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	[12]	9 trials	None of the trials include survival, HRQoL as outcomes[e]	High-quality RCTs with clinical outcomes (survival, HRQoL)

What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	[13] (includes only pharmacological interventions)	More than 10 published trials on lifestyle interventions and more than 20 trials on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> 44 trials	Lifestyle interventions and nutritional supplementation Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver disease (11 trials),	High-quality systematic reviews on lifestyle interventions (one review) and nutritional supplementation to cure or delay the progression of NAFLD and high-quality RCTs on pharmacological

			mortality (2 trials), cirrhosis (2 trials), cardiovascular events (2 trials)[e]	interventions with clinical outcomes (survival, HRQoL)
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[14] (covers only maintenance immunosuppression)	Induction immunosuppression More than 20 published trials Maintenance immunosuppression 4 trials	Induction immunosuppression Not applicable as there is no high quality systematic review Maintenance immunosuppression	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance immunos

			Graft survival (1 trial) Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	uppression with important clinical outcomes (overall survival, HRQoL)
Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	None	None	-	High-quality RCTs on education to prevent NAFLD
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	15 trials	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes (survival, HRQoL)

What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH			
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	None	5 trials	Overall survival (4 trials), graft survival (5 trials), health-related quality of life (2 trials)	Await results of the RCTs (all expected to complete by the end of 2019) and perform a high quality systematic review.
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[15]	24 trials	Health-related quality of life (5 trials), relief of	High-quality RCTs with clinical outcomes

			symptoms (5 trials)[e]	(survival, HRQoL)
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above) reported on liver fibrosis.			

a Numbers indicate the reference number.

b Further well-designed randomised controlled trials using clinical outcomes were recommended by all these systematic reviews.

c Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

The complete list of questions in the Delphi process, the proportion of respondents who considered a research question as very important and the summary scores in each Delphi round is available in Online Supplement Appendix 4. This appendix also has the breakdown of the proportion of patients, carers, and general public who considered a research question as very important and their summary scores in each Delphi round along with similar summary measures for healthcare professionals.

DISCUSSION

This is the first priority setting partnership on non-alcohol related liver and gallbladder disorders. This included a wide range of disease processes and a total of 428 unique research questions that met the scope of this priority setting partnership were identified. All the research questions were considered unanswered as there had been no high quality systematic reviews which indicated that no further research is required, i.e. all the research questions were uncertainties. Consensus that an uncertainty was a very important research priority was reached for six research questions. Four additional research questions with the highest proportion of Delphi panel members ranking the question as highly important were added to constitute the top 10 research priorities.

As evident from the online supplement Appendix 1, longevity of life and health-related quality of life are two major outcomes that appear important to patients, their carers, and healthcare professionals. However, even when there are ongoing trials, it appears that the outcomes in those trials will not address the outcomes listed in eight of the top 10 research questions (Table 2). Therefore, the next step in addressing these uncertainties is the design and conduct of randomised controlled trials. Such randomised controlled trials may involve qualitative studies to determine the design and should compare the treatments that improve the longevity of life and/or health-related quality of life.

It should be noted that uncertainties 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?' and 'what are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?' are related to each other. Although NAFLD includes NASH, most of the panel members felt that the research questions related to NAFLD and NASH should be kept separate uncertainties. While the same systematic review can cover both the uncertainties, the primary research study designed to address these two questions differ in terms of the setting, the outcomes used, and the period of follow-up. Any primary research that tries to answer these two questions in a single randomised controlled trial will be inefficient.

Similarly, for the uncertainties 'what are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)' and 'are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?', a single randomised controlled trial will be inefficient and the preference of most of the panel members was to keep these uncertainties as separate uncertainties.

There are several limitations to our priority setting process. The first one is deviation from the original protocol. To select the final top priorities, the initial plan was to arrive at consensus by open small group and large group discussions of patients, carers, and healthcare professionals as suggested by the standard James-Lind Alliance process [8], which provides an opportunity for a knowledge exchange of viewpoints and experience. However, part of the steering committee with experience in a similar priority setting partnership felt that open discussions resulted in 'loud voices' being given more importance resulting in an unrepresentative list of top priorities. While this can be mitigated by facilitated group discussions by neutral JLA facilitators to ensure that all voices were heard in the discussions, this was considered by the steering committee as an important source of bias based on their prior experience in participating in open discussions. The steering committee therefore decided to follow the Delphi-consensus method which is one of the major consensus methods[10]. The advantages of Delphi-consensus method over open discussions include anonymity of

the response and the equal weight given to the opinions of all members [10]. In addition, they are less costly to conduct without any limitation by geographical location compared to other methods of consensus[10] because of the lack of necessity to travel and take time off regular work. However, there is considerable variability in the previous performance of Delphi processes with regards to the number of rounds and the criteria for achieving consensus [16]. Arriving at consensus depends upon people revising their scores based on the other's scores. Our initial plan was to extend the Delphi to four rounds if consensus on 10 top research priorities was not reached in three rounds. However, there was minimal change in scores between the rounds for most questions (Online Supplement Appendix 3) and the Delphi process was completed in three rounds. Consensus on a top research priority was achieved for six questions only. However, the proportion of Delphi panel members ranking a question as highly important was greater than 70% for the remaining four questions added to the list of top research priorities. Previous Delphi consensus processes have used various cut-off points for defining consensus: greater than 70% agreement among panel members is well within the definition of consensus used in previous Delphi consensus processes [16].

The other major limitation of our priority setting process is the representativeness of the people who completed the survey and took part in the Delphi process. The online survey was shared among clinicians and members of general and disease-specific patient organisations. Most questions resulting from the online survey relate to chronic liver disease (in particular, autoimmune liver diseases), perhaps reflecting the high motivation to support research from those groups. The Delphi panel also had a high representation of people related to chronic liver disease (in particular, autoimmune liver diseases) as patients, carers, or healthcare professionals. Whilst people affected by different liver and gallbladder disorders were actively sought through both general and disease-specific patient support groups and organisations, only a few responded and completed all three rounds of the Delphi process. The potential bias towards prioritising chronic liver diseases is evident as nine of the top 10 research priorities relate to chronic liver diseases (four relate to autoimmune liver diseases, three related to non-alcohol related fatty liver disease, two related to liver

transplantation). It was surprising that the uncertainties related to the treatment of chronic viral diseases such as chronic hepatitis B and chronic hepatitis C were not identified within the top 10 research priorities. This may be because of the perception by the some of the panel members that the research questions related to the treatment of chronic hepatitis C were answered with the advent of directly acting antivirals (personal communication). The reason for non-prioritisation of chronic hepatitis B is not entirely clear. This may be because chronic hepatitis B may not have been considered as important as other chronic liver diseases or under-representation of chronic hepatitis B in the panel.

Cancer-related questions, childhood-related liver diseases, and other benign disorders did not end up in the top research priorities (except for the treatment of very early hepatocellular carcinoma, which is managed by hepatologists and surgeons) probably for the reasons described above. We recommend that separate prioritisation processes are carried out for people with gallstones, a condition that affects approximately 5% to 25% of the population [17], for people with primary and secondary liver cancer, and childhood liver disorders where significant uncertainties remain on the effectiveness of different treatments in decreasing mortality and improving health-related quality of life.

As well as the above limitation, we are aware of the inherent limitations of using solely technology to carry out the Delphi exercise. These are limitations that can potentially lead to bias in any consensus-building method including that of face-to-face consensus methods normally used in a JLA PSP.

One solution which might address the limitations of this priority setting process and the standard JLA process may be to collect information routinely from patients visiting hospitals using paper forms and conduct online meetings (video conferencing and presentation) before the final round of the Delphi (or the standard face-to-face priority setting workshop used by the JLA. Some JLA PSPs do use methods such as face-to face interviews and group discussions rather than solely

online surveys). By collecting information on paper forms and conducting the meetings in hospitals, it is possible to engage with people who do not have access to or are not familiar with computers. It is also possible to engage with people who have concerns regarding data confidentiality with the use of computers or social media by collecting information using paper forms. Ethical and confidentiality issues will need to be considered prior to engaging patients attending hospital in the research prioritisation process.

Another limitation of our priority setting process is the drop-outs during the Delphi process. While some of the drop-outs may be related to the ability to complete online surveys and use Microsoft Excel, some patient representatives or clinicians may have dropped out because they did not find any research question to be of direct relevance to them. Other reasons include lack of understanding of the conditions, feeling that the process was too complicated, feeling that the process would not work, and the time commitment for the process. This is because of the broad scope of this research prioritisation process and may be overcome by choosing a narrower focus while defining the scope of the prioritisation process, and by better explanation of the disease processes through presentations.

It should also be recognised that the Delphi panel was constituted of representatives from England, Scotland, and Wales. Therefore, the findings are applicable in only these countries. However, the findings are likely to be applicable throughout the NHS and in other European and Western countries with a similar spectrum of chronic liver diseases and similar treatment options available.

In summary, there are significant uncertainties in the management of liver and gallbladder disorders. Further high-quality research is necessary to address these uncertainties which may require programmes of basic, translational, clinical, and public health research. For issues with diverse and unproven treatment options, randomised controlled trials may be the only mechanism for identifying the most effective treatment and the treatments that represent good value for

money for the NHS. Such randomised controlled trials should assess the effect of different treatments in improving longevity of life and/or health-related quality of life.

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CONTRIBUTION OF AUTHORS

Kurinchi Gurusamy – conceptualisation, healthcare professional and methodological lead of steering committee, Delphi panel member, analysis, author of the manuscript.

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CONFLICTS OF INTEREST

The decisions made by healthcare professionals involved in the research prioritisation process might have been influenced by their professional interests, in addition to their own, or family member's experience of health conditions. Decisions made by patients and carers in the research prioritisation process might have been influenced by their particular experiences, health needs and interests.

DATA SHARING AGREEMENT

All data is available in the manuscript or in the supplementary file.

FIGURE 1

Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.

[a]The protocol was registered with James-Lind Alliance Priority Setting Partnership

[b]The final prioritisation was achieved by modified Delphi consensus method.

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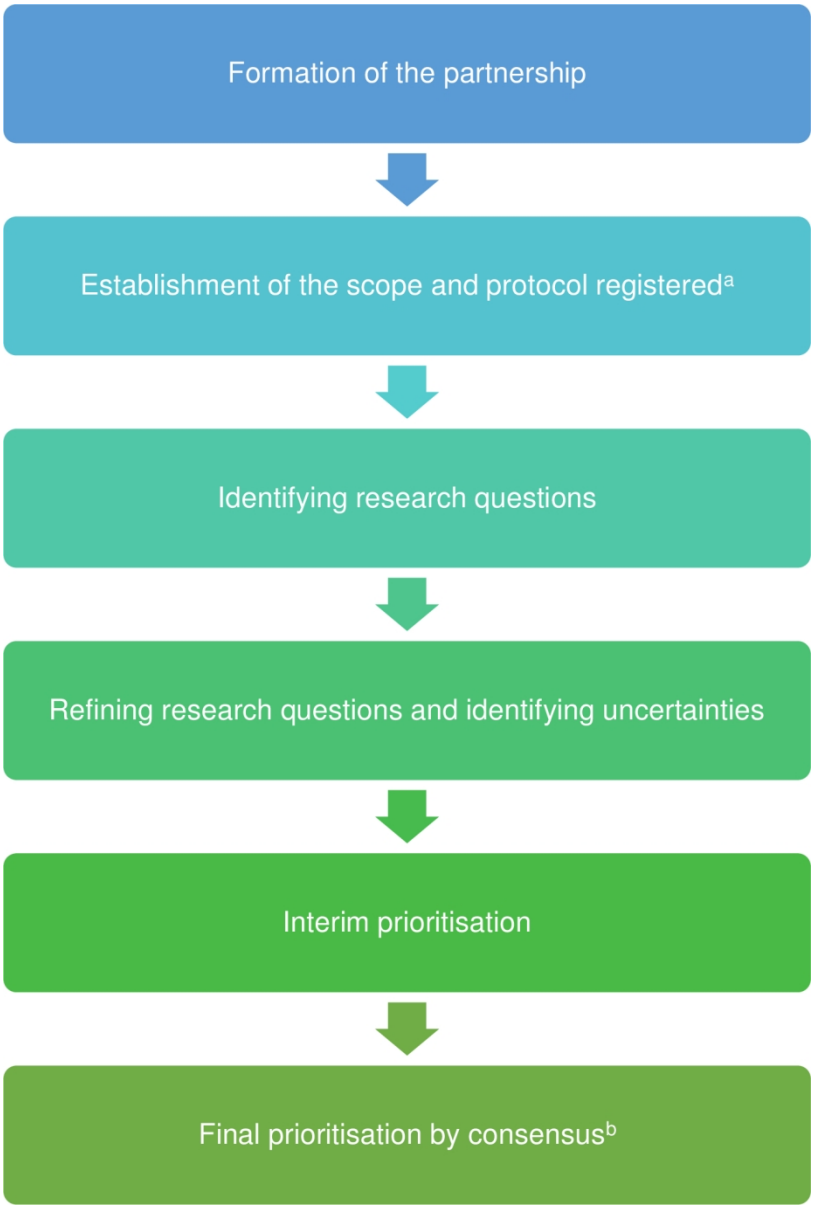

Figure 1: Research prioritisation steps

The major steps in the research prioritisation are shown in the figure.
aThe protocol was registered with James-Lind Alliance Priority Setting Partnership
bThe final prioritisation was achieved by modified Delphi consensus method.

119x177mm (300 x 300 DPI)

Appendix 1 List of all research questions

Patient/population	Intervention	Control	Outcomes
People with obesity	Lifestyle: diet	No intervention	1. Liver transplantation 2. Improvement in BMI. 3. Improved liver function
People with liver disease	Nurse-led care	Standard care	Ability to self-manage
People with asymptomatic chronic liver disease	Education of people	No intervention	1. Improvement in life style. 2. Fatty liver disease
People with NASH (non-alcoholic steatohepatitis)	Different medical treatments	No intervention	1. Halting disease progression. 2. Reversing disease progression. 3. Slowing disease progression. 4. Cure
People with primary sclerosing cholangitis	Treatment for primary sclerosing cholangitis	No intervention	1. Mortality 2. HRQoL (health-related quality of life)

			3. Fewer symptoms - pain, itching, fatigue 4. improved liver function 5. Cure 6. Time to liver transplantation 7. Improvement (no further details) 8. Decreased hospital admission 9. Disease progression 10. Remission from PSC 11. Cancer 12. Requirement for liver transplant.
People with liver disease	Methods to improve compliance to treatment	Not applicable	1. HRQoL 2. Mortality
General population	Screening: early identification of people at risk of liver disease	No screening	1. HRQoL 2. Mortality

People at risk of liver disease	Diagnosis: early identification of people with liver disease	Not applicable	1. HRQoL 2. Mortality 3. Prevention of liver disease 4. Slowing progression of liver disease 5. Reducing requirement for liver transplantation 6. Adverse events of medications
People with primary sclerosing cholangitis and who have had a liver transplant and still have ulcerative colitis even after a sub total colectomy	Symptomatic treatment for primary sclerosing cholangitis	Not applicable	1. HRQoL. 2. Decrease in symptoms (breathlessness and fatigue). 3. Mortality. 4. Decrease in medication. 5. Cure. 6. Decreased progression of primary sclerosing cholangitis.

			7. Improvement in symptoms (unspecified).
People at risk of liver disease (overweight or obese)	Diagnosis: Accurate non-invasive method for diagnosis of chronic liver disease	Not applicable	1. Death 2. Need for liver transplant 3. Requirement for hospital admission. 4. Demonstrating equivalence to biopsy 5. Demonstrating good reproducibility
People at risk of liver disease (overweight or obese)	Screening methods to diagnose liver disease (including history and diagnostic tests)	Not applicable	1. Proportion of people at risk of liver disease 2. Proportion of people at risk who have asymptomatic liver fibrosis 3. Early diagnosis and treatment
People with polycystic liver disease	Treatment for polycystic disease	Not applicable	1. Decrease symptoms 2. Increase quality of

			life 3. Decrease size of cyst or preventing cysts to enlarge 4. Increased longevity 5. Requirement for liver transplant.
People with autoimmune hepatitis	Treatments for autoimmune hepatitis.	Not applicable	1. HRQoL (including ability to carry out normal activities, study, work). 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Treatment related side-effects (unspecified). 8. Brittle teeth

			(treatment-related). 9. More effective treatment unspecified. 10. Complete recovery (unspecified). 11. Mortality. 12. Measure feeling well (unsepcified) 13. Fewer flare ups 14. Less joint pain. 15. Disability 16. Liver damage requiring hospital admission 17. Quicker recovery 18. More monitoring of patients 19. Symptom control. 20. Side-effects
People with autoimmune hepatitis	Standardised protocol care	Standard care	1. HRQoL. 2. Fatigue. 3. Osteoporosis

			(treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related).
People with autoimmune hepatitis	Treatment of fatigue/joint pain related to autoimmune hepatitis.	Not applicable	1. HRQoL. 2. Fatigue. 3. Osteoporosis (treatment-related). 4. Cataracts (treatment-related). 5. Infections (treatment-related). 6. Weight gain (treatment-related). 7. Joint pain. 8. Symptoms (unspecified).
People with autoimmune hepatitis	Nurse-led care	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.

People with autoimmune hepatitis	Education of healthcare professionals and patients	Standard care	1. Faster recovery. 2. HRQoL. 3. Symptoms.
People with autoimmune hepatitis	Lifestyle: diet	Standard care	1. Treatment related adverse events. 2. Requirements for liver transplantation. 3. NHS (National Health Service, UK) costs 4. HRQoL 5. Mortality. 6. Free from immunosuppressive therapies. 7. Fatigue. 8. Weight.
People with autoimmune hepatitis	Education of people	Standard care	Faster reduction in strong medications. Need for liver transplantation.
People with autoimmune hepatitis	Cannabis + standard care	Standard care	1. Reduction in immunosuppressants.

			2. Fatigue. 3. Treatment related side effects such as serious infections, anxiety, depression, cancer, physical side effects.
General population (> 40 years or >50 years or middle-aged people, particularly overweight/obese and/or have type 2 diabetes and/or a family history of chronic liver disease)	Screening for liver disease by GP using routine blood tests/other methods	Standard care	1. Earlier diagnosis and treatment. 2. Preventing liver disease progressing to cirrhosis. 3. More cost effective for NHS. 4. Preventing the complications of chronic liver disease such as hepatocellular carcinoma and varices.
People with autoimmune hepatitis	Prednisolone	No intervention	1. Obesity. 2. Osteoporosis. 3. Insomnia. 4. Hypertension.

People with genetic markers associated with autoimmune hepatitis.	Methods for prophylaxis	No intervention	Prevention of autoimmune hepatitis
People with autoimmune hepatitis	Lifestyle: optimal physical exercise	Not applicable	1. Weight 2. Fatigue
People with autoimmune hepatitis (stable)	Nurse-led care	Standard care	1. Fatigue
People with suspected autoimmune hepatitis	Methods to make a quicker diagnosis	Not applicable	1. Earlier diagnosis
People with NASH, diabetes, and gastroparesis	Treatments for breathlessness and pain	Not applicable	1. Breathlessness and pain.
People with NASH cirrhosis, diabetes, and anaemia	Treatments	Not applicable	HRQoL
People with NASH cirrhosis, diabetes, and anaemia	Education of people	Standard care	Better knowledge
General population	Education of people	Standard care	Better knowledge
People with NASH cirrhosis, diabetes, and anaemia	Non-pharmacological treatments to decrease pain and depression	Pharmacological interventions or no intervention	1. Pain 2. Depression
People with suspected autoimmune diseases with potential to cause acute liver failure	Diagnosis of autoimmune diseases that cause acute liver failure	Not applicable	Identification of specific autoimmune diseases

People with autoimmune diseases with potential to cause acute liver failure	Prophylactic treatments	Not applicable	Prevent acute liver failure
People with primary sclerosing cholangitis	Lifestyle: diet (including alcohol consumption) and physical exercise	Not applicable	1. Reduction in symptoms 2. Overall health benefits (unspecified) 3. Ability to return to useful occupation. 4. Reduce medication. 5. Reduce need for annual investigations.
People with primary sclerosing cholangitis	Azathioprine	Other interventions	Treatment related adverse events
People with autoimmune hepatitis	Non-pharmacological treatments to treat autoimmune hepatitis	Pharmacological interventions or no intervention	1. Reduction in symptoms 2. HRQoL (including the ability to do everyday tasks/ back into education or employment)

People with primary sclerosing cholangitis	Itching receptor blockers	No intervention/ other interventions	Reduction in itching
People with primary sclerosing cholangitis with and without Vitamin D deficiency	Vitamin D supplements	Standard care	1. Stop the progress of the disease. 2. Fewer flare ups of inflammatory bowel disease and primary sclerosing cholangitis. 3. Improve HRQoL 4. Less depression
People with primary sclerosing cholangitis and autoimmune hepatitis	Ursodeoxycholic acid	No intervention/ other interventions	Reducing symptoms
People at risk of primary sclerosing cholangitis and autoimmune hepatitis	Prophylactic treatments	No intervention	Prevention of the condition
People with autoimmune hepatitis	Non-steroidal interventions	Steroids	Adverse events
People at risk of autoimmune liver diseases	Prophylactic treatments	Not applicable	Reduction in those getting advanced liver disorders

People with autoimmune liver diseases (20 to 30 years old)	Treatments	Not applicable	1. Reduction in those getting advanced liver disorders. 2. Stabilisation of disorder. 3. Reduction in liver cancer rates.
People with autoimmune liver diseases (> 30 years)	Screening: Early diagnosis of liver cancer	No screening	Early diagnosis of liver cancer
People with NASH and stroke	Nurse-led care	Standard care	1. Recovery time 2. Amount of recovery that is made
People with haemochromatosis	Lifestyle: iron avoidance diet	Traditional phlebotomy	Reduction in iron levels
People with haemochromatosis	Acceleration of phlebotomy	Traditional phlebotomy	Reduction in iron levels
People with NAFLD	Nurse-led care	Standard care	1. Faster recovery. 2. Symptom relief (unspecified). 3. Prevention of more serious complications. 4. Patient education

			on diet and exercise to lose weight. 5. Preventing progression into NASH and cirrhosis. 6. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 7. Prevent heart attacks and strokes.
People with NAFLD	Treatments for pain	Not applicable	Reducing pain
People with NAFLD	Treatments for itching	Not applicable	Reduction in itching
People at risk of liver disease (overweight or obese)	Education of healthcare professionals about NAFLD	Standard care	1. Prevention of cirrhosis. 2. Prevention of other related liver complications. 3. Earlier diagnosis and treatment of liver diseases. 4. Increased knowledge.
Midwives and healthcare professionals coming into	Education of healthcare	Standard care	1. Prevention of cirrhosis.

contact with children and young adults	professionals about liver disease		2. Prevention of other related liver complications.
People with chronic hepatitis C	Newer treatments	Older interventions	1. Treatment-related complications 2. Ability to perform usual activities such as work, study, housework. 3. Severe liver damage requiring hospital admission. 4. Decreased anxiety.
New-borns	Screening test for biliary atresia	No screening	Earlier diagnosis and treatment
Children who have undergone liver transplantation	Immunosuppressive regimens	Not applicable	Adverse events
People with liver-related disorders	Treatment for itching	Not applicable	Reduction or eradication of itching
People with primary biliary cholangitis	Education of people	Standard care	Knowledge
People with positive AMA (antimitochondrial antibody) M2	Prophylactic treatments	Not applicable	1. Prevention of primary biliary cholangitis.

			2. Reversion to a negative AMA M2 before cirrhosis develops.
People with positive AMA M2	Standardised protocol care by GP	Standard care	1. Prevention of primary biliary cholangitis. 2. Reversion to a negative AMA M2 before cirrhosis develops.
People with liver disease	Stem cell therapy	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work) 3. Prolonging periods of remission 4. Reducing symptoms
People with liver disease	Bio-artificial livers	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities

			including study and work)
People with autoimmune hepatitis	Targeted therapy against autoimmunity	Standard care	1. Mortality 2. HRQoL (including ability to carry out normal activities including study and work)
People with primary biliary cholangitis not responding to ursodeoxycholic acid	Different treatments	Not applicable	1. Cure 2. Slowing of disease 3. Improved quality of life with respect to fatigue.
People with primary biliary cholangitis	Antiviral treatment	No intervention/ other interventions	1. Improvement in health (unspecified) 2. Mortality
People with primary biliary cholangitis	Treatment for itching and fatigue	Not applicable	1. HRQoL. 2. Anxiety. 3. Itching. 4. Fatigue. 5. Cure 6. Slowing of disease 7. Symptom relief
People with primary biliary cholangitis	Greater patient involvement	Standard care	1. HRQoL. 2. Anxiety.

People with liver and gallbladder disorders	Nurse-led care	Standard care	1. Symptoms. 2. Pain relief. 3. Quicker investigative measures.
People with pain after cholecystectomy (especially elderly and living alone)	Hospital based investigations to find the cause of pain, treatment of the cause of pain and discharged after pain relief	Symptomatic outpatient intervention	Pain relief
People with chronic hepatitis C	Ribavirin	No intervention/ other interventions	Osteoporosis
People with chronic hepatitis C taking ribavirin	Prophylactic treatments for osteoporosis	No prophylactic intervention	Osteoporosis
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about childhood liver disorders	Standard care	1. Knowledge 2. Better treatment of patients with primary biliary cholangitis
People with liver disease	Education of people	Standard care	1. Patient knowledge. 2. Visits to the

			hospital. 3. More patient responsibility
People with symptomatic primary sclerosing cholangitis	Different treatments	Not applicable	1. Cure of disease. 2. Delays progression of disease.
People with primary sclerosing cholangitis	Intervention to reverse liver damage	Not applicable	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation.
People with primary sclerosing cholangitis	Intervention to treat fatigue	Not applicable	1. HRQoL. 2. Fatigue.
People with primary sclerosing cholangitis	Intervention to treat itching	Not applicable	1. HRQoL. 2. Itching.
People with primary sclerosing cholangitis	Specialist interest doctor	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Symptom relief.
People at risk of oesophageal varices	Non-invasive assessment of oesophageal varices	Invasive assessment of oesophageal varices	Reduce bleeding oesophageal varices

People at risk of chronic liver disease	Alternative to biopsy for assessment of cirrhosis	Liver biopsy	Assessment of whole liver
People at risk of primary sclerosing cholangitis (PSC)	Early diagnosis of primary sclerosing cholangitis Alternate to liver biopsy	Not applicable	Not stated
People with primary sclerosing cholangitis with normal or relatively normal liver function tests	Alternative to UKELD (United Kingdom Model for End-Stage Liver Disease) scores for prioritisation for liver transplantation	UKELD	1. More accurate assessment of transplant need for transplant amongst PSC patients. 2. Reduction in numbers of 'low score' PSC patients becoming too ill for transplant, or not being offered a transplant once 'listed'.
People with positive AMA M2 with normal liver function tests	Ursodeoxycholic acid	No intervention	Slowing progression of primary biliary cholangitis

People with suspected primary sclerosing cholangitis	Nurse-led care	Standard care	Earlier diagnosis and treatment
People with liver failure of unknown reason	Investigations to find the cause of liver failure of unknown origin	Not applicable	More knowledge.
People with Gilbert's syndrome	Treatment of fatigue related to Gilbert's syndrome	Not applicable	1. HRQoL. 2. Chronic fatigue. 3. Depression
People with NAFLD (non-alcoholic fatty liver disease)	Breathing exercises	Standard care	1. Faster recovery. 2. Symptom relief 3. Prevention of more serious complications
People with NASH cirrhosis	Treatment of symptoms	Not applicable	Improvement of symptoms
People at risk of liver disease	Screening for autoimmune diseases	No screening	Earlier diagnosis and treatment
People with autoimmune hepatitis	Treatment of symptoms	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups.

			4. Less joint pain. 5. Disability.
People with autoimmune hepatitis	Methods to decrease stress	Not applicable	1. Measure feeling well (unspecified). 2. Fatigue having energy. 3. Fewer flare ups. 4. Less joint pain. 5. Disability.
People with liver disease	Counselling for tremors and confusion	No counselling	Coping with symptoms
People with NAFLD	Staging of liver disease	Not applicable	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Metformin	No intervention	1. Mortality. 2. Reversal of liver damage
People with NAFLD	Standardised protocol for diagnosis and treatment of NAFLD	Standard care	1. Mortality. 2. Reversal of liver damage
People with osteoarthritis	Anti-inflammatory drugs	Other interventions	Cirrhosis
People with diabetes	Adequate control of diabetes	Lack of adequate control of diabetes	1. NASH. 2. Cirrhosis.

People at risk of NAFLD	Screening: Early identification of causes	Standard care	Prevention of liver disease
People with NAFLD	Treatments	Not applicable	1. Cure 2. Prevention of liver disease 3. Disease progression 4. HRQoL
People with upper abdominal pain	Screening: Early scan with ultrasound, blood tests, and urine tests	Standard care	1. Early identification of liver and gallbladder diseases 2. Appropriate advice/treatment
People with NAFLD	Lifestyle: diet and exercise	Standard care	1. HRQoL
People with NAFLD	Specialist interest doctor	Standard care	1. HRQoL
People at risk of liver disease	Prophylactic interventions	Not applicable	1. Prevention of liver disease
People at risk of NAFLD	Prophylactic treatments	Not applicable	1. Prevention of NAFLD 2. Decrease NAFLD
People with NASH fibrosis	Lifestyle: exercise	Standard care	None stated

People with cryptogenic liver cirrhosis	Investigations to find the cause of cryptogenic cirrhosis	Not applicable	1. Reduction in liver disease diagnosis of the percentage regarded as cryptogenic. 2. Establishment of relevant treatment pathways. 3. Reduction in numbers of liver transplant required by earlier intervention using non-invasive treatment regimes.
People with cirrhosis	Community-led psychological support (on lifestyle: diet and exerise, stress, work-life balance, and general well-being)	Standard care	1. Reduction of symptoms such as nausea, fatigue. 2. Improved nutrition and healthier weights. 3. Improved HRQoL 4. Improved sense of wellbeing 5. Successful work

			and job retention 6. Good sense of self determination/empowerment and motivation 7. Improved clinical markers (unspecified)
Newborns	Screening for metabolic liver diseases	No screening	1. Early treatment for people with metabolic liver disease (including dietary advice) 2. Mortality. 3. HRQoL. 4. Prevent type 2 diabetes
People with autoimmune hepatitis	Telephone-based care	Standard care	1. Reduction in time spent in outpatients 2. Less spent on car-parking at hospitals
People with NASH and diabetes	Liver transplantation	Standard care	1. Mortality

People with primary biliary cholangitis (newly diagnosed)	Adequate drinking water	Standard care	1. HRQoL. 2. Liver function tests.
People with primary sclerosing cholangitis	Treatment targeted against deformation of bile duct	Standard care	1. Time to end-stage liver disease.
People with bile duct cancer	Treatment targeted against deformation of bile duct	Standard care	Not stated
People with gallbladder sludge with digestive symptoms	Avoiding surgery	Standard care	1. Symptom relief
People with NAFLD	Education of healthcare professionals	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.
People with NAFLD	Education of general public	Standard care	1. Greater awareness of conditions. 2. Preventative measures. 3. Greater knowledge base.

People with NAFLD	Methods to make an accurate diagnosis (including liver function tests)	Not applicable	Not stated
People with NAFLD (overweight)	Interventions to lose weight	Not applicable	Weight loss
People with liver disease (newly diagnosed)	Mental health support	Not applicable	Mental health
Children with multiple autoimmune disorders related to liver	Genetic testing of telomere lengths	Other tests/ no tests	Not stated
Children with multiple autoimmune disorders related to liver	Stem cell therapy	Standard care	Reduction in all conditions with only one drug with little side effects
People with primary biliary cholangitis (especially younger age group)	Treatments based on tools for predicting prognosis	Standard care	Better care for people with high risk of progression
People with chronic hepatitis C	Lifestyle: diet	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge.

			4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with chronic hepatitis C	Education of healthcare professionals (about diet)	Standard care	1. Improvement in overall health. 2. Decrease in liver damage requiring hospital admission. 3. Patient knowledge. 4. Healthcare professional knowledge. 5. Fewer treatment-related complications. 6. Decreasing pain

			and discomfort. 7. Clear guidelines for successful dietary needs.
Healthcare professionals dealing with people with NAFLD	Education of healthcare professionals (around support to patients on weight control, diet, exercise and life style)	Standard care	1. Preventing progression into NASH and cirrhosis. 2. Reducing symptoms of aching sides, leg weakness, sickness and nausea. 3. Prevent heart attacks and strokes.
Family members of people with primary biliary cholangitis	Screening of family members for primary biliary cholangitis	No screening	1. Establishing the genetic link for primary biliary cholangitis. 2. Earlier identification of primary biliary cholangitis who may have PBC or be at risk. 3. Cost-savings.

People with positive AMA M2 with normal liver function tests	Screening for cirrhosis using biopsy	No screening	Accurate diagnosis of primary biliary cholangitis.
People with primary biliary cholangitis	Screening for other autoimmune conditions associated with primary biliary cholangitis and complications related to primary biliary cholangitis	No screening	1. HRQoL. 2. Costs.
People with autoimmune liver disease	Treatment of fatigue and others symptoms	Not applicable	Remission
People with primary sclerosing cholangitis	Standardised protocol for follow-up of patients with primary sclerosing cholangitis	Standard care	1. Reduce need for annual investigations. 2. Costs.
People with other autoimmune disease	Screening for liver disease	No screening	1. Decreasing risk of severe liver damage and admission to hospital 2. Reducing the need for liver transplants 3. Decreasing the risk of liver cancer

			4. Mortality 5. HRQoL
People with NAFLD	Pathway for managing end of life care	Standard care	1. Patient and carer satisfaction 2. Patient HRQoL 3. Symptom relief.
People with decompensated liver disease	Lifestyle: nutritional treatment	Not applicable	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Measuring energy requirements with indirect calorimeters	Current UK guidance on requirements (Parenteral & Enteral Nutrition Group) (high energy requirements)	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with hepatic encephalopathy	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved

			nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Branch chain amino acids	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease with muscle wasting	Lifestyle: exercise	Standard care	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.
People with decompensated liver disease	Standardised nutritional assessment of patients and outcomes in nutritional intervention trials	Non-standardised assessment	1. Improved survival. 2. Reduced symptoms. 3. Improved nutritional status. 4. Improved Strength.

			5. Better conduct of future trials.
People with NAFLD	Methods to increase self care	Not applicable	Reducing symptoms
People with NAFLD	Methods to decrease shortness of breath	Not applicable	Reducing symptoms
People with liver disease	Interventions to decrease fatigue	Not applicable	Fatigue
Healthcare professionals dealing with people with cirrhosis	Education of healthcare professionals about cirrhosis (complications and benefits and harms of treatment)	Standard care	Better advice to patients by health professionals regarding complications and benefits and harms of different treatments
People with primary biliary cholangitis	Ursodeoxycholic acid (including optimal dose)	No intervention/ other interventions	1. Liver function tests. 2. Minimal effective dose of ursodeoxycholic acid. 3. Good sleep.
People with liver cancer and ascites	Different interventions	Not applicable	HRQoL

People with primary sclerosing cholangitis	Screening for cancer	No screening	1. Benefits 2. Earlier diagnosis of bile duct cancer 3. Mortality
People with primary or metastatic liver cancer	Nurse-led care (follow-up clinic)	Doctor-led follow-up	1. Patient satisfaction 2. Timely surveillance
People with cirrhosis	Life-style: nutritional advice	Not applicable	1. Fatigue 2. Muscle wasting
People with polycystic liver disease	Surgery	Non-surgical management	1. Recurrence 2. HRQoL
People with gallstones	Avoiding surgery	Surgery	1. Requirement for surgery 2. Costs to NHS
People at risk of NASH	Nurse-led care	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Screening for NASH using Fibroscan	No intervention	1. Early diagnosis of NASH. 2. Successful treatment of NASH. 3. Mortality

People at risk of NASH	Support group focussed on diet and exercise	No intervention	1. Prevention of NASH. 2. Successful treatment of NASH. 3. Mortality
People at risk of NASH	Emotional support group for carers	No intervention	HRQoL
People with NASH	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.
People with NASH	Lifestyle: diet	Standard care	1. Mortality. 2. HRQoL. 3. Requirement for liver transplantation. 4. Liver cancer. 5. Liver failure. 6. Treatment-related complications.

People with NASH	Different interventions to decrease anxiety and depression	Standard care	Anxiety and depression
People with NASH	Research design using support group	Standard research design	Help towards better research
General population	Life style: diet and exercise	No intervention	HRQoL
General population	Education of people (patient information leaflet at GP surgeries)	No intervention	1. Prevention of NASH. 2. HRQoL.
General population	Screening: for liver disease	No intervention	1. Early diagnosis of liver disease 2. Mortality 3. HRQoL 4. Requirement for liver transplantation 5. Costs 6. Requirement for hospital admission for severe liver damage 7. Primary liver cancer
Primary school children	Lifestyle: nutritional and dietary advice	No intervention	1. Adherence to healthy diet and

			exercise to sustain healthy life style.
People undergoing liver resection	Best method to assess function and volume of remnant liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Best method to assess cardiopulmonary function?	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pre-operative education	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Simulation and training of surgeons	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Growth factors to optimise muscle and fat content	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for weight loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein embolisation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Reducing systemic inflammation using steroids	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Open liver resection	Laparoscopic liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Tumour visualisation and localisation of the tumour	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy during operation	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
Surgeons treating people undergoing liver resection	Use of magnifying surgical loupes during liver surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) during surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Transection techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Vascular occlusion techniques	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Cardiopulmonary and pharmacological interventions for decreasing blood loss	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Use of peritoneal drains	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	ALPPS procedure (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Goal directed therapy (post-operative)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pain control protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Early mobilisation protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Early oral intake protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Portal vein pressure decrease (by the use of drugs such as vasopressin) post-operatively	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Radioembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	External beam radiotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Screening for cancer	No screening	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Systemic chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with early or very early hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with intermediate hepatocellular carcinoma	Treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Tamoxifen	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Tyrosine kinase inhibitors	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Neoadjuvant and adjuvant therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable hepatocellular carcinoma	Transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Interferon	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatocellular carcinoma	Surgical resection	Liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Anterior approach	Conventional liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatocellular carcinoma	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative transarterial chemoembolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for hepatocellular carcinoma	Post-operative lamivudine with or without adefovir dipivoxil	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with advanced biliary tract carcinoma	gemcitabine-based chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable cholangiocarcinoma	Endoscopic treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Pharmacological interventions for	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

	reducing ischaemia reperfusion injury		
People undergoing liver transplantation for hepatitis B infection	Antibiotic prophylaxis	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Hepatitis B immune globulin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Prostaglandins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to prevent hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing haemopoietic stem cell transplantation	Interventions to treat hepatic veno-occlusive disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Immunosuppressive regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Venovenous bypass	No intervention	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of biliary reconstruction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods of preventing bacterial sepsis and wound complications after liver transplantation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Techniques of flushing and reperfusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Abdominal drainage	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Piggy-back	Conventional liver transplantation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Methods to decrease blood loss and transfusion requirements	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver transplantation	Antiviral prophylaxis for prevention of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Antiviral treatment of hepatitis C infection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatitis B infection	Lamivudine or adefovir dipivoxil	No intervention/other interventions including immunoglobulin	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Nutritional interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Celsior solution	UW solution	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Pharmacological interventions for reducing ischaemia reperfusion injury	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Fibrin-based haemostatic agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for colorectal liver metastases	Neoadjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Resection	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Ischaemic preconditioning	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Interventions for reducing blood loss	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Methods of decreasing infection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic node positive colorectal liver metastases	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for resectable neuroendocrine tumours	Resection	No resection	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection or ablation of colorectal liver metastases	Hepatic artery adjuvant chemotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Laparoscopic liver resection	Open liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Nonabsorbable disaccharides	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Benzodiazepine receptor antagonists	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Antibiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Dopamine agents	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Rifaximin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Acetyl-L-carnitine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatic encephalopathy	Probiotics	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	Naloxone	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatic encephalopathy	L-ornithine-L-aspartate	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Herbal medicines	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Weight reduction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Transarterial (chemo)embolisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Microwave coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with liver metastases	Cryotherapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Radiofrequency ablation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable neuroendocrine liver metastases	Palliative cytoreductive surgery	Other palliative interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Hepatic arterial infusion	Systemic chemotherapy	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Electro-coagulation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver metastases	Percutaneous ethanol injection	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with unresectable colorectal liver metastases	Chemotherapy for downstaging	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Selective internal radiation therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with gallbladder polyp	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder dyskinesia	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of cystic duct occlusion	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for acute cholecystitis	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Laparoscopic cholecystectomy	Mini-incision cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Mini-incision cholecystectomy	Open cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Abdominal wall lift	Pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy for biliary colic	Early laparoscopic cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Intra-peritoneal saline instillation	No instillation	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of intraperitoneal local anaesthetic instillation	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of local anaesthetic wound infiltration	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Three-dimensional imaging	Two-dimensional imaging	1. Mortality. 2. HRQoL. 3. Complications.
People with asymptomatic gallstones	Cholecystectomy	No cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing open cholecystectomy	Abdominal drainage	No drain	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Robotic assistant	Human assistant	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Methods of gallbladder dissection	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Low pressure pneumoperitoneum	Standard pressure pneumoperitoneum	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Education of patients	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Miniports	Standard ports	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Number of ports	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Pharmacological interventions for prevention or treatment of postoperative pain	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing laparoscopic cholecystectomy	Glucocorticoids	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People who have undergone endoscopic sphincterotomy for gallstone related complications	Early cholecystectomy	Delayed or no cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Antibiotic prophylaxis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Day surgery	Overnight stay	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing day surgery laparoscopic cholecystectomy	Anaesthetic regimens	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones undergoing laparoscopic cholecystectomy	Per-operative endoscopic sphincterotomy	Pre-operative endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stenosis	Magnetic resonance cholangiopancreatography	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected bile duct stones	Endoscopic ultrasound	Magnetic resonance cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Endoscopic retrograde cholangiopancreatography	Intraoperative cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile duct stones	Liver function tests	Transabdominal ultrasound	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Pre-operative biliary stenting	No stenting	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated amoebic liver abscess	Percutaneous procedure plus metronidazole	Metronidazole alone	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver tumours	Liver resection	No liver resection	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Sphincterotomy	No sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with cirrhosis	Colchicine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with blunt liver injury	Non-surgical treatment	Surgery	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Surgical treatment	Endoscopic intervention	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Lifestyle: Diets for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Pharmacological interventions for primary prevention of gallstones	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Sphincteroplasty	Sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Bile acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary colic	Non-steroidal anti-inflammatory drugs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis D	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure vaccines	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
General population	Immunisation against Hepatitis A	No immunisation	1. Mortality. 2. HRQoL. 3. Complications.
People exposed to hepatitis A	Post-exposure immunoglobulins	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary stent	Ursodeoxycholic acid to prevent stent occlusion	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Healthcare professionals	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

Pregnant women with Hepatitis B	Immunoglobulins	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Newborns of HBSAg (hepatitis B surface antigen) positive mothers	Immunisation	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Asymptomatic Hepatitis B carriers	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis B	Acupuncture	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis B	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
General population	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Lamivudine	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with HIV infection	Hepatitis B vaccination	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People who have received Hepatitis B vaccination	Booster dose	No booster dose	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with renal failure	Hepatitis B vaccination	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and peripheral neuropathy	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People in haemodialysis units	Isolation to prevent Hepatitis C transmission	No isolation	1. Mortality. 2. HRQoL. 3. Complications.
People with acute hepatitis C	Pharmacological treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C and HIV	Antiviral treatment	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with chronic hepatitis C	Medicinal herbs	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with Hepatitis B	Caesarean section	Vaginal delivery	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C with vasculitis	Treatments	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with chronic hepatitis C	Staging of liver disease	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Biphosphonates	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with primary biliary cholangitis and osteoporosis	Hormonal replacement therapy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with bleeding oesophageal varices	People with portosystemic shunt	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with hepatorenal syndrome	Terlipressin	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.

People with hepatorenal syndrome	Transjugular intrahepatic portosystemic shunts	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing common bile duct exploration	T-tube	No T-tube	1. Mortality. 2. HRQoL. 3. Complications.
People with acute calculous cholecystitis (high risk)	Percutaneous cholecystostomy	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection	Enhanced recovery protocols	Standard intervention	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation	Perfusion techniques in donor	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
Pregnant women with cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
New-borns and infants receiving parenteral nutrition and jaundice	Pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

New-borns and infants receiving parenteral nutrition and jaundice	Alternate interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with sickle cell disease and intrahepatic cholestasis	Interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Human recombinant activated factor VII	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Vitamin K	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease with upper gastrointestinal bleeding	Antifibrinolytic amino acids	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Antioxidant supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Vitamin D supplements	No intervention	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Lifestyle: Nutritional support	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with adverse events related to chemoarterial embolisation for primary liver cancer	Chinese herbs	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with uncomplicated hepatic hydatid cysts	Percutaneous needle aspiration, injection, and re-aspiration with benzimidazole	Percutaneous needle aspiration, injection, and re-aspiration without benzimidazole	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder cancer	Chemotherapy	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with acute or acute-on-chronic liver failure	Granulocyte-colony stimulating factor	No intervention/other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with common bile duct stones	Early laparoscopic cholecystectomy following endoscopic sphincterotomy	Delayed laparoscopic cholecystectomy following endoscopic sphincterotomy	1. Mortality. 2. HRQoL. 3. Complications.

People with gallstones and common-bile duct stones	Model of service delivery	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing cholecystectomy	Routine intraoperative cholangiography	selective cholangiography	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstone pancreatitis	Early cholecystectomy	Delayed cholecystectomy	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Non-pharmacological interventions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with biliary obstruction due to cholangiocarcinoma	Endoscopic bipolar radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with colorectal liver metastases	Radiofrequency ablation	Other interventions	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected bile leak	Magnetic resonance cholangiopancreatography	Endoscopic retrograde cholangiopancreatography	1. Mortality. 2. HRQoL. 3. Complications.
People with cholangitis	Antibiotics	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected focal liver lesions	Imaging modalities to distinguish focal liver lesions	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with liver cancer who have undergone surgery	Optimal follow-up regimen to detect early recurrence	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing laparoscopic cholecystectomy	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver and bile duct resection	Evidence-based pain relief protocol	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallbladder polyp	Imaging modalities to confirm diagnosis of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallbladder polyp	Imaging modalities to distinguish nature of gallbladder polyp	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected gallstones	Methods to confirm diagnosis of gallstone	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected acute cholecystitis	Methods to confirm diagnosis of acute cholecystitis	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People with suspected gallbladder dyskinesia	Methods to confirm gallbladder dyskinesia	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with suspected Sphincter of Oddi dysfunction	Methods to confirm Sphincter of Oddi dysfunction	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People at risk of NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD	Motivational interviewing for lifestyle changes	standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver resection for liver cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing surgery for biliary tract cancer	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.

People undergoing liver resection	Imaging modalities to confirm resectability	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Imaging modalities to confirm that cancer is limited to liver	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Bridging ablative therapies	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People undergoing liver transplantation for hepatocellular carcinoma	Goal-directed therapy	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Direct access surgery (without seeing a specialist)	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with benign liver and gallbladder conditions	Nurse-led care	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Pharmacological interventions	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with sphincter of oddi dysfunction	Psychological counselling	Standard care	1. Mortality. 2. HRQoL. 3. Complications.

People with biliary stricture	Different diagnostic tests	Not applicable	1. Mortality. 2. HRQoL. 3. Complications.
People with gallstones	Routine magnetic resonance cholangio pancreatography	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver and gallbladder disorders	Methods to improve understanding of evidence	Not applicable	1.Improved knowledge. 2. Better involvement in decision making.
People undergoing liver transplantation	Routine fat-assessment in donor livers	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with NAFLD and obesity	Routine anti-obesity surgery	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with severe polycystic liver disease	Pharmacological interventions to improve functional volume	Standard care	1. Mortality. 2. HRQoL. 3. Complications.
People with liver disease	Interventions to achieve palliation	Not applicable	1. Palliation.

People with liver disease	Interventions to achieve symptom control	Not applicable	Symptom control
People with liver disease	Interventions to improve quality of life	Not applicable	Quality of life
Healthcare professionals dealing with people with primary sclerosing cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with Crohn's disease	Methods for screening for primary sclerosing cholangitis	Not applicable	Diagnosis of primary sclerosing cholangitis
People with NAFLD	Patient education	Standard care	1. Greater knowledge.
Healthcare professionals dealing with people with polycystic liver disease	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People with polycystic liver disease	Early liver transplantation	Standard care	1. Quality of life. 2. Reducing symptoms. 3. Reducing pain.
People with autoimmune hepatitis	Interventions that affect T cells	No intervention	1. Cure. 2. Improve quality of life

People at risk of liver disease	Screening	Not applicable	Early diagnosis and treatment
People with polycystic liver disease	Monitoring polycystic liver disease	Not applicable	
People with polycystic kidney disease	Diagnosis polycystic liver disease	Not applicable	
People with liver disease	Methods to improve early appropriate treatment	Not applicable	Early diagnosis and treatment
People with polycystic kidney disease	Methods to prevent symptomatic polycystic liver disease	Not applicable	1. Quality of life. 2. Liver function.
People undergoing liver transplantation	Various treatments	Not applicable	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work 6. Improvement of symptoms
People with polycystic liver disease	Diet (specifically soy proteins which contain oestrogen	Standard diet	1. Decrease size of cyst or preventing cysts to enlarge. 2. Decrease symptoms

People with NAFLD	Various treatments	Not applicable	1. Impact on health (no further details) 2. Progression to liver failure
People with suspected NAFLD	Diagnosis	Not applicable	1. Early diagnosis
People with gallstones	Various treatments	Not applicable	1. Impact on health (no further details)
People with polycystic liver disease	Genetic treatments	Standard therapy	1. Reduce symptoms. 2. Decrease occurrence and size of cysts. 3. Increased longevity
Healthcare professionals dealing with people with primary biliary cholangitis	Education of healthcare professionals about liver disease	Standard care	1. Early recognition. 2. Appropriate treatment.
People undergoing treatment for ulcerative colitis	Various treatments	Not applicable	1. Adverse events related to liver
People with cholangiocarcinoma	Liver transplantation	Standard therapy	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People undergoing liver transplantation	Machine perfusion of donor organ	Cold storage	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver cancer	Novel treatments (irreversible electropolation, high intensity focused ultrasound)		1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with hepatocellular carcinoma	Liver resection	Liver transplantation	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with colorectal liver metastases	Ablation	Surgery	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Ischaemic preconditioning	No IPC	1. Survival 2. Complications 3. QoL

			4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Remote ischaemic preconditioning	No RIPC	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with liver disease undergoing surgery	Goal-directed therapy	standard fluid treatment	1. Survival 2. Complications 3. QoL 4. Hospital stay 5. Return to work
People with compensated liver cirrhosis	Treatments (in particular statins)	Other interventions	1. Decompensation 2. Survival 3. Side effects 4. Quality of life.
People with chronic liver disease/ liver failure	Stem cell therapy	Standard therapy	1. Graft and patient survival 2. QoL. 3. Morbidity compared to conventional transplantation 4. Patient reported outcomes

People with Wilson's disease (and other rare non-alcohol liver related diseases)	Various treatments	Not applicable	Not stated
People with suspected autoimmune hepatitis	Diagnosis of autoimmune diseases	Not applicable	1. Costs of management

Appendix 2 List of unanswered research questions ('uncertainties') prioritised during the interim prioritisation

1. What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?
2. Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?
3. Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?
4. Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?
5. What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?
6. What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?
7. Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?

8. Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?
9. Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?
10. What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?
11. Should the methods used to assess nutrition of patients in liver disease be standardised?
12. Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?
13. Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?
14. What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?
15. Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?
16. What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?
17. What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?
18. Do statins (or other treatments) delay liver failure in people with advanced liver disease?
19. What are the best treatments that provide temporary symptom relief in people with advanced liver disease?
20. Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?

21. What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?
22. Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?
23. What are the best nutritional interventions in people undergoing liver transplantation?
24. What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?
25. Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?
26. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?
27. Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?
28. What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?
29. Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?
30. Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?
31. Is surgery (in the form of removal of gallbladder) required in people with gallstones?
32. Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis (NASH) receive additional education about the condition?
33. What is the best immunosuppressive regimen in adults undergoing liver transplantation?

34. Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangiopancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?
35. How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly follows medical advice) in people with liver disease?
36. What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?
37. What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?
38. Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?
39. What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?
40. Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or without chemotherapy drugs) effective in the treatment of people with liver metastases?
41. Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete hormones and nervous system) undergo liver resection?
42. What are the best methods available to decrease blood loss during liver resection?
43. What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?
44. What are the best treatments for people with polycystic liver disease?
45. Should the healthcare professionals dealing with childhood liver diseases be provided additional education about childhood liver diseases compared to standard education where childhood diseases are learnt as part of overall education?

46. What is the best immunosuppressive regimen in children undergoing liver transplantation?
47. Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?
48. What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent reinfection with chronic hepatitis B virus (HBV) infection?

Appendix 3 Next step to address the top 10 uncertainty based on current best evidence (detailed)

Treatment uncertainty (Research question)	High-quality systematic review[a]	Research recommendations of systematic review	RCTs not included in the systematic review[a,b,c]	Patient-oriented outcomes assessed in trials not included in the systematic review[d]	Next step
What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	[1]	High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period (approximately five years) are needed.	NCT02169765 NCT02704130 NCT02728193 NCT02243384 NCT00844454 NCT01918683 NCT01570075 NCT01351194	Survival (7 trials), recurrence (5 trials), morbidity (3 trials)	High-quality RCTs of interventions not covered in ongoing trials and comparison of health-related quality (HRQoL) in different treatments

What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	[2]	An urgent need exists to identify an effective medical treatment for primary sclerosing cholangitis through well-designed RCTs with adequate follow-up that aim to identify differences in outcomes important to people with primary sclerosing cholangitis.	NCT03394781 NCT02605213 NCT02943460 NCT02704364 NCT01688024 NCT02177136 NCT01672853 NCT03035058 NCT03333928	None of the trials include survival, HRQoL as outcomes[e]	High-quality RCTs with clinical outcomes (survival, HRQoL)
What are the best treatments that cure or delay the progression (worsening) of non-	[3] (includes only pharmacological interventions)	Further well-designed randomised clinical trials with sufficiently	More than 10 published trials on lifestyle interventions and more than 20 trials	Lifestyle interventions and nutritional supplementation	High-quality systematic reviews on lifestyle interventions (one review) and nutritional

alcohol-related fatty liver disease (NAFLD)?		large sample sizes are necessary.	on nutritional supplementation with no recent high-quality systematic reviews <u>Pharmacological interventions</u> NCT02605616 NCT01002547 NCT02927314 NCT03291249 NCT03166735 NCT03486899 NCT03061721 NCT02784444 NCT02077374 NCT03486912	Not applicable as there are no high quality systematic reviews <u>Pharmacological interventions</u> Health-related quality of life (2 trials), resolution of fatty liver disease (11 trials), mortality (2 trials), cirrhosis (2 trials), cardiovascular events (2 trials)[e]	supplementation to cure or delay the progression of NAFLD and high-quality RCTs on pharmacological interventions with clinical outcomes (survival, HRQoL)

			NCT02854605 NCT01963845 NCT03437720 NCT02684591 NCT02787304 NCT02466516 NCT02633956 NCT03008070 NCT03205150 NCT02923154 NCT02913105 NCT01899859 NCT02548351 NCT03053063 NCT03053050 NCT02413372		

			NCT02443116 NCT01464801 NCT03449446 NCT02912260 NCT02856555 NCT02704403 NCT01617772 NCT02217475 NCT01406704 NCT03248882 NCT01051219 NCT02316717 NCT02970942 NCT03439254 NCT02574325 NCT01703260		

			NCT01260246 NCT02960204		
What is the best immunosuppressive regimen in adults undergoing liver transplantation?	[4] (covers only maintenance immunosuppression)	Future randomised clinical trials should be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid postrandomisation dropouts or planned cross-overs; and use clinically important outcomes such as	<u>Induction immunosuppression</u> More than 20 published trials <u>Maintenance immunosuppression</u> NCT01998789 NCT01230502 NCT02909335 NCT00286871	<u>Induction immunosuppression</u> Not applicable as there is no high quality systematic review <u>Maintenance immunosuppression</u> Graft survival (1 trial) Adverse events (1 trial) Hepatocellular carcinoma (1 trial)[e]	High-quality systematic review on induction immunosuppressive regimen and high-quality RCTs on maintenance immunosuppression with important clinical outcomes (overall survival, HRQoL)

		mortality, graft loss, renal impairment, chronic kidney disease, and retransplantation. Such trials should use tacrolimus as one of the control groups. Moreover, such trials ought to be designed in such a way as to ensure low risk of bias and low risks of random errors.			
Should general public be educated about non-alcohol-related	None	-	None	-	High-quality RCTs on education to prevent NAFLD

fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?					
What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	None	-	[5-7] NCT02050646 NCT02463331 NCT00608894 NCT02900443 NCT02239562 NCT01170351 NCT03217422 NCT01661842 NCT00687180 NCT01980745 NCT02878863	Survival (1 trial), health-related quality of life (1 trial)[e]	High quality RCTs with clinical outcomes (survival, HRQoL)

			NCT02936596		
What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	The evidence related to this question is covered under non-alcohol related fatty liver disease by performing a subgroup analysis of people with NASH				
Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine	None	-	NCT02775162 NCT03124641 NCT02940600 NCT02584283 NCT01317342	Overall survival (4 trials), graft survival (5 trials), health-related quality of life (2 trials)	Await results of the RCTs (all expected to complete by the end of 2019) and perform a high quality systematic review.

perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?					
What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	[8]	Further well-designed randomised clinical trials are necessary. Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the	NCT02937012 NCT01473524 NCT02823353 NCT02135536 NCT01614405 NCT02609048 NCT00746486 NCT02955602 NCT03226067	Health-related quality of life (5 trials), relief of symptoms (5 trials)[e]	High-quality RCTs with clinical outcomes (survival, HRQoL)

		clinic rather than in highly selected participants; employ blinding; avoid post-randomisation dropouts or planned cross-overs; should have sufficient follow-up period (e.g. five or 10 years or more); and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated	NCT03112681 NCT01904058 NCT02943447 NCT03124108 NCT03345589 NCT03092765 NCT03394924 NCT02516605 NCT03253276 NCT02965911 NCT01899703 NCT01654731 NCT02308111 NCT00125281 NCT02701166		

		cirrhosis, and liver transplantation. Alternatively, very large groups of participants should be randomised to facilitate shorter trial duration.			
Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	The evidence related to this question is covered under treatments for primary sclerosing cholangitis. The systematic review did not include fibrosis as one of the outcomes. Nine of the trials included in the systematic review reported on fibrosis. Two of the trials not included in the systematic review (and listed above) reported on liver fibrosis.				

a Numbers indicate the reference number.

b Ongoing trials, unpublished trials, or trials published since the search date for the systematic review when a high-quality systematic review based on randomised controlled trials exists. If no systematic reviews based on randomised controlled trials exist, these are either published trials or ongoing studies.

c NCT followed by a number indicates trial registration number

d This information is reported to find out whether the important patient-oriented outcomes are reported in the trials not covered by high-quality systematic reviews. This is to help with deciding whether new randomised controlled trials are necessary on the topic.

e The remaining trials reported treatment-related adverse events, composite outcomes and surrogate markers.

Appendix 4 Scores obtained by each question in the different Delphi rounds

Questions[a]	**Delphi 1: Proportion who rated this question as highly important**	**Delphi 1: Median (IQR)**	**Delphi 2: Proportion who rated this question as highly important**	**Delphi 2: Median (IQR)**	**Delphi 3: Proportion who rated this question as highly important**	**Delphi 3: Median (IQR)**	**Consensus reached in Delphi 3?**[b]

1.What are the best treatments that cure or delay the progression (worsening) of primary sclerosing cholangitis (PSC)?	All: 78.8% HCP: 80.0% PCP: 76.9%	All: 8(7,9) HCP: 8.5(7,9) PCP: 8(6.5,9)	All: 83.9% HCP: 83.3% PCP: 84.6%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	All: 93.3% HCP: 94.1% PCP: 92.3%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	Yes
2.Should all people above 40 years of age or those considered to be at risk of liver disease (because of family history of liver disease or because of their lifestyle) be tested for the presence of liver disease to identify liver diseases at an early stage?	All: 44.4% HCP: 40.0% PCP: 50.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(4,7.75)	All: 35.3% HCP: 27.8% PCP: 43.8%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7.75)	All: 33.3% HCP: 29.4% PCP: 37.5%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7.75)	No
3.Should people with primary sclerosing cholangitis (PSC) undergo screening (tested routinely) for cancer?	All: 46.9% HCP: 40.0% PCP: 58.3%	All: 6(5,9) HCP: 6(5,9) PCP: 6(5,9)	All: 50.0% HCP: 38.9% PCP: 66.7%	All: 6.5(5.75,8) HCP: 6(5.75,7.25) PCP: 6.5(5.25,9)	All: 44.8% HCP: 35.3% PCP: 58.3%	All: 6(6,7.5) HCP: 6(5.5,7) PCP: 6(6,9)	No

4.Are there any treatments that reverse the liver damage in primary sclerosing cholangitis (PSC)?	All: 59.4% HCP: 55.0% PCP: 66.7%	All: 7.5(5,8.75) HCP: 7.5(4.25,8) PCP: 7.5(6,9)	All: 70.0% HCP: 61.1% PCP: 83.3%	All: 7.5(6,9) HCP: 7.5(4.75,8.25) PCP: 7.5(7,9)	All: 72.4% HCP: 64.7% PCP: 83.3%	All: 7(6,9) HCP: 7(5,8) PCP: 7(7,9)	No
5.What are the best treatments that cure or delay the progression (worsening) of non-alcohol-related fatty liver disease (NAFLD)?	All: 76.5% HCP: 75.0% PCP: 78.6%	All: 8(6.75,9) HCP: 8.5(6.25,9) PCP: 8(6.75,9)	All: 87.5% HCP: 83.3% PCP: 92.9%	All: 8.5(7,9) HCP: 8.5(7,9) PCP: 8.5(7,9)	All: 90.3% HCP: 88.2% PCP: 92.9%	All: 9(8,9) HCP: 9(7.5,9) PCP: 9(7.75,9)	Yes
6.What are the best symptomatic treatments for itching in people with primary sclerosing cholangitis (PSC)?	All: 48.5% HCP: 45.0% PCP: 53.8%	All: 6(5,7.5) HCP: 6(5,7) PCP: 6(5.5,8)	All: 48.4% HCP: 38.9% PCP: 61.5%	All: 6(5,7) HCP: 6(4.75,7) PCP: 6(6,8)	All: 50.0% HCP: 41.2% PCP: 61.5%	All: 6.5(5,7) HCP: 6(4.5,7) PCP: 6.5(6,8)	No

7.Are there alternatives to invasive assessment of oesophageal varices in people with chronic liver disease?	All: 48.6% HCP: 30.0% PCP: 73.3%	All: 6(5,8) HCP: 6(3,7) PCP: 6(6,9)	All: 54.5% HCP: 33.3% PCP: 80.0%	All: 7(5.5,8) HCP: 6(4,7) PCP: 7(7,9)	All: 56.3% HCP: 29.4% PCP: 86.7%	All: 7(6,8) HCP: 6(4,7) PCP: 7(7,9)	No
8.Does vitamin D supplementation (adding Vitamin D in food or providing it in tablet form) increase the lifespan, health-related quality of life, and decrease complications in people with liver disease?	All: 37.1% HCP: 21.1% PCP: 56.3%	All: 6(4,7) HCP: 4(4,6) PCP: 6(6,9)	All: 39.4% HCP: 23.5% PCP: 56.3%	All: 6(4,7) HCP: 5(4,6.5) PCP: 6(6,9)	All: 37.5% HCP: 18.8% PCP: 56.3%	All: 6(4.25,7.75) HCP: 5(4,6) PCP: 6(6,8.75)	No
9.Should new methods to improve the understanding of evidence be developed for people with liver and gallbladder diseases?	All: 38.2% HCP: 25.0% PCP: 57.1%	All: 6(4,8) HCP: 5(4,6.75) PCP: 6(5,9)	All: 46.9% HCP: 27.8% PCP: 71.4%	All: 6(4,8) HCP: 5(4,7) PCP: 6(5,9)	All: 48.4% HCP: 29.4% PCP: 71.4%	All: 6(5,8) HCP: 6(4.5,7) PCP: 6(5,9)	No
10.What is the best treatment for people with early or very early hepatocellular carcinoma (HCC)?	All: 76.5% HCP: 75.0% PCP: 78.6%	All: 8(6.75,9) HCP: 7(6.25,9)	All: 87.5% HCP: 88.9% PCP: 85.7%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	All: 93.5% HCP: 94.1% PCP: 92.9%	All: 8(7,9) HCP: 8(7,9)	Yes

		PCP: 8(6.75,9)				PCP: 8(7.75,9)	
11.Should the methods used to assess nutrition of patients in liver disease be standardised?	All: 57.1% HCP: 60.0% PCP: 53.3%	All: 7(5,9) HCP: 7(5,8.75) PCP: 7(5,9)	All: 54.5% HCP: 55.6% PCP: 53.3%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,9)	All: 59.4% HCP: 58.8% PCP: 60.0%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,8)	No
12.Does dieting improve liver function and decrease the requirement for liver transplantation in obese people?	All: 48.6% HCP: 38.1% PCP: 62.5%	All: 6(4,8) HCP: 6(3,8) PCP: 6(5.25,7)	All: 44.1% HCP: 27.8% PCP: 62.5%	All: 6(4,7.25) HCP: 6(3.75,7.25) PCP: 6(5.25,7.75)	All: 48.5% HCP: 29.4% PCP: 68.8%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5.25,7)	No
13.Should general public be educated about non-alcohol-related fatty liver disease (NAFLD) with an aim to reduce the numbers of those that have it?	All: 72.2% HCP: 75.0% PCP: 68.8%	All: 7.5(6,9) HCP: 8(6.25,9) PCP: 7.5(6,9)	All: 73.5% HCP: 72.2% PCP: 75.0%	All: 8(6,9) HCP: 7.5(5.75,9) PCP: 8(6.25,9)	All: 81.8% HCP: 82.4% PCP: 81.3%	All: 8(7,9) HCP: 8(7,9) PCP: 8(7,9)	Yes

14.What are the best symptomatic treatments for itching in people with chronic liver diseases other than primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)?	All: 48.5% HCP: 35.0% PCP: 69.2%	All: 6(4.5,7) HCP: 6(4,7) PCP: 6(5,7.5)	All: 48.4% HCP: 27.8% PCP: 76.9%	All: 6(5,7) HCP: 6(4,7) PCP: 6(6,8)	All: 50.0% HCP: 29.4% PCP: 76.9%	All: 6.5(5,7) HCP: 6(4.5,7) PCP: 6.5(6.5,8)	No
15.Do treatments targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to the illness) work better than other treatments in people with primary sclerosing cholangitis (PSC)?	All: 19.4% HCP: 21.1% PCP: 16.7%	All: 5(4,6) HCP: 5(4,6) PCP: 5(4,6)	All: 20.0% HCP: 16.7% PCP: 25.0%	All: 5(4,6) HCP: 5(3.75,6) PCP: 5(4,6.75)	All: 20.7% HCP: 17.6% PCP: 25.0%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,6.75)	No
16.What are the treatments available to decrease weight in overweight people with non-alcohol-related fatty liver disease (NAFLD)?	All: 37.1% HCP: 35.0% PCP: 40.0%	All: 5(4,8) HCP: 5.5(4,7) PCP: 5(4,8)	All: 27.3% HCP: 22.2% PCP: 33.3%	All: 6(4,7) HCP: 6(4,6.25) PCP: 6(3,8)	All: 28.1% HCP: 23.5% PCP: 33.3%	All: 5(4,7) HCP: 5(5,6.5) PCP: 5(3,7)	No

17.What are the best treatments that cure or delay the progression (worsening) of non-alcohol related steatohepatitis (NASH)?	All: 67.6% HCP: 71.4% PCP: 61.5%	All: 8(5,8.25) HCP: 8(5.5,9) PCP: 8(5,8)	All: 71.0% HCP: 77.8% PCP: 61.5%	All: 8(6,9) HCP: 7.5(6.75,9) PCP: 8(5,8.5)	All: 76.7% HCP: 82.4% PCP: 69.2%	All: 8(6.75,9) HCP: 8(7,9) PCP: 8(5,8.5)	No
18.Do statins (or other treatments) delay liver failure in people with advanced liver disease?	All: 45.7% HCP: 36.8% PCP: 56.3%	All: 6(5,7) HCP: 6(4,7) PCP: 6(6,7.75)	All: 39.4% HCP: 35.3% PCP: 43.8%	All: 6(6,7) HCP: 6(3.5,7) PCP: 6(6,7.75)	All: 43.8% HCP: 37.5% PCP: 50.0%	All: 6(6,7) HCP: 6(5.25,7) PCP: 6(6,7.75)	No
19.What are the best treatments that provide temporary symptom relief in people with advanced liver disease?	All: 50.0% HCP: 35.0% PCP: 68.8%	All: 6.5(5,7.75) HCP: 6(5,7) PCP: 6.5(5.25,8.75)	All: 52.9% HCP: 33.3% PCP: 75.0%	All: 7(5.75,7.25) HCP: 6(5,7) PCP: 7(6.25,8)	All: 54.5% HCP: 35.3% PCP: 75.0%	All: 7(6,7) HCP: 6(5,7) PCP: 7(6.25,8)	No

20.Which is the most suitable antibiotic (or combination of antibiotics) in people with cholangitis (biliary infection)?	All: 64.7% HCP: 70.0% PCP: 57.1%	All: 7(5,8) HCP: 7(6,8) PCP: 7(5,8)	All: 68.8% HCP: 72.2% PCP: 64.3%	All: 7(5.25,8) HCP: 7(6,8) PCP: 7(5,8)	All: 67.7% HCP: 70.6% PCP: 64.3%	All: 7(5,8) HCP: 7(6,8) PCP: 7(5,8)	No
21.What are the best treatments that cure or delay the progression (worsening) of autoimmune hepatitis (AIH)?	All: 75.8% HCP: 68.4% PCP: 85.7%	All: 7(6.5,9) HCP: 7(6,8) PCP: 7(7,9)	All: 81.3% HCP: 77.8% PCP: 85.7%	All: 7.5(7,9) HCP: 7(6.75,8) PCP: 7.5(7,9)	All: 80.6% HCP: 76.5% PCP: 85.7%	All: 8(7,9) HCP: 7(6.5,8) PCP: 8(7,9)	Yes
22.Are there any methods other than liver biopsy (obtaining a piece of liver, usually using a needle, for examination under microscope) for the early diagnosis of primary sclerosing cholangitis (PSC) in people at risk of developing PSC?	All: 53.1% HCP: 36.8% PCP: 76.9%	All: 7(5,8) HCP: 6(5,7) PCP: 7(6.5,8)	All: 60.0% HCP: 47.1% PCP: 76.9%	All: 7(5,8) HCP: 6(5,8) PCP: 7(6.5,8)	All: 58.6% HCP: 43.8% PCP: 76.9%	All: 7(5,8) HCP: 6(5,7.75) PCP: 7(6.5,8)	No
23.What are the best nutritional interventions in people undergoing liver transplantation?	All: 52.8% HCP: 42.9% PCP: 66.7%	All: 7(5,8) HCP: 6(4,8) PCP: 7(5,8)	All: 51.5% HCP: 38.9% PCP: 66.7%	All: 7(5,8) HCP:	All: 53.1% HCP: 41.2% PCP: 66.7%	All: 7(5,8) HCP: 6(5,7) PCP: 7(6,8)	No

				6(4,7.25) PCP: 7(5,8)			
24.What are the best symptomatic treatments for fatigue (tiredness), joint pain, and other symptoms in people with people with autoimmune hepatitis (AIH)?	All: 61.8% HCP: 45.0% PCP: 85.7%	All: 7(6,8) HCP: 6(3.25,7) PCP: 7(7,9)	All: 65.6% HCP: 50.0% PCP: 85.7%	All: 7(6,8) HCP: 6.5(3.75,7) PCP: 7(7,9)	All: 64.5% HCP: 47.1% PCP: 85.7%	All: 7(6,8) HCP: 6(4,7) PCP: 7(7,9)	No
25.Prior to liver transplantation, is it better to transport the donor liver using a machine which pumps blood or preservation solution through the liver (machine perfusion) or is it better to transport it in the standard way of transporting it immersed in cold preservation solution (cold storage)?	All: 54.5% HCP: 42.1% PCP: 71.4%	All: 7(5,9) HCP: 6(5,8) PCP: 7(6,9)	All: 68.8% HCP: 61.1% PCP: 78.6%	All: 7(6,8.75) HCP: 7(5,8) PCP: 7(6.75,9)	All: 74.2% HCP: 70.6% PCP: 78.6%	All: 7(6,9) HCP: 7(6,8) PCP: 7(6.75,9)	No

26.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis C virus (HCV) infection?	All: 42.4% HCP: 42.9% PCP: 41.7%	All: 6(2,8) HCP: 5(1,8) PCP: 6(4.25,7.75)	All: 40.0% HCP: 44.4% PCP: 33.3%	All: 5.5(2,7) HCP: 4.5(1,8) PCP: 5.5(4.25,7)	All: 37.9% HCP: 47.1% PCP: 25.0%	All: 5(2,7) HCP: 5(1,8) PCP: 5(4.25,6.75)	No
27.Does education of people with liver disease about the natural course and treatment of liver disease improve the patient knowledge, patient responsibility, and decrease hospital visits?	All: 51.4% HCP: 52.4% PCP: 50.0%	All: 7(4,8) HCP: 7(4.5,7.5) PCP: 7(3.25,8.75)	All: 58.8% HCP: 50.0% PCP: 68.8%	All: 7(4,7.25) HCP: 6.5(4,7) PCP: 7(4,8.75)	All: 57.6% HCP: 47.1% PCP: 68.8%	All: 7(4,8) HCP: 6(4,7) PCP: 7(4,8)	No
28.What are the best treatments that cure or delay the progression (worsening) of primary biliary cholangitis (PBC)?	All: 61.8% HCP: 60.0% PCP: 64.3%	All: 7(5.75,8) HCP: 7(6,8) PCP: 7(5,8)	All: 68.8% HCP: 66.7% PCP: 71.4%	All: 7(6,8) HCP: 7(5.75,8) PCP: 7(5.75,8.25)	All: 74.2% HCP: 70.6% PCP: 78.6%	All: 7(6,8) HCP: 7(6,8) PCP: 7(6.5,8.25)	No

29.Is nurse-led care as effective or better than doctor-led care for non-alcohol related fatty liver disease (NAFLD)?	All: 38.2% HCP: 35.0% PCP: 42.9%	All: 5(4,8) HCP: 4.5(3,7.75) PCP: 5(4,8)	All: 31.3% HCP: 27.8% PCP: 35.7%	All: 5(4,7) HCP: 4(3,7) PCP: 5(4,7.25)	All: 25.8% HCP: 23.5% PCP: 28.6%	All: 5(4,7) HCP: 4(3.5,6.5) PCP: 5(4,7)	No
30.Is treatment targeted against deformation of bile duct (biliary stricture or narrowing of bile duct due to cancer) better than standard treatment for people with bile duct cancer?	All: 35.5% HCP: 27.8% PCP: 46.2%	All: 5(4,7) HCP: 5(2.75,7) PCP: 5(4,7.5)	All: 22.6% HCP: 11.1% PCP: 38.5%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,7)	All: 20.0% HCP: 11.8% PCP: 30.8%	All: 5(4,6) HCP: 5(3.5,6) PCP: 5(4,7)	No
31.Is surgery (in the form of removal of gallbladder) required in people with gallstones?	All: 24.2% HCP: 23.8% PCP: 25.0%	All: 5(4,6.5) HCP: 5(4,6.5) PCP: 5(4.25,6.75)	All: 30.0% HCP: 33.3% PCP: 25.0%	All: 5(4,7) HCP: 5(4,7) PCP: 5(3.5,6.75)	All: 24.1% HCP: 29.4% PCP: 16.7%	All: 5(4.5,6.5) HCP: 5(4.5,7) PCP: 5(3.5,6)	No
32.Should people with non-alcohol-related fatty liver disease (NAFLD) and non-alcohol-related steatohepatitis	All: 52.9% HCP: 50.0% PCP: 57.1%	All: 7(4,8) HCP:	All: 56.3% HCP: 50.0% PCP: 64.3%	All: 7(4.25,8) HCP: 6.5(2,7.25)	All: 54.8% HCP: 47.1% PCP: 64.3%	All: 7(5,8) HCP: 6(4,7.5)	No

(NASH) receive additional education about the condition?		6.5(2.5,7.75) PCP: 7(4,9)		PCP: 7(5.75,8.25)		PCP: 7(5.75,8.25)	
33.What is the best immunosuppressive regimen in adults undergoing liver transplantation?	All: 73.5% HCP: 60.0% PCP: 92.9%	All: 7(6,9) HCP: 7(5,8) PCP: 7(7,9)	All: 84.4% HCP: 77.8% PCP: 92.9%	All: 8(7,9) HCP: 7(6.5,8) PCP: 8(7,9)	All: 90.3% HCP: 82.4% PCP: 100.0%	All: 8(7,9) HCP: 8(7,8) PCP: 8(7.75,9)	Yes
34.Is endoscopic ultrasound (EUS) (using a ultrasound attached to the end of an endoscope) or magnetic resonance cholangio pancreatography (MRCP, a form of MRI scan) better in the diagnosis of common bile duct (CBD) stones?	All: 36.7% HCP: 22.2% PCP: 58.3%	All: 5(4,7) HCP: 4(3.75,6.25) PCP: 5(5,7)	All: 30.0% HCP: 22.2% PCP: 41.7%	All: 5(4,7) HCP: 5(4,6.25) PCP: 5(5,7)	All: 20.7% HCP: 11.8% PCP: 33.3%	All: 5(4,6) HCP: 5(4,6) PCP: 5(5,7)	No
35.How can we improve compliance to treatment (adherence to treatment or the degree to which a patient correctly	All: 67.6% HCP: 75.0% PCP: 57.1%	All: 7(5,8) HCP: 7(6.25,8)	All: 69.7% HCP: 72.2% PCP: 66.7%	All: 7(5,8) HCP: 7(4.75,8) PCP: 7(5,8)	All: 71.9% HCP: 70.6% PCP: 73.3%	All: 7(5,8) HCP: 7(5,8) PCP: 7(5,8)	No

follows medical advice) in people with liver disease?		PCP: 7(4.75,8)					
36.What are the best symptomatic treatments for relief of ulcerative colitis (UC) in people with primary sclerosing cholangitis (PSC) who have undergone liver transplantation?	All: 51.6% HCP: 36.8% PCP: 75.0%	All: 7(5,8) HCP: 6(4,7) PCP: 7(5.5,8.75)	All: 56.7% HCP: 44.4% PCP: 75.0%	All: 7(5,8) HCP: 6(4.75,7) PCP: 7(6.25,8.75)	All: 55.2% HCP: 41.2% PCP: 75.0%	All: 7(6,8) HCP: 6(5.5,7) PCP: 7(6.25,9)	No
37.What are the best symptomatic treatments for itching and fatigue (tiredness) in people with primary biliary cholangitis (PBC)?	All: 50.0% HCP: 45.0% PCP: 57.1%	All: 6.5(5,7) HCP: 6(5,7) PCP: 6.5(5,7.25)	All: 43.8% HCP: 33.3% PCP: 57.1%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,8)	All: 41.9% HCP: 29.4% PCP: 57.1%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,8)	No
38.Does education of people with asymptomatic (absence of symptoms) liver disease result in change of life style and cure/delay the progression (worsening) of liver disease?	All: 54.3% HCP: 45.0% PCP: 66.7%	All: 7(5,8) HCP: 6(4.25,7.75) PCP: 7(5,8)	All: 51.5% HCP: 38.9% PCP: 66.7%	All: 7(4.5,8) HCP: 5(3.5,7.25) PCP: 7(5,8)	All: 53.1% HCP: 35.3% PCP: 73.3%	All: 7(5,7.75) HCP: 5(4,7) PCP: 7(5,8)	No

39.What are the best treatments that are available for the treatment of pregnant women with cholestasis (condition where bile flow from the liver is obstructed)?	All: 38.7% HCP: 25.0% PCP: 63.6%	All: 6(4,7) HCP: 5(4,6.75) PCP: 6(6,8)	All: 31.0% HCP: 27.8% PCP: 36.4%	All: 6(4.5,7) HCP: 5(4,7) PCP: 6(6,8)	All: 27.6% HCP: 23.5% PCP: 33.3%	All: 6(5,7) HCP: 5(4.5,6.5) PCP: 6(5.25,7)	No
40.Is transarterial chemoembolisation (TACE) or transarterial embolisation (TAE) (blocking the blood supply to cancer with or without chemotherapy drugs) effective in the treatment of people with liver metastases?	All: 40.6% HCP: 36.8% PCP: 46.2%	All: 6(4,8) HCP: 6(3,8) PCP: 6(5,8.5)	All: 34.4% HCP: 22.2% PCP: 50.0%	All: 6(4,7) HCP: 5.5(3,6.25) PCP: 6(5,7)	All: 32.3% HCP: 23.5% PCP: 42.9%	All: 6(5,7) HCP: 6(3.5,6.5) PCP: 6(5,7)	No
41.Should people with liver metastases (cancer spread to the liver) from neuroendocrine cancer (a form of cancer that arises from cells that secrete	All: 36.7% HCP: 31.6% PCP: 45.5%	All: 6(4,7.25) HCP: 6(4,7) PCP: 6(5,8)	All: 40.0% HCP: 38.9% PCP: 41.7%	All: 6(4.75,7.25) HCP: 6(4,7) PCP: 6(5.25,8)	All: 37.9% HCP: 41.2% PCP: 33.3%	All: 6(5.5,7) HCP: 6(5,7) PCP: 6(5.25,8)	No

hormones and nervous system) undergo liver resection?							
42.What are the best methods available to decrease blood loss during liver resection?	All: 43.8% HCP: 26.3% PCP: 69.2%	All: 6(5,7.75) HCP: 5(3,7) PCP: 6(6,8)	All: 48.4% HCP: 27.8% PCP: 76.9%	All: 6(5,8) HCP: 5.5(4,7) PCP: 6(6.5,8)	All: 46.7% HCP: 29.4% PCP: 69.2%	All: 6(5,7.25) HCP: 6(5,7) PCP: 6(6,8)	No
43.What are the best treatments that cure or delay the progression (worsening) of chronic hepatitis B virus (HBV) infection?	All: 51.6% HCP: 42.1% PCP: 66.7%	All: 7(4,8) HCP: 6(4,7) PCP: 7(6,8)	All: 46.7% HCP: 38.9% PCP: 58.3%	All: 6(4.75,7.25) HCP: 5.5(4,7) PCP: 6(6,8)	All: 48.3% HCP: 41.2% PCP: 58.3%	All: 6(5,7.5) HCP: 6(4.5,7) PCP: 6(6,8)	No
44.What are the best treatments for people with polycystic liver disease?	All: 39.3% HCP: 17.6% PCP: 72.7%	All: 6(4,8) HCP: 5(4,6) PCP: 6(6,8)	All: 34.5% HCP: 16.7% PCP: 63.6%	All: 6(4,8) HCP: 5(3.75,6) PCP: 6(6,8)	All: 35.7% HCP: 17.6% PCP: 63.6%	All: 6(5,7) HCP: 5(4,6) PCP: 6(6,7)	No
45.Should the HCP dealing with childhood liver diseases be provided additional education about childhood liver diseases	All: 35.5% HCP: 15.0% PCP: 72.7%	All: 5(3,8) HCP:	All: 37.9% HCP: 16.7% PCP: 72.7%	All: 5(3.5,7.5) HCP:	All: 37.9% HCP: 17.6% PCP: 66.7%	All: 5(4.5,7.5) HCP: 5(2,5.5)	No

compared to standard education where childhood diseases are learnt as part of overall education?		5(2,5.75) PCP: 5(5,9)		5(2,5.25) PCP: 5(6,9)		PCP: 5(6,8.75)	
46.What is the best immunosuppressive regimen in children undergoing liver transplantation?	All: 65.6% HCP: 57.9% PCP: 76.9%	All: 8(4.25,9) HCP: 7(4,8) PCP: 8(6,9)	All: 67.7% HCP: 61.1% PCP: 76.9%	All: 8(6,9) HCP: 7.5(4,8) PCP: 8(6.5,9)	All: 70.0% HCP: 64.7% PCP: 76.9%	All: 8(6,9) HCP: 8(5,8) PCP: 8(6.5,9)	No
47.Should blood vessels supplying the liver be temporarily blocked in people undergoing liver resection? If so, what is the best way of performing this?	All: 31.0% HCP: 11.1% PCP: 63.6%	All: 6(4,7) HCP: 5(2.75,6) PCP: 6(5,7)	All: 26.7% HCP: 11.1% PCP: 50.0%	All: 5.5(4,7) HCP: 5(3.75,6) PCP: 5.5(5.25,7.75)	All: 27.6% HCP: 11.8% PCP: 50.0%	All: 6(5,7) HCP: 5(4,6) PCP: 6(5.25,7)	No
48.What is the best treatment that should be given to people who undergo liver transplantation for chronic hepatitis B virus (HBV) infection to prevent	All: 46.9% HCP: 40.0% PCP: 58.3%	All: 6(3.5,7) HCP: 6(3,7) PCP: 6(6,8)	All: 36.7% HCP: 22.2% PCP: 58.3%	All: 6(3,7) HCP: 6(2.75,6.25)	All: 37.9% HCP: 23.5% PCP: 58.3%	All: 6(5,7) HCP: 6(4,6.5) PCP: 6(6,7.75)	No

reinfection with chronic hepatitis B virus (HBV) infection?				PCP: 6(6,7.75)			
49.Are there alternatives to steroids in treating people with autoimmune hepatitis (AIH)?	-	-	All: 51.9% HCP: 40.0% PCP: 66.7%	All: 7(5,8) HCP: 6(4,7) PCP: 7(6,9)	All: 50.0% HCP: 35.7% PCP: 66.7%	All: 6.5(5,8) HCP: 5.5(3.75,7) PCP: 6.5(6,9)	No
50.What impact does the home situation have on recovery from chronic liver disease and its treatment?	-	-	All: 34.5% HCP: 13.3% PCP: 57.1%	All: 5(3.5,7.5) HCP: 4(3,6) PCP: 5(5,8)	All: 32.1% HCP: 0.0% PCP: 64.3%	All: 5(4,7) HCP: 4(3,5.25) PCP: 5(5,8)	No
51.Does cure of hepatitis C provide benefits to the patient outside reduction in liver related complications?	-	-	All: 29.2% HCP: 33.3% PCP: 22.2%	All: 5.5(3.25,7) HCP: 5(3,7) PCP: 5.5(4.5,6.5)	All: 30.4% HCP: 35.7% PCP: 22.2%	All: 6(4,7) HCP: 5.5(3,7.25) PCP: 6(4.5,6.5)	No

52.How fast does liver fibrosis (scarring) actually progress in non-alcoholic liver disease patients and does this predict overall outcome?	-	-	All: 62.1% HCP: 40.0% PCP: 85.7%	All: 7(6,8) HCP: 6(5,8) PCP: 7(7,8.25)	All: 64.3% HCP: 42.9% PCP: 85.7%	All: 7.5(6,8) HCP: 6(5,8) PCP: 7.5(7,8.25)	No
53.Should direct-acting antiviral treatments therapies be made more easily accessible to GPs and drug service clinics for treatment of hepatitis C virus?	-	-	All: 50.0% HCP: 46.7% PCP: 55.6%	All: 6.5(3.5,7) HCP: 6(3,7) PCP: 6.5(5.5,8)	All: 52.2% HCP: 50.0% PCP: 55.6%	All: 7(5,7) HCP: 6.5(4.5,7.25) PCP: 7(5.5,8)	No
54.Should patients diagnosed with liver fibrosis/cirrhosis related to NAFLD (non-alcoholic fatty liver disease) be offered more intensive nutritional support or dietician review?	-	-	All: 60.7% HCP: 46.7% PCP: 76.9%	All: 7(5,8) HCP: 6(3,8) PCP: 7(6.5,9)	All: 63.0% HCP: 50.0% PCP: 76.9%	All: 7(5,8) HCP: 7(4.5,8) PCP: 7(6.5,8.5)	No
55.Why have there been no alternatives to surgery in the form of new drug	-	-	All: 29.2% HCP: 20.0% PCP: 44.4%	All: 4.5(1.25,7) HCP: 4(1,6)	All: 26.1% HCP: 21.4% PCP: 33.3%	All: 4(2,7) HCP:	No

treatments for gall bladder disease & biliary sludge?				PCP: 4.5(2,7.5)		4(1.75,5.5) PCP: 4(2,7.5)	
56.Why is there no proper evidence-based research on nutrition as a way of managing gall bladder disease/biliary sludge?	-	-	All: 36.0% HCP: 26.7% PCP: 50.0%	All: 5(1.5,7) HCP: 4(1,7) PCP: 5(2.5,7.5)	All: 33.3% HCP: 28.6% PCP: 40.0%	All: 5(2,7) HCP: 4.5(1.75,7) PCP: 5(2.5,7.5)	No
57.Why is there such variability in the natural progression of people with primary sclerosing cholangitis: some are very sick and require a transplant whereas others can remain relatively healthy for a long period?	-	-	All: 56.0% HCP: 42.9% PCP: 72.7%	All: 7(6,7) HCP: 6(4,7) PCP: 7(6,8)	All: 54.2% HCP: 38.5% PCP: 72.7%	All: 7(6,7) HCP: 6(4,7) PCP: 7(6,8)	No
58.What are the warning signals that primary sclerosing cholangitis will be aggressive or cancerous?	-	-	All: 57.7% HCP: 53.3% PCP: 63.6%	All: 7(5.75,8.25)	All: 60.0% HCP: 50.0% PCP: 72.7%	All: 7(5.5,8) HCP:	No

				HCP: 7(5,8) PCP: 7(6,9)		6.5(4.75,8) PCP: 7(6,9)	
59.Does information on the impact of the complication on the people's quality of life improve the patient's informed decision- making process about treatment of liver and gallbladder diseases?	-	-	All: 46.4% HCP: 40.0% PCP: 53.8%	All: 6(4,7) HCP: 6(4,7) PCP: 6(4.5,8)	All: 44.4% HCP: 35.7% PCP: 53.8%	All: 6(4,7) HCP: 5.5(4,7) PCP: 6(5,8)	No
60.Will clinical pathways developed with patients and HCP having an equal say result in greater patient satisfaction and health in people with liver and gallbladder diseases?	-	-	All: 44.8% HCP: 33.3% PCP: 57.1%	All: 6(4.5,8) HCP: 5(4,8) PCP: 6(5,8)	All: 46.4% HCP: 35.7% PCP: 57.1%	All: 6(4.25,8) HCP: 5(3.75,8) PCP: 6(5.75,8.25)	No
61.Should high school teenagers be educated about the risks of hepatitis C?	-	-	All: 53.8% HCP: 40.0% PCP: 72.7%	All: 7(3.75,8) HCP: 5(2,7) PCP: 7(6,9)	All: 57.7% HCP: 42.9% PCP: 75.0%	All: 7(4.75,7.25) HCP: 5.5(2,7)	No

						PCP: 7(6.25,8.75)	
62.How can patients with end stage liver failure be better prepared for end of life. How can the HCP supporting them be better prepared to provide that support?	-	-	All: 65.5% HCP: 46.7% PCP: 85.7%	All: 7(6,8) HCP: 6(5,8) PCP: 7(7,9)	All: 67.9% HCP: 50.0% PCP: 85.7%	All: 7(6,8) HCP: 6.5(4.75,8) PCP: 7(7,9)	No
63.Is aggressive control of inflammation on colonic inflammatory bowel disease in primary sclerosing cholangitis associated with improved liver outcomes?	-	-	All: 48.0% HCP: 46.7% PCP: 50.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(6,8)	All: 50.0% HCP: 42.9% PCP: 60.0%	All: 6.5(5.25,7) HCP: 6(5,7) PCP: 6.5(6,8)	No
64.What is the best way to survey for cholangiocarcinoma in primary sclerosing cholangitis?	-	-	All: 61.5% HCP: 60.0% PCP: 63.6%	All: 7(5.75,8) HCP: 7(5,7) PCP: 7(6,9)	All: 60.0% HCP: 57.1% PCP: 63.6%	All: 7(6,8) HCP: 7(5,7) PCP: 7(6,9)	No
65.Should the criteria for polycystic liver disease and transplantation be changed to take into account the size the liver	-	-	All: 29.2% HCP: 13.3% PCP: 55.6%	All: 4.5(2,7) HCP: 4(2,6)	All: 30.4% HCP: 7.1% PCP: 66.7%	All: 6(3,7) HCP: 4(2,6) PCP: 6(6,7.5)	No

cysts can grow and the additional pressures on all the internal organs?				PCP: 4.5(5.5,7)			
66.Does control of colitis at the time of liver transplant reduce the risk of recurrent primary sclerosing cholangitis?	-	-	All: 36.0% HCP: 33.3% PCP: 40.0%	All: 6(5,7) HCP: 6(4,7) PCP: 6(5,8.25)	All: 33.3% HCP: 28.6% PCP: 40.0%	All: 6(5,7) HCP: 6(3.75,7) PCP: 6(5,8.25)	No
67.Are people with liver disease likely to develop other conditions, if so, what other conditions?	-	-	All: 42.9% HCP: 13.3% PCP: 76.9%	All: 6(3.25,7) HCP: 5(2,6) PCP: 6(6.5,8.5)	All: 46.4% HCP: 14.3% PCP: 78.6%	All: 6(3.25,7.75) HCP: 4.5(2,5.25) PCP: 6(6.75,8.25)	No
68.Do people with liver disease have a reduced life expectancy?	-	-	All: 30.0% HCP: 0.0% PCP: 60.0%	All: 5.5(3,8) HCP: 4(1,5) PCP: 5.5(6,9)	All: 34.5% HCP: 0.0% PCP: 66.7%	All: 6(3,8) HCP: 3.5(1.75,5.25	No

						) PCP: 6(6,9)	
69.Should transjugular intrahepatic portosystemic shunt (TIPS) be used earlier in management of variceal haemorrhage?	-	-	All: 51.9% HCP: 53.3% PCP: 50.0%	All: 7(5,7) HCP: 7(5,8) PCP: 7(5,7)	All: 55.6% HCP: 57.1% PCP: 53.8%	All: 7(6,7) HCP: 7(5.75,8) PCP: 7(5.5,7)	No
70.Should abnormal alanine transaminase (ALT) reference ranges be revised downwards in line with ACG (American College of Gastroenterology) guidance?	-	-	All: 36.0% HCP: 33.3% PCP: 40.0%	All: 6(5,7) HCP: 6(5,7) PCP: 6(5,7)	All: 37.5% HCP: 35.7% PCP: 44.4%	All: 6(5,7) HCP: 6(4.5,7.25) PCP: 6(5.875,7)	No

a Questions from 49 to 70 were collected during the first round of Delphi.

b Consensus was reached when at least 80% of Delphi-panel members scored between 7 and 9 for the specific question.

Abbreviations:

HCP = Healthcare professionals

IQR = interquartile range

PCP = Patients, carers, and public

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