

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a multicenter nationwide prospective cohort study to investigate the natural course and clinical outcome in benign liver tumors and cysts in the Netherlands: the BELIVER study
AUTHORS	Furumaya, Alicia; Haring, Martijn; van Rosmalen, Belle; Klompenhouwer, Anne; Besselink, Marc; de Man, Robert; IJzermans, Jan; Thomeer, Maarten; Kramer, Matthijs; Coolson, Mariëlle; Tushuizen, Maarten; Schaapherder, A.F.M.; de Haas, Robbert; Duiker, Evelien; Kazemier, Geert; van Delden, Otto; Verheij, Joanne; Takkenberg, R.; Cuperus, Frans; De Meijer, Vincent; Erdmann, Joris

VERSION 1 – REVIEW

REVIEWER	Oldhafer, K Asklepios Hospital Group
REVIEW RETURNED	06-Nov-2021

GENERAL COMMENTS	This is a very interesting study on benign liver tumors. The natural history over several years is not known. With this Dutch study, many questions about benign liver tumors can probably be answered, even in the long-term course. A comparable study on this topic has not been done so far.
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REVIEWER	Bernon, Marc University of Cape Town, Surgery
REVIEW RETURNED	24-Jan-2022

GENERAL COMMENTS	<p>The study is well constructed and has scientific merit. I have two comments for the authors:</p> <p>1. Exclusion of uncommon and clinically less relevant BLTCs</p> <p>Exclusion of hepatic angiomyolipomas, biliary hamartomas and polycystic disease makes sense. It would also make sense to exclude biliary cysts (intrahepatic choledochal cysts).</p> <p>In my opinion MCNs and IPNBs (previous cystadenomas) should be included even though they are rare. These lesions are often part of the differential diagnosis of simple cystic lesions and visa versa.</p> <p>Potential examples: A patient with a suspected MCN undergoes surgery but histology confirms a simple cyst. Equally a patient with a suspected simple cyst is followed up, but the cyst increases in size and turns out to be a MCN when it is operated on.</p>
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	<p>Exclusion of these cystic lesions may limit the clinical relevance of the study.</p> <p>2. Minimum follow up period</p> <p>The minimum follow up period of one year may not be long enough to adequately assess the primary and secondary objectives of the study. Consideration should be given to extending the follow up period in order for the findings to be clinically relevant. This would seem to mainly be a problem for patients who are included towards the end of the study period.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. K Oldhafer, Asklepios Hospital Group Comments to the Author:

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This is a very interesting study on benign liver tumors. The natural history over several years is not known. With this Dutch study, many questions about benign liver tumors can probably be answered, even in the long-term course. A comparable study on this topic has not been done so far.

Reviewer: 2

Dr. Marc Bernon, University of Cape Town Comments to the Author:

Comments to the Author:

The study is well constructed and has scientific merit. I have two comments for the authors:

Reviewer 2, comment 1. Exclusion of uncommon and clinically less relevant BLTCs

Exclusion of hepatic angiomyolipomas, biliary hamartomas and polycystic disease makes sense. It would also make sense to exclude biliary cysts (intrahepatic choledochal cysts).

In my opinion MCNs and IPNBs (previous cystadenomas) should be included even though they are rare. These lesions are often part of the differential diagnosis of simple cystic lesions and visa versa.

Potential examples: A patient with a suspected MCN undergoes surgery but histology confirms a simple cyst. Equally a patient with a suspected simple cyst is followed up, but the cyst increases in size and turns out to be a MCN when it is operated on.

Exclusion of these cystic lesions may limit the clinical relevance of the study.

Response: We highly appreciate the in-depth evaluation of our study protocol by the reviewer. We acknowledge that choledochal cysts will not be included in the BELIVER study, and have clarified this in the revised study protocol (L87).

Dr. Bernon brings up an important point regarding MCNs and IPNBs. At time of submission of the protocol, we did not plan to include MCNs and IPNBs. However, at study commencement (eventually October 2021 rather than August 2021, adjusted in L11-12, L81-82), we realized excluding MNs and IPNBs would not be feasible due to challenging differentiation with simple cysts. We have adjusted the revised study protocol accordingly (L43-46, L51-52, L86-88).

Reviewer 2, comment 2. Minimum follow up period

The minimum follow up period of one year may not be long enough to adequately assess the primary and secondary objectives of the study. Consideration should be given to extending the follow up period in order for the findings to be clinically relevant. This would seem to mainly be a problem for patients who are included towards the end of the study period.

Response: We acknowledge that a longer follow-up would be preferable. Therefore, we have decided to extend the minimum follow-up to two years.

VERSION 2 – REVIEW

REVIEWER	Bernon, Marc University of Cape Town, Surgery
REVIEW RETURNED	12-Apr-2022
GENERAL COMMENTS	The concerns that I raised have been addressed. I look forward to the results of the study