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## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055104
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2021
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Keywords:	Hepatobiliary surgery < SURGERY, Hepatobiliary tumours < ONCOLOGY, Hepatobiliary disease < GASTROENTEROLOGY



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## Study protocol for a multicenter nationwide prospective cohort study to investigate the natural course and clinical outcome in benign liver tumours and cysts in the Netherlands: the BELIVER study

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51 **Key words:** Benign Liver Tumours and Cysts, Patient Reported Outcomes, Surgery, Interventional Radiology, Study Protocol

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3 **1 Abstract**

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5 **2 Introduction:** Benign liver tumours and cysts (BLTCs) comprise a heterogeneous group of cystic and  
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7 solid lesions, including hepatic hemangioma, focal nodular hyperplasia and hepatocellular adenoma.  
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9 Some BLTCs, for example (large) hepatocellular adenoma, are at risk of complications. Incidence of  
10  
11 malignant degeneration or hemorrhage is low in most other BLTCs. Nevertheless, the diagnosis BLTC  
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13 may carry a substantial burden and patients may be symptomatic, necessitating treatment. The  
14  
15 indications for interventions remain matter of debate. The primary study aim is to investigate patient  
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17 reported outcomes (PROs) of patients with BLTCs, with special regard to the influence of invasive  
18  
19 treatment as compared to the natural course of the disease.  
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23 **10 Methods and analysis:** A nationwide observational cohort study of BLTC patients will be performed  
24  
25 between August 2021 and August 2026. Inclusion will be open from August 2021 until August 2025.  
26  
27 During surveillance, a questionnaire regarding symptoms and their impact will be sent to participants  
28  
29 on a biannual basis and more often in case of invasive intervention. The questionnaire was previously  
30  
31 developed based on patient reported outcomes (PROs) considered relevant to patients with BLTCs  
32  
33 and their caregivers. Most questionnaires will be administered by computerized adaptive testing  
34  
35 through the Patient-Reported Outcomes Measurement Information System (PROMIS). Data, such as  
36  
37 treatment outcomes, will be extracted from electronic patient files. Multivariable analysis will be  
38  
39 performed to identify patient and tumour characteristics associated with significant improvement in  
40  
41 PROs or a complicated postoperative course.  
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45 **20 Ethics and dissemination:** The study was assessed by the Medical Ethics Committee of the University  
46  
47 Medical Center Groningen and the Amsterdam UMC. Local consultants will provide information and  
48  
49 informed consent will be asked of all patients. Results will be published in a peer-reviewed journal.  
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52 **23 Study registration:** Netherlands Trial Register - NL8231 - 10-12-2019  
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3 24 **Strengths and limitations of this study**  
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- 5 25 • The BELIVER-study will lead to an expansion of the current knowledge on patient reported  
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7 26 outcomes (PROs) in patients with benign liver tumours and cysts (BLTCs) in the  
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9 27 Netherlands and the influence of interventions hereupon  
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12 28 • The long-term, biannual follow-up and increased frequency of questionnaires  
13  
14 29 postoperatively will provide data to enable professionals to better inform patients what  
15  
16 30 to expect and to enable patients and professionals to make well-informed treatment  
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18 31 decisions together  
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21 32 • As the study is conducted nationwide, the extent of medical practice variation regarding  
22  
23 33 management of BLTCs can be assessed  
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25 34 • Questionnaires are continued even after cessation of medical follow-up, which may  
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27 35 introduce disease burden but may just as well be a confirmation of wellbeing for patients  
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30 36 • Patient burden is minimized through use of questionnaires using computerized adaptive  
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32 37 testing  
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## 38 Introduction

39 Benign liver tumours and cysts (BLTCs) comprise a heterogeneous groups of cystic and solid  
40 lesions.<sup>1</sup> Although extensive research has been performed in the field of BLTCs, their natural course  
41 including their influence on patient reported outcomes (PROs) has been underexposed. The most  
42 common and relevant BLTC are simple non-parasitic liver cysts (estimated incidence of 18%) and the  
43 solid lesions hepatic hemangioma (0.4-20%), focal nodular hyperplasia (FNH, 0.4-3%), and  
44 hepatocellular adenoma (HCA, 0.001-0.004%).<sup>2-5</sup>

45 Many BLTCs are found incidentally on routine imaging for unrelated pathology.<sup>2,6</sup> The rising  
46 incidence of those so called incidentalomas is at least partly attributable to the increasing use of non-  
47 invasive imaging modalities.<sup>7</sup> Main complications of BLTCs are bleeding and malignant  
48 transformation - both of which rarely occur.<sup>8,9</sup> Of the four most common and relevant solid and cystic  
49 lesions, only (large) HCAs have a known risk of malignant transformation.<sup>9</sup> Treatment indications  
50 remain an important matter of debate. In general, treatment of BLTCs is only recommended when  
51 they either have a risk of complications or cause severe complaints often with associated impairment  
52 of quality of life. When little or no risk of complications is present, the latter is often the sole  
53 indication for treatment.<sup>2</sup>

54 However, this recommendation has various nuances which hampers shared decision and makes  
55 the management of BLTCs exceptionally prone to undesirable practice variation.<sup>10,11</sup> Firstly, the  
56 influence of treatment on PROs is important but rarely reported.<sup>12</sup> Secondly, in current literature,  
57 PROs after treatment by surgery or interventional radiology are rarely compared with conservative  
58 management.<sup>12,13</sup> Finally, variations in diagnostic methods may be present, for example FNH is easily  
59 misdiagnosed as HCA when inadequate diagnostics are applied.<sup>2,14,15</sup>

60 Therefore, this observational cohort study aims to investigate the PROs of patients with BLTCs  
61 during their natural courses as well as after treatment. These data will enable patients and  
62 professionals to make well-informed treatment decisions together to optimize value-based  
63 outcomes. In addition, the study will provide an overview of the clinical practice in the Netherlands.

## 64 **Methods and analysis**

### 65 *Study design*

66 The BELIVER study (Natural Course and Clinical Outcome in BEnign LIVER Tumours and Cysts) is an  
67 investigator-initiated, nationwide, multicenter observational cohort study. All Dutch medical centers  
68 treating patients with BLTCs are eligible for participation, facilitated and coordinated through the  
69 Dutch Benign Liver Tumor Group (DBLTG) network. The study was registered in the Netherlands Trial  
70 Register (NTR NL8231).

71

### 72 *Study population*

73 Adult patients ( $\geq 18$  years old) presenting with a common and/or clinically relevant BLTC at  
74 participating centers are eligible for inclusion. Clinically relevant BLTCs are defined as all BLTCs  
75 potentially eligible for either surgical intervention or follow-up. Strict cut-off values regarding BLTC  
76 size will not be defined and are assessed on a per patient basis by treating professionals.

77 The study will be conducted from August 2021 till August 2026, with inclusion during the period of  
78 August 2021 till August 2025. Thus, the minimal follow-up for each patient will be one year. Patients  
79 diagnosed with an uncommon BLTC, unwilling or unable to provide written informed consent or to  
80 fill in the questionnaire and patients with another disease substantially affecting PROs will be  
81 excluded. Uncommon BLTCs and clinically less relevant are excluded. These include: mucinous cystic  
82 lesions of the liver and biliary system and intraductal papillary neoplasms of the liver and bile ducts  
83 (MCNs and IPNBs, "cystadenomas"), hepatic angiomyolipoma and biliary hamartoma / Von  
84 Meyenburg complexes.<sup>16</sup> Additionally, patients with polycystic liver disease are excluded as they  
85 form a circumscript group of patients with very typical symptoms and treatments, including liver  
86 transplantation and they are currently already included in another international study.<sup>17</sup>

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### 88 *Study objectives and outcomes*



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3 89 The primary study objective is to systematically record the PROs during the natural course and  
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5 90 after (minimally) invasive treatment of patients with BLTCs. Secondary study objectives are to  
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7 91 evaluate changes in tumour/cyst diameter and the occurrence of any mortality and complications,  
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9 92 related to either the natural course of the disease (malignant transformation or hemorrhage) or  
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11 93 related to tumour or cyst treatment. The study will also provide an overview of potential variation in  
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13 94 management and outcomes of Dutch patients with BLTCs.

16 95 The primary study outcome measure is change in PROs including severity of symptoms from the  
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18 96 start compared to the end of the follow-up period. Symptoms are measured by a questionnaire,  
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20 97 focusing on PROs relevant to patients with BLTCs and their caregivers and partly administered  
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22 98 through the Patient-Reported Outcomes Measurement Information System (PROMIS).

25 99 The questionnaire is administered biannually. Although a multiplicity would have enabled a more  
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27 100 accurate longitudinal study with correction for confounding events, increasing questionnaire  
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29 101 frequency will also probably lead to a reduction of study adherence and result in an increased patient  
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31 102 burden. Moreover, one might argue that continuing surveys even after cessation of medical follow-  
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33 103 up may introduce disease burden that remind patients of their diagnosis. However, the biannual  
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35 104 questionnaires may just as well be a confirmation of wellbeing for patients. In addition, currently  
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37 105 some patients might be subjected to extended periods of follow-up even in the absence of this study  
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39 106 as a consequence of practice variation.

43 107 Secondary outcomes related to interventions include: postoperative complications according to  
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45 108 Clavien-Dindo Classification, the Comprehensive Complication Index, 30 and 90-day mortality, and  
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47 109 the Society of Interventional Radiology classification for adverse events.<sup>18-20</sup> Treatment effects will be  
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49 110 evaluated with additional questions regarding intervention indication, the effectiveness of the  
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51 111 treatment on symptoms, and the likeliness of patients to choose the treatment again. If surgical  
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53 112 intervention is applied, questions on incisional herniation are added to the questionnaire after  
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55 113 intervention. Supplementary questionnaires will be sent after interventions at three, six, and twelve  
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3 114 months, thereafter resuming to biannual questionnaires. An example of two cases and their follow-  
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5 115 up with questionnaires is shown in figure 1.  
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7 116 In addition to data collected from questionnaires, data will be extracted from local electronic  
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9 117 patient files. This includes the following data: 1) baseline patient characteristics (age, gender,  
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11 118 comorbidity); 2) tumour or cyst characteristics (among which diameter, imaging, and  
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13 119 histopathological examination), 3) certain data specific for the type of BLTC the patient was  
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15 120 diagnosed with, and 4) details on the intervention performed. Table 1 summarizes collected  
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17 121 variables. All tumour and cyst diameters will be measured according to RECISTv1.1 criteria.<sup>21</sup>  
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### 23 123 *Patient involvement and questionnaire selection*

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25 124 Various questionnaires have been used to evaluate PROs of patients with BLTCs. However, these  
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27 125 questionnaires were not developed for the evaluation of outcomes of BLTC patients and therefore  
28  
29 126 most likely do not appropriately measure outcomes relevant to patients with BLTCs. Based on  
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31 127 literature and focus groups with patients with BLTCs and their caregivers, we selected relevant  
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33 128 patient-reported outcomes (PROs). These were: insecurity/anxiety, pain, fatigue and limitations in  
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35 129 daily life. The domains anxiety, fatigue, ability to participate and pain interference will be evaluated  
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37 130 in the current study using computerized adaptive testing through the Dutch-Flemish Patient-  
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39 131 Reported Outcomes Measurement Information System (PROMIS).<sup>22-24</sup> PROMIS instruments have  
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41 132 recently successfully been used in research on various patient groups.<sup>25,26</sup> Additionally, numerical  
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43 133 rating scales for pain (current and most, least, and average pain over a week) and two general health  
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45 134 and quality of life questions will be assessed.  
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### 52 136 *Data collection*

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54 137 Data will be collected using electronic case report forms using an online based platform which  
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56 138 automatically generates patient identifiers consisting of the hospital code and a number. A subject  
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58 139 identification log will be kept in each center by the principal investigator or local coordinating  
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3 140 investigator. This subject identification log will contain the personal details which can be used to  
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5 141 send questionnaires to patients. Only this dedicated person has the key for decoding patient data. At  
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7 142 completion of the follow-up period, the database will be exported from the online platform. The  
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9 143 database will be hosted on a secure server with the infrastructure, configuration, and licenses that  
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11 144 are consistent with current norms and laws to ensure safe and secure data storage and processing.  
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#### 146 *Sample size and statistical analysis*

147 No sample size calculation was conducted as this is an observational cohort study. A previous  
148 single center prospective cohort study on the (conservative and surgical) treatment of HCAs and  
149 FNHs included 110 patients in 4.5 years.<sup>27</sup> This current study has a broader scope as it spans across at  
150 least seven medical centers, includes more BLTC types, and also includes patients treated by  
151 interventional radiological procedures. Therefore, the aim is to include at least 450 patients.

152 Statistical analyses will be performed using SPSS statistics for Windows version 24.0 (SPSS Inc.,  
153 Chicago, IL, USA) and R for Windows version 3.6.3 (R Core Team, Vienna, Austria). Categorical data  
154 will be presented as proportions. Continuous data will be presented as mean and standard deviation  
155 (SD) or median and interquartile range (IQR). Categorical variables will be compared using the Fisher  
156 exact test or the Chi-square test. Continuous variables will be compared using the Mann-Whitney U  
157 test or the Student's t-test. Cox proportional hazards model will be used when appropriate. A two-  
158 tailed  $P < 0.05$  will be considered statistically significant.

159 Scores for each patient-reported outcome measure at the start and end of follow-up will be  
160 compared using a paired t-test, and factors associated with significant gain in these measures will be  
161 evaluated. Patients will be stratified according to treatment strategy (conservative, surgical,  
162 transarterial (chemo-)embolization and lipiodolization, aspiration and sclerotherapy, or  
163 radiofrequency or microwave ablation). Sensitivity analyses will be performed for the type of BLTC,  
164 and for the time between questionnaires and hospital visits, as hospital visits and imaging may

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3 165 increase the extent of the emotional burden experienced by patients. For surgically treated patients,  
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5 166 predictors of a complicated course (Clavien Dindo  $\geq 3b$ ) will also be evaluated.  
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10 168 *Trial sites*

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12 169 Initiating centers are Amsterdam UMC and University Medical Center Groningen. At least all other  
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14 170 centers participating in the DBLTG will be included. Participating centers will at least include:

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- 17 1. Amsterdam University Medical Centers, Amsterdam, The Netherlands
  - 18 172 2. University Medical Center Groningen, Groningen, The Netherlands
  - 19 173 3. Erasmus Medical Center, Rotterdam, The Netherlands
  - 20 174 4. Maastricht University Medical Center+, Maastricht, The Netherlands
  - 21 175 5. Radboud University Medical Center, Nijmegen, The Netherlands
  - 22 176 6. Leiden University Medical Center, Leiden, The Netherlands

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30 177 In order to identify and/or avoid selection bias, non-DBLTG and non-academic centers will also be  
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32 178 enabled to join during the course of the study.  
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3 179 **Ethics and dissemination**

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5 180 *Ethical considerations*

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7 181 This trial will be conducted in accordance with the principles of the Declaration of Helsinki and as  
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9 182 stated in the laws governing human research and Good Clinical Practice. The study does not interfere  
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11 183 or change the process of treatment of the BLTCs in the included patients. The study was determined  
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13 184 to be beyond the scope of the Dutch law on research on human subjects (WMO) according to the  
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15 185 Medical Ethics Committee (MEC) of the Amsterdam UMC, location AMC (MEC AMC W19\_134 #  
16  
17 186 19.167) and the MEC of the University Medical Center Groningen (MEC UMCG 201900292). The  
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19 187 study will be evaluated by MECs of all participating centers. Moreover, the study will also be  
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21 188 reviewed according to local requirements of each center. Finally, the study proposal was reviewed by  
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23 189 the scientific committee of the DBLTG. All substantial amendments will be notified to these  
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25 190 committees and organizations. Data will be kept for at least fifteen years after study completion.  
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32 192 *Informed consent and withdrawal of consent*

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34 193 Informed consent for use of the questionnaires and the data collected from the electronic patient  
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36 194 files will be obtained from all patients by the treating professional in participating centers.  
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38 195 Information will be provided to patients by physicians. This will consist of both printed folders and  
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40 196 links to digital information. A dedicated website has been created (URL:  
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42 197 <https://www.DBLTG.nl/BELIVER/>). Also, dedicated e-mailboxes have been constructed.  
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45 198 Patients can withdraw from study participation at any time and without consequences or reason.  
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47 199 With each questionnaire that is sent, it is noted that if patients wish to withdraw, they can do so at  
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49 200 any time. In case of withdrawal, patients will be contacted and asked for allowance of data analysis  
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51 201 until that point. There is no specific replacement of individual subjects after withdrawal. Patients  
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53 202 who have chosen to withdraw from the study will receive follow-up and treatment according to  
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55 203 current standard of care by their treating physician. If participants do not respond to questionnaires,  
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3 204 a reminder will be sent after one month. If there is no reaction to this reminder, patients will be  
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5 205 contacted by telephone to verify if they still wish to participate or not.  
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10 207 *Additional burden and risk associated with study participation*

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12 208 The proposed study does not interfere with standard patient care. No additional blood samples,  
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14 209 increase in number of hospital visits, physical examination or other tests are indicated. However, in  
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16 210 case of cessation of medical follow-up, patients included in the study will still receive questionnaires.  
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19 211 There are no direct benefits for patients participating in this study. There are no risks involved  
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21 212 with participating in this study. The additional burden of the study is considered to be minimal.  
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23 213 Completion of the questionnaire will take approximately 15 minutes. The questionnaires might  
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25 214 remind patients of their BLTC diagnosis. Some of the questions might be confronting (i.e. questions  
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27 215 regarding the impact of complaints on daily life and work).  
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32 217 *Administrative aspects, monitoring and publication*

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34 218 All results, either positive or negative, will be published in a peer-reviewed journal. All results will  
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36 219 be reported suiting reporting guidelines provided by the EQUATOR-network (URL:

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38 220 <https://www.equator-network.org/>). All Dutch centers collaborating in the DBLTG will be invited to  
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40 221 participate in this study. All results originating from this study will be published on behalf of the

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42 222 DBLTG. Co-authorship is available for one physician at each center supplying at least five cases and  
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44 223 for two physicians at each center supplying at least ten cases. In each center it may be decided

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46 224 individually which one or two physicians will be mentioned as co-authors. Co-authorships may also  
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48 225 be offered to persons who contributed substantially to the conceptualization and execution of the

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50 226 study. All co-authorships will have to fulfill the international committee of medical journal editors  
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52 227 (ICMJE) regulations.<sup>28</sup>  
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55 228 In addition to these co-authorships, others involved may be listed as collaborator and the journal  
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57 229 will be asked to list them as such also in MEDLINE/PubMed. For each center supplying at least thirty  
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230 cases, one collaborator may be included; for centers supplying at least forty cases, two collaborators;  
231 for centers supplying fifty or more cases, three collaborators.

For peer review only

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3 **List of abbreviations**  
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6 BLTCs Benign liver tumours and cysts  
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8 FNH Focal nodular hyperplasia  
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10 HCA Hepatocellular adenoma  
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13 MEC Medical ethics committee  
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15 PRO Patient reported outcome  
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17 WMO Medical research involving human subjects act; in Dutch: wet medisch-wetenschappelijk  
18 onderzoek met mensen  
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5 *Authors' contributions*  
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9 BVvR, AJK, MGB, RAdM, JNMIIJ, MGJT, MK, MMEC, MET, AEB, RJdH, EWD, GK, OMvD, JV, RBT, FJCC:  
10  
11 conceptualization of the manuscript and revision of the manuscript  
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14 All collaborating authors approved the final manuscript.  
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19 *Funding statement*  
20

21 This work was supported by a grant from the Dutch Society of Gastroenterology (Nederlandse  
22  
23 Vereniging voor Gastroenterologie) to the Dutch Benign Liver Tumour Group, and by a personal grant  
24  
25 from Amsterdam UMC location AMC to A. Furumaya  
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30 *Competing interests*  
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32 The authors declare that they have no competing interests.  
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36 *Word count: 2754/4000 words*  
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## Acknowledgements

Collaborating authors on behalf of the Dutch Benign Liver Tumour Group (DBLTG)

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## Figures

Figure title: Figure 1

Figure legend: An overview of the hospital visits and study questionnaires of two fictional patients included in the study are shown. In general, patients receive a questionnaire every six months. Deviations from this normal course of follow-up caused by patients undergoing an intervention are indicated by red questionnaires. Please note that these two patients were included around similar dates, but total follow-up durations might differ between patients depending on the date of inclusion.



Table 1 Overview of recorded variables

Baseline information		Tumour or cyst specific questions		Treatment characteristics		
Patient characteristics	Tumour/cyst characteristics*	Solid lesions	Cystic lesions	Intervention	Surgery	Interventional radiology
Age	Total number of lesions at baseline	Focal nodular hyperplasia	Simple hepatic cysts	Date of intervention	Type of approach (open, laparoscopic, robot)	Type of procedure (aspiration sclerotherapy, TAE, RFA/MWA)
Sex	Location of lesion (left hemiliver, right hemiliver, bilobar)	Hemangioma		Duration of hospital stay	Occurrence and reason for conversion	Sclerotherapy (volume of aspiration, length of sclerosing, type of sclerosing agent)
Mortality If yes, reason	Type of lesion	Hepatocellular adenoma		Operation or procedure time	Type of procedure (fenestration, wedge resection, segmental resection, hemihepatectomy, transplantation)	TAE (volume and type of embolization agent [simple embolization, chemo-embolization or lipiodolization])
Comorbidity (ASA score and Elixhauser comorbidity index)	Diameter, date and modality of diagnosis			30-day and 90-day mortality	Specification of resected segments	
	Diameter, date and modality of follow-up				Amount of blood loss	
	Occurrence of misdiagnosis If so, revised diagnosis and diagnostic modality				Additional procedures (e.g. argon beam coagulation, omental transposition, concurring cholecystectomy)	
	Histopathological diagnosis with immunohistochemistry if available				Complications (type, CD, CCI & SIR)	

Abbreviations: ASA: American society of anesthesiologists; TAE, transarterial embolization; RFA, radiofrequency ablation; MWA, microwave ablation; CD, Clavien-Dindo; CCI, comprehensive complication index; SIR, society of interventional radiologists classification for adverse events.\* According to RECISTv1.1 criteria, lesions will only be measured on CT or MRI (longest diameter), measured on the transversal plane on post-contrast series. Maximum of two lesions. If the target lesion is not visible on follow-up imaging (index imaging is imaging shortest before inclusion), then the diameter of the next largest tumour will be measured.

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**Example patient A**

Hospital visits

Inclusion



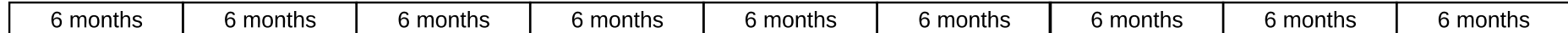
Visit



BMJ Open Visit



End of follow-up



Study questionnaires



**Example patient B**

Hospital visits

Inclusion



Visit, intervention planned



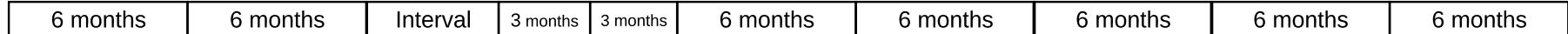
Visit



Visit



End of follow-up



Study questionnaires



**Legend**



Deviation from regular follow-up after an intervention (surgery or interventional radiology), after which follow-up frequency is temporarily increased.



Intervention: surgery or interventional radiology.

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055104.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Mar-2022
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<b>Primary Subject Heading</b> :	Gastroenterology and hepatology
Secondary Subject Heading:	Patient-centred medicine, Radiology and imaging, Surgery
Keywords:	Hepatobiliary surgery < SURGERY, Hepatobiliary tumours < ONCOLOGY, Hepatobiliary disease < GASTROENTEROLOGY

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## 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

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15 \* Shared first authorship

16 # Shared senior authorship

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51 **Key words:** Benign Liver Tumours and Cysts, Patient Reported Outcomes, Surgery, Interventional Radiology, Study Protocol

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1  
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3 **1 Abstract**

4  
5 **2 Introduction:** Benign liver tumours and cysts (BLTCs) comprise a heterogeneous group of cystic and  
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7 solid lesions, including hepatic hemangioma, focal nodular hyperplasia and hepatocellular adenoma.  
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9 Some BLTCs, for example (large) hepatocellular adenoma, are at risk of complications. Incidence of  
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11 malignant degeneration or hemorrhage is low in most other BLTCs. Nevertheless, the diagnosis BLTC  
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13 may carry a substantial burden and patients may be symptomatic, necessitating treatment. The  
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15 indications for interventions remain matter of debate. The primary study aim is to investigate patient  
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17 reported outcomes (PROs) of patients with BLTCs, with special regard to the influence of invasive  
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19 treatment as compared to the natural course of the disease.  
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23 **10 Methods and analysis:** A nationwide observational cohort study of BLTC patients will be performed  
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25 between October 2021 and October 2026, the minimal follow-up will be two years. During  
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27 surveillance, a questionnaire regarding symptoms and their impact will be sent to participants on a  
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29 biannual basis and more often in case of invasive intervention. The questionnaire was previously  
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31 developed based on patient reported outcomes (PROs) considered relevant to patients with BLTCs  
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33 and their caregivers. Most questionnaires will be administered by computerized adaptive testing  
34  
35 through the Patient-Reported Outcomes Measurement Information System (PROMIS). Data, such as  
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37 treatment outcomes, will be extracted from electronic patient files. Multivariable analysis will be  
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39 performed to identify patient and tumour characteristics associated with significant improvement in  
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41 PROs or a complicated postoperative course.  
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45 **20 Ethics and dissemination:** The study was assessed by the Medical Ethics Committee of the University  
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47 Medical Center Groningen and the Amsterdam UMC. Local consultants will provide information and  
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49 informed consent will be asked of all patients. Results will be published in a peer-reviewed journal.  
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52 **23 Study registration:** Netherlands Trial Register - NL8231 - 10-12-2019  
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3 24 **Strengths and limitations of this study**  
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- 5 25 • The BELIVER-study will lead to an expansion of the current knowledge on patient reported  
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7 26 outcomes (PROs) in patients with benign liver tumours and cysts (BLTCs) in the  
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9 27 Netherlands and the influence of interventions hereupon  
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12 28 • The long-term, biannual follow-up and increased frequency of questionnaires  
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14 29 postoperatively will provide data to enable professionals to better inform patients what  
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16 30 to expect and to enable patients and professionals to make well-informed treatment  
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18 31 decisions together  
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21 32 • As the study is conducted nationwide, the extent of medical practice variation regarding  
22  
23 33 management of BLTCs can be assessed  
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25 34 • Questionnaires are continued even after cessation of medical follow-up, which may  
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27 35 introduce disease burden but may just as well be a confirmation of wellbeing for patients  
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30 36 • Patient burden is minimized through use of questionnaires using computerized adaptive  
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## 38 Introduction

39 Benign liver tumours and cysts (BLTCs) comprise a heterogeneous groups of cystic and solid  
40 lesions.<sup>1</sup> Although extensive research has been performed in the field of BLTCs, their natural course  
41 including their influence on patient reported outcomes (PROs) has been underexposed. The most  
42 common and relevant cystic lesions are simple non-parasitic liver cysts (estimated incidence of 18%)  
43 and “cystadenomas” (1-5% of all liver cysts),<sup>2</sup> now referred to as mucinous cystic lesions of the liver  
44 and biliary system and intraductal papillary neoplasms of the liver and bile ducts, MCNs and IPNBs).  
45 Solid lesions include hepatic hemangioma (0.4-20%), focal nodular hyperplasia (FNH, 0.4-3%), and  
46 hepatocellular adenoma (HCA, 0.001-0.004%).<sup>3-6</sup>

47 Many BLTCs are found incidentally on routine imaging for unrelated pathology.<sup>3,7</sup> The rising  
48 incidence of those so called incidentalomas is at least partly attributable to the increasing use of non-  
49 invasive imaging modalities.<sup>2</sup> Main complications of BLTCs are bleeding and malignant  
50 transformation - both of which rarely occur.<sup>8,9</sup> Of the five most common and relevant solid and cystic  
51 lesions, only (large) HCAs and “cystadenomas” have a known risk of malignant transformation.<sup>9</sup>  
52 Treatment indications remain an important matter of debate. In general, treatment of BLTCs is only  
53 recommended when they either have a risk of complications or cause severe complaints often with  
54 associated impairment of quality of life. When little or no risk of complications is present, the latter is  
55 often the sole indication for treatment.<sup>3</sup>

56 However, this recommendation has various nuances which hampers shared decision and makes  
57 the management of BLTCs exceptionally prone to undesirable practice variation.<sup>10,11</sup> Firstly, the  
58 influence of treatment on PROs is important but rarely reported.<sup>12</sup> Secondly, in current literature,  
59 PROs after treatment by surgery or interventional radiology are rarely compared with conservative  
60 management.<sup>12,13</sup> Finally, variations in diagnostic methods may be present, for example FNH is easily  
61 misdiagnosed as HCA when inadequate diagnostics are applied.<sup>3,14,15</sup>

62 Therefore, this observational cohort study aims to investigate the PROs of patients with BLTCs  
63 during their natural courses as well as after treatment. These data will enable patients and



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3 64 professionals to make well-informed treatment decisions together to optimize value-based  
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5 65 outcomes. In addition, the study will provide an overview of the clinical practice in the Netherlands.  
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## 66 **Methods and analysis**

### 67 *Study design*

68 The BELIVER study (Natural Course and Clinical Outcome in BEnign LIVER Tumours and Cysts) is an  
69 investigator-initiated, nationwide, multicenter observational cohort study. All Dutch medical centers  
70 treating patients with BLTCs are eligible for participation, facilitated and coordinated through the  
71 Dutch Benign Liver Tumor Group (DBLTG) network. The study was registered in the Netherlands Trial  
72 Register (NTR NL8231). Reporting of the study protocol and, eventually, of the full study is done  
73 according to the STROBE statement (Supplemental File 1)

74

### 75 *Study population*

76 Adult patients ( $\geq 18$  years old) presenting with a common and/or clinically relevant BLTC at  
77 participating centers are eligible for inclusion. Clinically relevant BLTCs are defined as all BLTCs  
78 potentially eligible for either surgical intervention or follow-up. Strict cut-off values regarding BLTC  
79 size will not be defined and are assessed on a per patient basis by treating professionals.

80 The study will be conducted from October 2021 till October 2026, . the minimal follow-up will be  
81 two years. Patients diagnosed with an uncommon BLTC, unwilling or unable to provide written  
82 informed consent or to fill in the questionnaire and patients with another disease substantially  
83 affecting PROs will be excluded. Uncommon BLTCs and clinically less relevant are excluded. These  
84 include choledochal cysts, hepatic angiomyolipoma and biliary hamartoma / Von Meyenburg  
85 complexes.<sup>16</sup> Additionally, patients with polycystic liver disease are excluded as they form a  
86 circumscribed group of patients with very typical symptoms and treatments, including liver  
87 transplantation and they are currently already included in another international study.<sup>17</sup>

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### 89 *Study objectives and outcomes*

90 The primary study objective is to systematically record the PROs during the natural course and  
91 after (minimally) invasive treatment of patients with BLTCs. Secondary study objectives are to

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3 92 evaluate changes in tumour/cyst diameter and the occurrence of any mortality and complications,  
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5 93 related to either the natural course of the disease (malignant transformation or hemorrhage) or  
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7 94 related to tumour or cyst treatment. The study will also provide an overview of potential variation in  
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9  
10 95 management and outcomes of Dutch patients with BLTCs.

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12 96 The primary study outcome measure is change in PROs including severity of symptoms from the  
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14 97 start compared to the end of the follow-up period. Symptoms are measured by a questionnaire,  
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16 98 focusing on PROs relevant to patients with BLTCs and their caregivers and partly administered  
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18  
19 99 through the Patient-Reported Outcomes Measurement Information System (PROMIS).

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21 100 The questionnaire is administered biannually. Although a multiplicity would have enabled a more  
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23 101 accurate longitudinal study with correction for confounding events, increasing questionnaire  
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25 102 frequency will also probably lead to a reduction of study adherence and result in an increased patient  
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28 103 burden. Moreover, one might argue that continuing surveys even after cessation of medical follow-  
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30 104 up may introduce disease burden that remind patients of their diagnosis. However, the biannual  
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32 105 questionnaires may just as well be a confirmation of wellbeing for patients. In addition, currently  
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34 106 some patients might be subjected to extended periods of follow-up even in the absence of this study  
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37 107 as a consequence of practice variation.

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39 108 Secondary outcomes related to interventions include: postoperative complications according to  
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41 109 Clavien-Dindo Classification, the Comprehensive Complication Index, 30 and 90-day mortality, and  
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43 110 the Society of Interventional Radiology classification for adverse events.<sup>18-20</sup> Treatment effects will be  
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45 111 evaluated with additional questions regarding intervention indication, the effectiveness of the  
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48 112 treatment on symptoms, and the likeliness of patients to choose the treatment again. If surgical  
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50 113 intervention is applied, questions on incisional herniation are added to the questionnaire after  
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52 114 intervention. Supplementary questionnaires will be sent after interventions at three, six, and twelve  
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54 115 months, thereafter resuming to biannual questionnaires. An example of two cases and their follow-  
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57 116 up with questionnaires is shown in figure 1.

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3 117 In addition to data collected from questionnaires, data will be extracted from local electronic  
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5 118 patient files. This includes the following data: 1) baseline patient characteristics (age, gender,  
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7 119 comorbidity); 2) tumour or cyst characteristics (among which diameter, imaging, and  
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9 120 histopathological examination), 3) certain data specific for the type of BLTC the patient was  
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11 121 diagnosed with, and 4) details on the intervention performed. Table 1 summarizes collected  
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13 122 variables. All tumour and cyst diameters will be measured according to RECISTv1.1 criteria.<sup>21</sup>  
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#### 18 124 *Patient involvement and questionnaire selection*

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21 125 Various questionnaires have been used to evaluate PROs of patients with BLTCs. However, these  
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23 126 questionnaires were not developed for the evaluation of outcomes of BLTC patients and therefore  
24  
25 127 most likely do not appropriately measure outcomes relevant to patients with BLTCs. Based on  
26  
27 128 literature and focus groups with patients with BLTCs and their caregivers, we selected relevant  
28  
29 129 patient-reported outcomes (PROs). These were: insecurity/anxiety, pain, fatigue and limitations in  
30  
31 130 daily life. The domains anxiety, fatigue, ability to participate and pain interference will be evaluated  
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33 131 in the current study using computerized adaptive testing through the Dutch-Flemish Patient-  
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35 132 Reported Outcomes Measurement Information System (PROMIS).<sup>22-24</sup> PROMIS instruments have  
36  
37 133 recently successfully been used in research on various patient groups.<sup>25, 26</sup> Additionally, numerical  
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39 134 rating scales for pain (current and most, least, and average pain over a week) and two general health  
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41 135 and quality of life questions will be assessed.  
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#### 47 137 *Data collection*

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50 138 Data will be collected using electronic case report forms using an online based platform which  
51  
52 139 automatically generates patient identifiers consisting of the hospital code and a number. A subject  
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54 140 identification log will be kept in each center by the principal investigator or local coordinating  
55  
56 141 investigator. This subject identification log will contain the personal details which can be used to  
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58 142 send questionnaires to patients. Only this dedicated person has the key for decoding patient data. At  
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3 143 completion of the follow-up period, the database will be exported from the online platform. The  
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5 144 database will be hosted on a secure server with the infrastructure, configuration, and licenses that  
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7 145 are consistent with current norms and laws to ensure safe and secure data storage and processing.  
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12 147 *Sample size and statistical analysis*

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14 148 No sample size calculation was conducted as this is an observational cohort study. A previous  
15  
16 149 single center prospective cohort study on the (conservative and surgical) treatment of HCAs and  
17  
18 150 FNHs included 110 patients in 4.5 years.<sup>27</sup> This current study has a broader scope as it spans across at  
19  
20 151 least seven medical centers, includes more BLTC types, and also includes patients treated by  
21  
22 152 interventional radiological procedures. Therefore, the aim is to include at least 450 patients.  
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25 153 Statistical analyses will be performed using SPSS statistics for Windows version 24.0 (SPSS Inc.,  
26  
27 154 Chicago, IL, USA) and R for Windows version 3.6.3 (R Core Team, Vienna, Austria). Categorical data  
28  
29 155 will be presented as proportions. Continuous data will be presented as mean and standard deviation  
30  
31 156 (SD) or median and interquartile range (IQR). Categorical variables will be compared using the Fisher  
32  
33 157 exact test or the Chi-square test. Continuous variables will be compared using the Mann-Whitney U  
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35 158 test or the Student's t-test. Cox proportional hazards model will be used when appropriate. A two-  
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37 159 tailed  $P < 0.05$  will be considered statistically significant.  
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41 160 Scores for each patient-reported outcome measure at the start and end of follow-up will be  
42  
43 161 compared using a paired t-test, and factors associated with significant gain in these measures will be  
44  
45 162 evaluated. Patients will be stratified according to treatment strategy (conservative, surgical,  
46  
47 163 transarterial (chemo-)embolization and lipiodolization, aspiration and sclerotherapy, or  
48  
49 164 radiofrequency or microwave ablation). Sensitivity analyses will be performed for the type of BLTC,  
50  
51 165 and for the time between questionnaires and hospital visits, as hospital visits and imaging may  
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53 166 increase the extent of the emotional burden experienced by patients. For surgically treated patients,  
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55 167 predictors of a complicated course (Clavien Dindo  $\geq 3b$ ) will also be evaluated.  
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3 169 *Trial sites*  
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5 170 Initiating centers are Amsterdam UMC and University Medical Center Groningen. At least all other

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7 171 centers participating in the DBLTG will be included. Participating centers will at least include:  
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9  
10 172 1. Amsterdam University Medical Centers, Amsterdam, The Netherlands

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12 173 2. University Medical Center Groningen, Groningen, The Netherlands

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14 174 3. Erasmus Medical Center, Rotterdam, The Netherlands

15  
16 175 4. Maastricht University Medical Center+, Maastricht, The Netherlands

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18 176 5. Radboud University Medical Center, Nijmegen, The Netherlands

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20 177 6. Leiden University Medical Center, Leiden, The Netherlands  
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22  
23 178 In order to identify and/or avoid selection bias, non-DBLTG and non-academic centers will also be

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25 179 enabled to join during the course of the study.  
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3 **180 Ethics and dissemination**  
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5 **181** *Ethical considerations*  
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7 **182** This trial will be conducted in accordance with the principles of the Declaration of Helsinki and as  
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10 **183** stated in the laws governing human research and Good Clinical Practice. The study does not interfere  
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12 **184** or change the process of treatment of the BLTCs in the included patients. The study was determined  
13  
14 **185** to be beyond the scope of the Dutch law on research on human subjects (WMO) according to the  
15  
16 **186** Medical Ethics Committee (MEC) of the Amsterdam UMC, location AMC (MEC AMC W19\_134 #  
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18 **187** 19.167) and the MEC of the University Medical Center Groningen (MEC UMCG 201900292). The  
19  
20 **188** study will be evaluated by MECs of all participating centers. Moreover, the study will also be  
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22 **189** reviewed according to local requirements of each center. Finally, the study proposal was reviewed by  
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24 **190** the scientific committee of the DBLTG. All substantial amendments will be notified to these  
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26 **191** committees and organizations. Data will be kept for at least fifteen years after study completion.  
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30 **192**

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32 **193** *Informed consent and withdrawal of consent*  
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34 **194** Informed consent for use of the questionnaires and the data collected from the electronic patient  
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36 **195** files will be obtained from all patients by the treating professional in participating centers.  
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38 **196** Information will be provided to patients by physicians. This will consist of both printed folders and  
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40 **197** links to digital information. A dedicated website has been created (URL:  
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42 **198** <https://www.DBLTG.nl/BELIVER/>). Also, dedicated e-mailboxes have been constructed.  
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45 **199** Patients can withdraw from study participation at any time and without consequences or reason.  
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47  
48 **200** With each questionnaire that is sent, it is noted that if patients wish to withdraw, they can do so at  
49  
50 **201** any time. In case of withdrawal, patients will be contacted and asked for allowance of data analysis  
51  
52 **202** until that point. There is no specific replacement of individual subjects after withdrawal. Patients  
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54 **203** who have chosen to withdraw from the study will receive follow-up and treatment according to  
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56 **204** current standard of care by their treating physician. If participants do not respond to questionnaires,  
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3 205 a reminder will be sent after one month. If there is no reaction to this reminder, patients will be  
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5 206 contacted by telephone to verify if they still wish to participate or not.  
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10 208 *Additional burden and risk associated with study participation*  
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12 209 The proposed study does not interfere with standard patient care. No additional blood samples,  
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14 210 increase in number of hospital visits, physical examination or other tests are indicated. However, in  
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16 211 case of cessation of medical follow-up, patients included in the study will still receive questionnaires.  
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18 212 There are no direct benefits for patients participating in this study. There are no risks involved  
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20 213 with participating in this study. The additional burden of the study is considered to be minimal.  
21

22 214 Completion of the questionnaire will take approximately 15 minutes. The questionnaires might  
23  
24 215 remind patients of their BLTC diagnosis. Some of the questions might be confronting (i.e. questions  
25  
26 216 regarding the impact of complaints on daily life and work).  
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30 218 *Administrative aspects, monitoring and publication*  
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32 219 All results, either positive or negative, will be published in a peer-reviewed journal. All results will  
33  
34 220 be reported suiting reporting guidelines provided by the EQUATOR-network (URL:  
35

36 221 <https://www.equator-network.org/>). All Dutch centers collaborating in the DBLTG will be invited to  
37  
38 222 participate in this study. All results originating from this study will be published on behalf of the  
39

40 223 DBLTG. Co-authorship is available for one physician at each center supplying at least five cases and  
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42 224 for two physicians at each center supplying at least ten cases. In each center it may be decided  
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44 225 individually which one or two physicians will be mentioned as co-authors. Co-authorships may also  
45  
46 226 be offered to persons who contributed substantially to the conceptualization and execution of the  
47

48 227 study. All co-authorships will have to fulfill the international committee of medical journal editors  
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50 228 (ICMJE) regulations.<sup>28</sup>  
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55 230 In addition to these co-authorships, others involved may be listed as collaborator and the journal  
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57 231 will be asked to list them as such also in MEDLINE/PubMed. For each center supplying at least thirty  
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3 231 cases, one collaborator may be included; for centers supplying at least forty cases, two collaborators;  
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5 232 for centers supplying fifty or more cases, three collaborators.  
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**List of abbreviations**

BLTCs	Benign liver tumours and cysts
FNH	Focal nodular hyperplasia
HCA	Hepatocellular adenoma
MEC	Medical ethics committee
PRO	Patient reported outcome
WMO	Medical research involving human subjects act; in Dutch: wet medisch-wetenschappelijk onderzoek met mensen

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## Declarations

### *Authors' contributions*

AF, MPDH, BVvR, MGB, VEdM, JIE: conceptualization of the study

MGB, RAdM, JNMIJ, MGJT, MK, MMEC, MET, AEB, RJdH, EWD, GK, OMvD, JV, RBT, FJCC: investigation and data curation

AF, MPDH, VEdM, JIE: drafting of the manuscript, study coordinators

BVvR, AJK, MGB, RAdM, JNMIJ, MGJT, MK, MMEC, MET, AEB, RJdH, EWD, GK, OMvD, JV, RBT, FJCC: methodology of the study, revision of the manuscript

AF, MPDH, BVvR, AJK, MGB, RAdM, JNMIJ, MGJT, MK, MMEC, MET, AEB, RJdH, EWD, GK, OMvD, JV, RBT, FJCC, VEdM, JIE: approval of the final manuscript.

### *Funding statement*

This work was supported by a grant from the Dutch Society of Gastroenterology (Nederlandse Vereniging voor Gastroenterologie) to the Dutch Benign Liver Tumour Group, and by a personal grant from Amsterdam UMC location AMC to A. Furumaya

### *Competing interests*

The authors declare that they have no competing interests.

*Word count: 2754/4000 words*

## Acknowledgements

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## Figures

Figure title: Figure 1

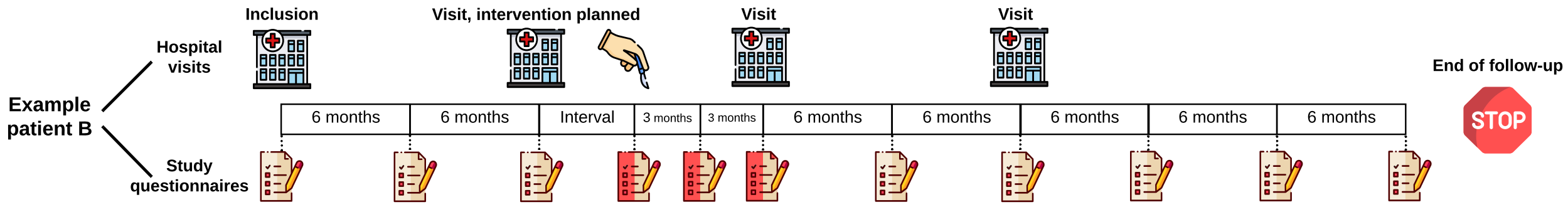
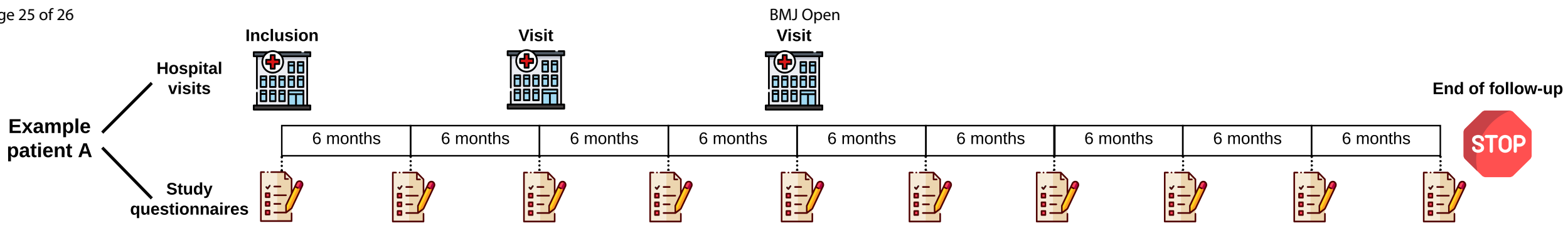
Figure legend: An overview of the hospital visits and study questionnaires of two fictional patients included in the study are shown. In general, patients receive a questionnaire every six months. Deviations from this normal course of follow-up caused by patients undergoing an intervention are indicated by red questionnaires. Please note that these two patients were included around similar dates, but total follow-up durations might differ between patients depending on the date of inclusion.

Table 1 Overview of recorded variables

Baseline information		Tumor or cyst specific questions		Treatment characteristics		
Patient characteristics	Tumor/cyst characteristics*	Solid lesions	Cystic lesions	Intervention	Surgery	Interventional radiology
Age	Total number of lesions at baseline	Focal nodular hyperplasia	Simple hepatic cysts	Date of intervention	Type of approach (open, laparoscopic, robot)	Type of procedure (aspiration sclerotherapy, TAE, RFA/MWA)
Sex	Location of lesion (left hemiliver, right hemiliver, bilobar)	Hemangioma	Mucinous cystic neoplasms	Duration of hospital stay	Occurrence and reason for conversion	Sclerotherapy (volume of aspiration, length of sclerosing, type of sclerosing agent)
Mortality If yes, reason	Type of lesion	Hepatocellular adenoma	Intraductal papillary neoplasms	Operation or procedure time	Type of procedure (fenestration, wedge resection, segmental resection, hemihepatectomy, transplantation)	TAE (volume and type of embolization agent [simple embolization, chemo-embolization or lipiodolization])
Comorbidity (ASA score and Elixhauser comorbidity index)	Diameter, date and modality of diagnosis			30-day and 90-day mortality	Specification of resected segments	
	Diameter, date and modality of follow-up				Amount of blood loss	
	Occurrence of misdiagnosis If so, revised diagnosis and diagnostic modality				Additional procedures (e.g. argon beam coagulation, omental transposition, concurring cholecystectomy)	
	Histopathological diagnosis with immunohistochemistry if available				Complications (type, CD, CCI & SIR)	

Abbreviations: ASA: American society of anesthesiologists; TAE, transarterial embolization; RFA, radiofrequency ablation; MWA, microwave ablation; CD, Clavien-Dindo; CCI, comprehensive complication index; SIR, society of interventional radiologists classification for adverse events.\* According to RECISTv1.1 criteria, lesions will only be measured on CT or MRI (longest diameter), measured on the transversal plane on post-contrast series. Maximum of two lesions. If the target lesion is not visible on follow-up imaging (index imaging is imaging shortest before inclusion), then the diameter of the next largest tumor will be measured.

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**Legend**

- Deviation from regular follow-up after an intervention (surgery or interventional radiology), after which follow-up frequency is temporarily increased.
- Intervention: surgery or interventional radiology.

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**Supplemental Material to “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”**

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Line No
<b>Title and abstract</b>	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	Title page
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-23
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	38-61
Objectives	3	State specific objectives, including any prespecified hypotheses	62-65
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	68-69
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	80-81 171-180 195-207
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	76-79 82-88
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	91-123
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	97-123
Bias	9	Describe any efforts to address potential sources of bias	104-108
Study size	10	Explain how the study size was arrived at	149-153
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	154-160
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	161-168
		(b) Describe any methods used to examine subgroups and interactions	163-165 167-168
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	165-167
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A

1		(b) Indicate number of participants with missing data for each variable of interest	N/A
2		(c) Summarise follow-up time (eg, average and total amount)	N/A
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4	Outcome data	15* Report numbers of outcome events or summary measures over time	N/A
5	Main results	16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
6		(b) Report category boundaries when continuous variables were categorized	N/A
7		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
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12	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
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15	<b>Discussion</b>		
16	Key results	18 Summarise key results with reference to study objectives	N/A
17	Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	101-108 126-134 210-217
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21	Interpretation	20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
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25	Generalisability	21 Discuss the generalisability (external validity) of the study results	N/A
26			
27	<b>Other information</b>		
28	Funding	22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title Page
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32 \*Give information separately for exposed and unexposed groups.

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35 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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