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Study protocol for a multicentre 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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ABSTRACT

Introduction Benign liver tumours and cysts (BLTCs) comprise a heterogeneous group of cystic and solid lesions, including hepatic haemangioma, focal nodular hyperplasia and hepatocellular adenoma. Some BLTCs, for example, (large) hepatocellular adenoma, are at risk of complications. Incidence of malignant degeneration or haemorrhage is low in most other BLTCs. Nevertheless, the diagnosis BLTC may carry a substantial burden and patients may be symptomatic, necessitating treatment. The indications for interventions remain matter of debate. The primary study aim is to investigate patient-reported outcomes (PROs) of patients with BLTCs, with special regards to the influence of invasive treatment as compared with the natural course of the disease.

Methods and analysis A nationwide observational cohort study of patients with BLTC will be performed between October 2021 and October 2026, the minimal follow-up will be 2 years. During surveillance, a questionnaire regarding symptoms and their impact will be sent to participants on a biannual basis and more often in case of invasive intervention. The questionnaire was previously developed based on PROs considered relevant to patients with BLTCs and their caregivers. Most questionnaires will be administered by computerised adaptive testing through the Patient-Reported Outcomes Measurement Information System. Data, such as treatment outcomes, will be extracted from electronic patient files. Multivariable analysis will be performed to identify patient and tumour characteristics associated with significant improvement in PROs or a complicated postoperative course.

Ethics and dissemination The study was assessed by the Medical Ethics Committee of the University Medical Center Groningen and the Amsterdam UMC. Local consultants will provide information and informed consent will be asked of all patients. Results will be published in a peer-reviewed journal.

Study registration NL8231—10 December 2019; Netherlands Trial Register.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The BELIVER study will lead to an expansion of the current knowledge on patient-reported outcomes in patients with benign liver tumours and cysts (BLTCs) in the Netherlands and the influence of interventions hereupon.
⇒ The long-term, biannual follow-up and increased frequency of questionnaires postoperatively will provide data to enable professionals to better inform patients what to expect and to enable patients and professionals to make well-informed treatment decisions together.
⇒ As the study is conducted nationwide, the extent of medical practice variation regarding management of BLTCs can be assessed.
⇒ Questionnaires are continued even after cessation of medical follow-up, which may introduce disease burden but may just as well be a confirmation of well-being for patients.
⇒ Patient burden is minimised through use of questionnaires using computerised adaptive testing.

INTRODUCTION

Benign liver tumours and cysts (BLTCs) comprise a heterogeneous groups of cystic

and solid lesions.[1] Although extensive research has been performed in the field of BLTCs, their natural course including their influence on patient reported outcomes (PROs) has been underexposed. The most common and relevant cystic lesions are simple non-parasitic liver cysts (estimated incidence of 18%) and 'cystadenomas' (1%–5% of all liver cysts),[2] now referred to as mucinous cystic lesions of the liver and biliary system and intraductal papillary neoplasms of the liver and bile ducts (MCNs and IPNBs). Solid lesions include hepatic haemangioma (0.4%–20%), focal nodular hyperplasia (FNH, 0.4%–3%) and hepatocellular adenoma (HCA, 0.001%–0.004%).[3–6]

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

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

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

METHODS AND ANALYSIS

Study design

The BELIVER study (Natural Course and Clinical Outcome in BEnign LIVER tumours and Cysts) is an investigator-initiated, nationwide, multicentre observational cohort study. All Dutch medical centres treating patients with BLTCs are eligible for participation, facilitated and coordinated through the Dutch Benign Liver Tumor Group (DBLTG) network. The study was registered in the Netherlands Trial Register. Reporting of the study protocol and, eventually, of the full study is done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (online supplemental file 1).

Study population

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

The study will be conducted from October 2021 till October 2026, the minimal follow-up will be 2 years. Patients diagnosed with an uncommon BLTC, unwilling or unable to provide written informed consent or to fill in the questionnaire and patients with another disease substantially affecting PROs, will be excluded. Uncommon BLTCs and clinically less relevant are excluded. These include choledochal cysts, hepatic angiomyolipoma and biliary hamartoma/Von Meyenburg complexes.[16] Additionally, patients with polycystic liver disease are excluded as they form a circumscript group of patients with very typical symptoms and treatments, including liver transplantation and they are currently already included in another international study.[17]

Study objectives and outcomes

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

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

The questionnaire is administered biannually. Although a multiplicity would have enabled a more accurate longitudinal study with correction for confounding events, increasing questionnaire frequency will also probably lead to a reduction of study adherence and result in an increased patient burden. Moreover, one might argue that continuing surveys even after cessation of medical follow-up may introduce disease burden that remind patients of their diagnosis. However, the biannual questionnaires may just as well be a confirmation of well-being for patients. In addition, currently some patients might be subjected to extended periods of follow-up even in

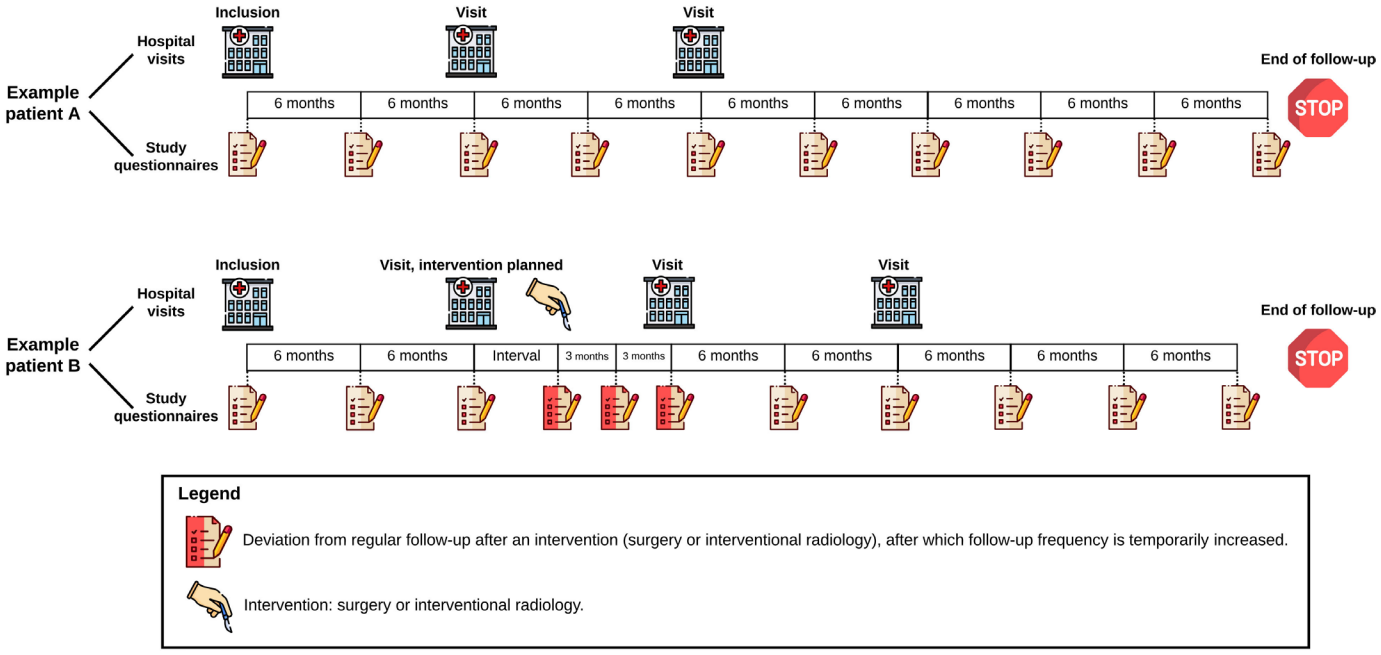

Figure 1 An overview of the hospital visits and study questionnaires of two fictional patients included in the study are shown. In general, patients receive a questionnaire every 6 months. Deviations from this normal course of follow-up caused by patients undergoing an intervention are indicated by red 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.

the absence of this study as a consequence of practice variation.

Secondary outcomes related to interventions include postoperative complications according to Clavien-Dindo Classification, the Comprehensive Complication Index, 30 and 90-day mortality and the Society of Interventional Radiology classification for adverse events.[18–20] Treatment effects will be evaluated with additional questions regarding intervention indication, the effectiveness of the treatment on symptoms and the likeliness of patients to choose the treatment again. If surgical intervention is applied, questions on incisional herniation are added to the questionnaire after intervention. Supplementary questionnaires will be sent after interventions at 3, 6 and 12 months, thereafter resuming to biannual questionnaires. An example of two cases and their follow-up with questionnaires is shown in figure 1.

In addition to data collected from questionnaires, data will be extracted from local electronic patient files. This includes the following data: (1) baseline patient characteristics (age, gender, comorbidity), (2) tumour or cyst characteristics (among which diameter, imaging and histopathological examination), (3) certain data specific for the type of BLTC the patient was diagnosed with and (4) details on the intervention performed. Table 1 summarises collected variables. All tumour and cyst diameters will be measured according to RECIST V.1.1 criteria.[21]

Patient involvement and questionnaire selection

Various questionnaires have been used to evaluate PROs of patients with BLTCs. However, these questionnaires were not developed for the evaluation of outcomes of patients with BLTC and, therefore, most likely do not appropriately measure outcomes relevant to patients with BLTCs. Based on the literature and focus groups with patients with BLTCs and their caregivers, we selected relevant PROs. These were: insecurity/anxiety, pain, fatigue and limitations in daily life. The domains anxiety, fatigue, ability to participate and pain interference will be evaluated in the current study using computerised adaptive testing through the Dutch-Flemish PROMIS.[22–24] PROMIS instruments have recently successfully been used in research on various patient groups.[25 26] Additionally, numerical rating scales for pain (current and most, least, and average pain over a week) and two general health and quality of life questions will be assessed.

Data collection

Data will be collected using electronic case report forms using an online-based platform, which automatically generates patient identifiers consisting of the hospital code and a number. A subject identification log will be kept in each centre by the principal investigator or local coordinating investigator. This subject identification log will contain the personal details, which can be used to send questionnaires to patients. Only this dedicated person has the key for decoding patient data. At completion of the follow-up period, the database will be exported from the online platform. The database will be hosted on a secure server with the infrastructure, configuration and licenses that are consistent with current norms and laws to ensure safe and secure data storage and processing.

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)	Haemangioma	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 embolisation agent(simple embolisation, chemo-embolisation or lipiodolisation))
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 (eg, argon beam coagulation, omental transposition, concurring cholecystectomy)	
	Histopathological diagnosis with immunohistochemistry if available				Complications (type, CD, CCI and SIR)	

*According to RECIST V.1.1 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.
ASA, American Society of Anesthesiologists; CCI, comprehensive complication index; CD, Clavien-Dindo; MWA, microwave ablation; RFA, radiofrequency ablation; SIR, society of interventional radiologists classification for adverse events; TAE, transarterial embolisation.

Sample size and statistical analysis

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

Statistical analyses will be performed using SPSS statistics for Windows V.24.0 (SPSS, Chicago, Illinois) and R for Windows V.3.6.3 (R Core Team, Vienna, Austria). Categorical data will be presented as proportions. Continuous data will be presented as mean and SD or median and IQR. Categorical variables will be compared using the Fisher exact test or the χ^2 test. Continuous variables will be compared using the Mann-Whitney U test or the Student's t test. Cox proportional hazards model will be used when appropriate. A two-tailed $p<0.05$ will be considered statistically significant.

Scores for each PRO measure at the start and end of follow-up will be compared using a paired t test, and factors associated with significant gain in these measures

will be evaluated. Patients will be stratified according to treatment strategy (conservative, surgical, transarterial (chemo-) embolisation and lipiodolisation, aspiration and sclerotherapy or radiofrequency or microwave ablation). Sensitivity analyses will be performed for the type of BLTC, and for the time between questionnaires and hospital visits, as hospital visits and imaging may increase the extent of the emotional burden experienced by patients. For surgically treated patients, predictors of a complicated course (Clavien Dindo ≥3b) will also be evaluated.

Study sites

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

1. Amsterdam University Medical Centers, Amsterdam, The Netherlands.
2. University Medical Center Groningen, Groningen, The Netherlands.
3. Erasmus Medical Center, Rotterdam, The Netherlands.
4. Maastricht University Medical Center+, Maastricht, The Netherlands.
5. Radboud University Medical Center, Nijmegen, The Netherlands.
6. Leiden University Medical Center, Leiden, The Netherlands.

In order to identify and/or avoid selection bias, non-DBLTG and non-academic centres will also be enabled to join during the course of the study.

ETHICS AND DISSEMINATION

Ethical considerations

This trial will be conducted in accordance with the principles of the Declaration of Helsinki and as stated in the laws governing human research and Good Clinical Practice. The study does not interfere or change the process of treatment of the BLTCs in the included patients. The study was determined to be beyond the scope of the Dutch law on research on human subjects (Wet medisch-wetenschappelijk onderzoek met mensen, WMO) according to the Medical Ethics Committee (MEC) of the Amsterdam UMC, location AMC (MEC AMC W19_134 # 19.167) and the MEC of the University Medical Center Groningen (MEC UMCG 201900292). The study will be evaluated by MECs of all participating centres. Moreover, the study will also be reviewed according to local requirements of each centre. Finally, the study proposal was reviewed by the scientific committee of the DBLTG. All substantial amendments will be notified to these committees and organisations. Data will be kept for at least 15 years after study completion.

Informed consent and withdrawal of consent

Informed consent for use of the questionnaires and the data collected from the electronic patient files will be obtained from all patients by the treating professional in participating centres. Information will be provided to patients by physicians. This will consist of both printed folders and links to digital information. A dedicated website has been created (URL: https://www.DBLTG.nl/BELIVER/). Also, dedicated e-mailboxes have been constructed.

Patients can withdraw from study participation at any time and without consequences or reason. With each questionnaire that is sent, it is noted that if patients wish to withdraw, they can do so at any time. In case of withdrawal, patients will be contacted and asked for allowance of data analysis until that point. There is no specific replacement of individual subjects after withdrawal. Patients who have chosen to withdraw from the study will receive follow-up and treatment according to current standard of care by their treating physician. If participants do not respond to questionnaires, a reminder will be sent after 1 month. If there is no reaction to this reminder, patients will be contacted by telephone to verify whether they still wish to participate or not.

Additional burden and risk associated with study participation

The proposed study does not interfere with standard patient care. No additional blood samples, increase in number of hospital visits, physical examination or other tests are indicated. However, in case of cessation of medical follow-up, patients included in the study will still receive questionnaires.

There are no direct benefits for patients participating in this study. There are no risks involved with participating in this study. The additional burden of the study is considered to be minimal. Completion of the questionnaire will take approximately 15 min. The questionnaires might remind patients of their BLTC diagnosis. Some of the questions might be confronting (ie, questions regarding the impact of complaints on daily life and work).

Administrative aspects, monitoring and publication

All results, either positive or negative, will be published in a peer-reviewed journal. All results will be reported suiting reporting guidelines provided by the EQUATOR-network (URL: https://www.equator-network.org/). All Dutch centres collaborating in the DBLTG will be invited to participate in this study. All results originating from this study will be published on behalf of the DBLTG. Coauthorship is available for one physician at each centre supplying at least five cases and for two physicians at each centre supplying at least 10 cases. In each centre, it may be decided individually which one or two physicians will be mentioned as coauthors. Coauthorships may also be offered to persons who contributed substantially to the conceptualisation and execution of the study. All coauthorships will have to fulfil the international committee of medical journal editors regulations.[28]

In addition to these coauthorships, others involved may be listed as collaborator and the journal will be asked to list them as such also in MEDLINE/PubMed. For each

centre supplying at least 30 cases, one collaborator may be included; for centres supplying at least 40 cases, two collaborators; for centres supplying 50 or more cases, three collaborators.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
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

		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A
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
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
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

*Give information separately for exposed and unexposed groups.

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.