Protocol of a randomised controlled phase II clinical trial investigating PREoperative endoscopic injection of BOTulinum toxin into the sphincter of Oddi to reduce bile leakage after hepatic resection: the PREBOT-II trial

Claudia Eva Mack, Ulla Klaiber, Peter Sauer, Laura Kohlhas, Lukas Baumann, Eike Martin, Arianeb Mehrabi, Markus W Buchler, Thilo Hackert

ABSTRACT

Introduction Bile leakage represents a major cause of morbidity following hepatic resection. Although most patients can be managed non-operatively, this complication requires diagnostics and therapeutic interventions. Preoperative endoscopic injection of botulinum toxin (BTX) into the sphincter of Oddi represents an innovative approach to prevent bile leakage. The aim of the PREBOT-II trial is to generate the first randomised controlled trial data on the safety, feasibility and efficacy of preoperative endoscopic BTX injection into the sphincter of Oddi to prevent bile leakage following hepatic resection.

Methods and analysis The PREBOT-II trial is an investigator-initiated, exploratory, multicentre, randomised, controlled, open-label, phase II clinical trial with two parallel study groups. 70 patients scheduled for hepatic resection will be randomised to either the intervention or the control group. Patients of the intervention group will undergo preoperative endoscopic injection of BTX into the sphincter of Oddi 3–10 days before surgery, whereas in the control group only hepatic resection will be performed. The primary endpoint is the occurrence of a postoperative bile leakage within 30 days after hepatic resection according to the definition of the International Study Group of Liver Surgery. The secondary endpoints comprise further postoperative morbidity parameters such as severity of postoperative bile leakage, post-hepatectomy haemorrhage or liver failure, mortality and quality of life up to 3 months after hepatic resection. Safety and feasibility of the procedure will also be recorded.

Ethics, funding and dissemination The PREBOT-II trial has been approved by the German Federal Institute for Drugs and Medical Devices (reference number 4044932) and the Ethics Committee of Heidelberg University (reference number AFmu-558/2021). This trial is supported by the German Federal Ministry of Education and Research. The results will be presented at national and international conferences and published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of this trial is the prospective investigation of preoperative endoscopic injection of botulinum toxin into the sphincter of Oddi to prevent postoperative bile leakage after hepatic resection under strict monitoring of adverse events and a randomly assigned control group.
⇒ A limitation of this trial is the relatively small number of patients which is limited to 70 patients to be randomised due to the exploratory character of this trial.
⇒ The significance of the study could be limited due to the number of participants which may require a further confirmation in a larger randomised controlled trial and the open-label trial design as potential source of bias.
⇒ Since the primary endpoint can be assessed objectively, risk of bias is limited despite a non-blinded study design.

Trial registration number DRKS00024061, EudraCT: 2020-006001-35.

INTRODUCTION

Rationale of the trial

Hepatic resection is the treatment of choice for various hepatobiliary diseases. When performed in specialised institutions it has now mortality rates below 6%, but morbidity rates of up to 43% still remain high. Despite improvements in surgical techniques and perioperative management, bile leakage remains a major cause of postoperative morbidity and mortality. The incidence of postoperative bile leakage as defined by the International Study Group of Liver Surgery
Postoperative bile leakage is classified into grades A, B and C depending on the impact on the patient’s postoperative outcome. Even though most cases can be managed non-operatively, bile leakage often requires interventional management and prolongs the hospital stay, which considerably increases healthcare costs. In patients with malignant diseases, postoperative bile leakage frequently results in a delayed start of adjuvant treatment, which potentially impairs the patient’s oncological outcome. Even though treatment strategies for postoperative bile leakage following hepatic resection are available, so far effective treatments for prevention do not exist.

Preliminary data

During the past few decades, several methods to prevent postoperative bile leakage following hepatic resection have been investigated. A recent systematic review and meta-analysis on this topic studied the role of bile leak testing during liver resection including test substances like normal saline, methylene blue, fat emulsion, indocyanine green and air. The results showed that the evidence is scanty and unconvincing. Furthermore, the kind of surgical transection and surgical closure techniques have been evaluated. In the early 1970s the clamp-crushing technique as a novel technique for hepatic resections was introduced. Since these days several dissection devices like vascular staplers or the vessel sealing systems have been developed but failed to prove superiority.

Endoscopic retrograde cholangiography with sphincterotomy and bile duct stenting represents the preferred non-surgical treatment strategy for the management of bile leakage from the cut surface of the liver following hepatic resection. Biliary stenting aims to promote closure of the leakage by either bridging the leak or improving drainage of bile towards the duodenum, thereby reducing intraductal pressure at the leakage site. However, due to potential prosthesis associated complications biliary stenting is recommended only in the treatment of evident bile leakage and not for bile leakage prevention.

Botulinum toxin (BTX) is an inhibitor of acetylcholine release from nerve endings which has a temporary but potent effect on smooth muscle cells when injected locally. It has been widely used in the treatment of gastrointestinal diseases such as achalasia and sphincter of Oddi dysfunction with convincing results in terms of safety and efficacy. Recently, preoperative injection of BTX into the sphincter of Oddi was shown to be safe and feasible in the prevention of pancreatic fistula after distal pancreatectomy.

Regarding the endoscopic injection of BTX into the sphincter of Oddi, the possible risk of acute pancreatitis must be considered, but no significant adverse effects have been reported apart from subclinical, self-limiting elevation of serum pancreatic enzymes and mild pancreatitis in rare cases.

The most severe complication of the gastroscopy itself is perforation injury with an incidence of up to 0.4%, requiring immediate intensive care treatment as well as another endoscopy or an operation. But as removal of tissue is not performed in this study, risk of bleeding, perforation or tear of the wall is very low.

Preoperative injection of BTX into the sphincter of Oddi in patients undergoing hepatic resection is supposed to improve drainage of bile towards the duodenum and thereby reduce back pressure on the resection margin of the liver by BTX mediated relaxation of the sphincter of Oddi. The rationale of this procedure is derived from the principle of bile duct stenting for treatment of bile leakage. The effect of one single BTX injection covers the critical postoperative period for bile leakage and its effect fades spontaneously after approximately 3 months, which makes a repetition of the intervention and a second BTX injection needless. Long-term side effects have not been reported so far. PREBOT-II is the first trial to investigate the reduction of postoperative bile leakage by preoperative injection of BTX into the sphincter of Oddi. Based on the results of this trial future trials to prove the effectiveness of this approach are necessary. In addition, postoperative injection of BTX into the sphincter of Oddi in patients with evident biliary fistula may be evaluated as treatment possibility.

METHODS AND ANALYSIS

PREBOT-II was registered at ClinicalTrialsRegister.eu (EudraCT 2020-006001-35) and the German Clinical Trials register (DRKS 00024061) before enrolment of the first patient.

Trial design and trial supporting facilities

This is an investigator-initiated, exploratory, multicentre, randomised, controlled, open-label, phase-II clinical trial with two parallel study groups. The trial protocol was approved by the ethics committee of the University of Heidelberg. The sponsor of the PREBOT-II trial is the University Hospital of Heidelberg, Germany. The principal investigator is the sponsor’s representative. The trial will be conducted at the Department of General, Visceral and Transplantation Surgery, University of Heidelberg, the Department of Visceral, Thoracic and Vascular Surgery, Dresden University Hospital Carl Gustav Carus of the Technical University Dresden and the Department of Surgery, Klinikum Rechts der Isar, Technical University of Munich, Germany in accordance with the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The trial will be carried out in close cooperation with the Coordinating Centre for Clinical Trials (KKS) and the Institute of Medical Biometry (IMBI), belonging to the University of Heidelberg, Germany. The KKS is in charge of pharmacovigilance and monitoring, while the IMBI is responsible for data management and biostatistics.

Trial population

During a pretreatment visit all patients scheduled for hepatic resection will be screened. The trial population...
Table 1  Eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td>▶ Patients scheduled for elective, primary hepatic resection without planned biliary reconstruction requiring a biliodigestive anastomosis.</td>
<td>▶ Patients who already underwent papillotomy for any reason or have an inlaying bile stent.</td>
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<tr>
<td>▶ Male or female patients ≥18 years of age.</td>
<td>▶ Serious cardiovascular disease (eg, myocardial infarction in the last 12 months, congestive heart failure NYHA III/IV, unstable angina pectoris).</td>
</tr>
<tr>
<td>▶ Ability of patient to understand character and individual consequences of the clinical trial.</td>
<td>▶ Serious renal insufficiency, ie, creatinine clearance &lt;30 mL/min (estimated by Cockcroft-Gault).</td>
</tr>
<tr>
<td>▶ Written informed consent (must be available before enrolment in the trial).</td>
<td>▶ Liver cirrhosis (child B/C).</td>
</tr>
<tr>
<td>▶ For women with childbearing potential, presence of negative urine or blood pregnancy test and adequate contraception until 14 days after trial intervention.</td>
<td>▶ American Society of Anesthesiologists score &gt;III.</td>
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<td></td>
<td>▶ Hypersensitivity to any BTX preparation or to any of the components in the formulation.</td>
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<td>▶ Neuromuscular disorder, eg, peripheral motor neuropathic disease, amyotrophic lateral sclerosis or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome), or any other neurological disorder with associated increased risk for the patient undergoing BTX injection.</td>
</tr>
<tr>
<td></td>
<td>▶ Any condition in which duodenoscopy and/or the trial intervention is not possible, eg, for anatomical reasons, or obsolete in the actual situation, eg, in patients with acute pancreatitis.</td>
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<td>▶ History of BTX application.</td>
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<td>▶ Understanding or language problems.</td>
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<td>▶ Inability to comply with study and/or follow-up procedures.</td>
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<td>▶ Pregnancy or lactation.</td>
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<td>▶ Concurrent participation in another interventional clinical trial.</td>
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<td></td>
<td>▶ Any condition or situation which could result in an undue risk for the patient and/or influence outcome measures in the opinion of the investigator.</td>
</tr>
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</table>

BTX, botulinum toxin; NYHA, New York Heart Association.

Consists of patients scheduled for primary, elective hepatic resection for any underlying disease fulfilling the eligibility criteria (table 1).

Seventy patients will be allocated to the trial. Recruitment and treatment of patients will be performed in a multicentre assessment with three trial centres. Patients must provide written informed consent to the responsible study physician and must be able to understand the individual consequences of the clinical trial.

Patient recruitment and trial timeline

The trial preparation phase started in November 2020. The first patient was included in April 2022. The duration of the clinical trial for each individual patient will be 3 months (figure 1). The recruitment of 70 patients in three centres is expected to last 10 months.

Randomisation

Applying a central online randomisation system (www.randomizer.at) patients will be assigned 1:1 to intervention and control groups in order to achieve comparable groups. The randomisation will take place shortly after written consent has been documented. As soon as the individual participant is allocated to one of the two study groups, the upcoming procedures (ie, preoperative
endoscopy for patients in the intervention group and surgery for patients in both groups) will be scheduled. Randomisation will be performed only by authorised trial personnel with their login data.

**Interventions**

**Trial intervention (intervention group): oesophagogastroduodenoscopy with sphincter of Oddi BTX injection**

Participants in the intervention group will undergo oesophagogastroduodenoscopy with injection of BTX into the sphincter of Oddi between 3 and 10 days before hepatic resection in an outpatient setting. The study medication BTX (Allergan Pharmaceuticals, Dublin, Ireland) is stored and reconstituted according to the summary of product characteristics. The procedure will be carried out only once per patient as follows: the duodenoscope is inserted into the upper gastrointestinal tract under adequate sedation and positioned in front of the papilla of Vater. Then 100 units of BTX reconstituted in 1 mL 0.9% sodium chloride is injected into the intraduodenal sphincter of Oddi segment. For the administration of the medication the needle is deeply inserted into the central papillary region, injecting the solution as a single deposit. After BTX injection, the procedure is terminated and patients are closely monitored.

**Control group**

Participants in the control group will not undergo preoperative endoscopy because ‘placebo endoscopy’ is not justified in this phase II clinical trial. Patients in the control group will be treated according to the standard procedures since no effective treatment options for prevention of bile leakage are known. Thus, clinical equipoise is given.

**Risk of bias**

The open-label trial design is a potential source of performance and detection bias. Since the primary endpoint can be assessed objectively, however, risk of bias is reduced despite a non-blinded study design. Additionally, to expose the patients to the risks of placebo endoscopy, even though they are low, is not justified. Procedures will be standardised and the trial personnel will be trained at the site initiation visit to reduce performance bias. Regular monitoring procedures will control adherence to the protocol.

**Surgical intervention: exploratory laparoscopy/laparotomy and hepatic resection**

In both study groups exploratory laparoscopy or laparotomy will be performed depending on the individual preoperative findings and the surgeon’s preferences. After confirming technical resectability hepatic resection is performed according to the centre’s standard surgical procedures. The kind of hepatic transection will be performed according to the opinion of the surgeon depending on the individual intraoperative findings. Additional resections are performed if necessary and the intraoperative placement of drains is optional. Any kind of an additional covering of the transection side is permitted.

**Outcome parameters**

**Primary outcome parameter**

The primary endpoint is the occurrence of a postoperative bile leakage within 30 days after hepatic resection according to the definition of the ISGLS. A bile leakage is defined as a discharge of fluid with an increased bilirubin concentration greater than three times the serum bilirubin concentration measured at the same time according to or after postoperative day 3. The ISGLS defines three grades of bile leakage, grade A, B and C, depending on the invasiveness of change in the patient’s clinical management.

**Secondary outcome parameters**

The secondary endpoints comprise the severity of bile leakage, post-hepatectomy liver failure and post-hepatectomy haemorrhage according to the ISGLS, post-interventional pancreatitis according to the International Association of Pancreatology and the American Pancreatic Association, perioperative sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock, intra-abdominal fluid collections or abscesses, reinterventions and reoperations due to any cause and mortality according to Clavien-Dindo Classification. The duration of intensive/intermediate care unit and total hospital stay as well as readmission to hospital for management of postoperative complications will also be evaluated. Additionally, Quality of Life using the Short Form (SF)-12 Health Survey will be assessed.

**Assessment of feasibility**

Feasibility will be measured by calculating the proportion of patients undergoing both successful BTX injection in the sphincter of Oddi and hepatic resection in the intervention group.

**Schedule of trial procedures**

Table 2 presents an overview of the scheduled study procedures.

From screening until the last follow-up visit 3 months after surgery, seven study visits will take place, whereby visit 2 will be exclusive to the intervention group. During visit 1, inclusion and exclusion criteria will be checked. After the patient has given his informed consent, the patient will be randomised to one of the two groups and the baseline and demographic data as well as liver specific medical history will be assessed and documented. Additionally, Quality of Life will be assessed with the SF-12 Health Survey questionnaire. Laboratory parameters will be determined pre-interventionally and/or preoperatively. During visit 2, the peri-interventional parameters regarding the endoscopy and BTX injection will be documented. During visit 3, the perioperative parameters will be documented. If an additional (interventional) drainage is inserted postoperatively (between visit 4 and...
7), measurements of bilirubin will be performed. Visit 4 and 5 are in-hospital visits and visit 6 and 7 are follow-up visits. For women with childbearing potential a urine or blood pregnancy test will be performed during visit 1 and 5.

### Safety and pharmacovigilance

Patients will be monitored closely for the occurrence of adverse events (AEs) and serious adverse events (SAEs). All AEs will be documented in the case report form and will be reported regardless of causality. All patients who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome. Any AE occurring during the observation period that results in death, is life threatening, requires or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is otherwise medically relevant and/or requires intervention to prevent any of these outcomes is defined as SAE. After the SAE becomes known, it will have to be reported immediately, but not later than 24 hours by the investigator to the responsible safety officer at KKS Heidelberg. The initial report must include details of the current illness and the SAE and an assessment of the causal relationship between the event and the trial medication. A second independent assessment of each reported SAE will take place to evaluate causality and expectedness and to judge whether the benefit/risk assessment for the trial did change as a result of the SAE. An SAE that potentially may be attributed to the study medication is to be classified as serious adverse reaction. An SAE, that is, both ‘suspected’, that is, possibly related to the study medication and ‘unexpected’, that is, the nature and/or severity of which is not consistent with the applicable product information is to be classified as suspected unexpected serious adverse reaction (SUSAR). All SUSAR occurring after administration of the study medication will be subject to expedited reporting by the responsible safety officer at KKS Heidelberg. All SAEs and their relevance for the benefit/risk assessment of the study will also be evaluated continuously during the study and for the final report.

### Statistical methods

#### Sample size calculation

Given that this is a phase II exploratory trial, no formal sample size calculation has been performed. Based on previous data from randomised controlled trials the rate of postoperative bile leakage as defined by the ISGLS ranges between 20% and 30% (average 25%). A sample size of 100 patients per group is estimated to provide 80% power to detect a 5% difference in bile leakage rates between the groups with a significance level of 5%.
size of 30 patients per group leads to a two-sided 90% CI of (−9% to 25%) (with a width equal to 34.4%) for the difference in rates when assuming a reduction from 25% (control group) to 17% (intervention group). The width of the 90% CI for the rates per group of 25% and 17% will then be 28.5% (0.127% to 0.412%) and 25.3% (0.070% to 0.323%), respectively. It is expected that about 15% of randomised patients will not be available for primary analysis for intraoperative reasons (eg, unresectable disease). Loss to follow-up is expected to be close to zero (please see below). To account for a rate of about 15%, a total of 70 (35 per group) patients will be randomised. The extent of resection may be a risk factor for bile leakage. However, randomisation should balance the differences in type and extent of resections. Depending on the results of this trial, stratification regarding the type of resection may be done in a future confirmatory trial.

Compliance/rate of loss to follow-up
In a previous series published by Hackert et al.15 on a similar topic none of the participants were lost to follow-up. Based on the experience of this previous series, patients are expected to be highly motivated to take part in the PREBOT-II trial and comply with study procedures well. The primary endpoint will be assessed 30 days after hepatic resection and the last follow-up visit will be scheduled not later than 3 months after surgery. Therefore, the rate of loss to follow-up after hepatic resection is expected to be close to zero.

Primary estimand
In the addendum to the International Council for Harmonisation (ICH) E9 guideline (final version),25 the estimands framework is recommended as clear and transparent definition of ‘what is to be estimated’ (International Council for Harmonisation 2019). An estimand is defined through the treatment, the targeted population, the variable, a specification of how to handle intercurrent events (post-randomisation events) and a population-level summary. In the following, the primary estimand corresponding to the primary objective is described.

Treatment: One single preoperative injection of 100 units of BOTOX into the sphincter of Oddi during oesophagogastroduodenoscopy within 3–10 days before hepatic resection versus hepatic resection without any endoscopic intervention.

Population: The targeted population is defined through the inclusion and exclusion criteria with status post hepatic resection without biliary reconstruction within the trial.

Variable: Occurrence of bile leakage within 30 days after hepatic resection.

Intercurrent events: In case of death only the time prior to death is considered relevant (while alive strategy). All protocol deviations will be ignored (treatment policy strategy).

Summary measure: Rate difference between the two treatment groups.

Statistical analysis
Due to the nature of the trial as an exploratory study, no confirmatory statistical test will be applied. The rate for the primary endpoint ‘bile leakage within 30 days after hepatic resection’ will be calculated for both groups, together with the difference between the two groups and 90% CIs. A logistic regression model with ‘center’ as a covariate will be conducted to compare both groups in a descriptive manner. In a further analysis, possible centre effects will be evaluated descriptively by including an interaction term for centre and treatment in the logistic regression model. Subgroup analyses will be performed for minor and major resections.

The analysis will primarily be performed based on the modified intention-to-treat (mITT) population, considering patients in the group as randomised but including only patients with status post hepatic resection without biliary reconstruction. This is reasonable, as patients undergoing explorative laparotomy alone will distort the trial results since they will generally not have any risk of bile leakage. An analysis based on the per-protocol set (patients with no major protocol violations) will be performed as a sensitivity analysis. The assignment of each patient to the mITT population and the per-protocol population will be defined before database closure in the statistical analysis plan.

In this multicentre trial with closely monitored patients we do not expect any missing value of the primary endpoint in the mITT population. Nevertheless, if a missing value occurs, for example, due to loss to follow-up, we assume that no bile leakage occurred, because the longer the operation has passed, the less likely is the occurrence of a bile leakage. As a sensitivity analysis, the primary endpoint of patients with missing values will be set to bile leakage. In case of patient’s death within 30 days after hepatic resection, an analysis that corresponds to the while alive strategy within the estimands framework is conducted, that is, only the time prior to death is considered relevant. For all secondary endpoints, appropriate summary measures as well as descriptive p values to compare the two groups will be reported, along with 95% CIs. The safety analysis will be based on all randomised patients and includes calculation and comparison of frequencies of AEs and SAEs. Appropriate statistical methods will be used to assess the quality of data and the homogeneity of intervention groups. All analyses will be performed using SAS V.9.4 or higher.

Data collection and data management
An electronic case-report-form (eCRF) will be used for data collection. The investigator or a designated representative will enter all protocol-required information in the eCRF. The eCRF will be completed as soon as possible after the information are collected and the reason for any missing data should be provided. The completeness, validity and plausibility of data will be checked at the time of data entry and by using validating programmes that will generate queries. The investigator or a designated
subinvestigator then must review the completed eCRF. Once no further corrections are to be made in the database, it will be closed and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures (SOP) of the IMBI that guarantee efficient conduct complying with GCP. For archiving purposes and to ensure future accessibility of the data, the data will be transformed into different formats at the end of the study.

**ETHICS AND DISSEMINATION**

The clinical trial protocol, V.2.0 (2021/09/08) and informed consent documents as well as patient information was approved by the independent ethics committee of the University of Heidelberg on 28 October 2021 in consensus with the ethic committee of the Technical University Dresden and Munich (AFmu-558/2021). Additionally, the trial was approved by the German Federal Institute for Drugs and Medical devices (BfArM) on the 27 October (reference number 4044932). All planned substantial changes will be submitted to the independent ethics committee of the University of Heidelberg and the BfArM in writing as protocol amendments. They will be signed by the sponsor’s representative and biometrician and approved by the ethics committee and the competent authority.

The trial was registered with the DRKS. Furthermore, the trial was registered with the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT).

The results of this trial will be presented at national and international conferences and submitted for publication in a peer-reviewed journal.

**Screening and informed consent**

All patients scheduled for elective hepatic resection will be screened consecutively at the outpatient clinic of each trial site and will be informed about the PREBOT-II trial. Eligible for participation are all adult patients who fulfil eligibility criteria. Patient information and informed consent documents will be provided for the patient. Patients must be able to understand the nature, scope and possible individual consequences of the clinical trial. Before admission to the clinical trial each patient will have to give consent in writing. Participants may withdraw from the trial at their own request at any time without giving reasons. The withdrawal can be performed verbally in the presence of, or in written form directed to the investigator or a member of the investigating team. If hepatic resection cannot be performed due to any reason, but the patient has undergone the intervention including the BTX injection, follow-up visits will be performed.

**Quality control and quality assurance**

**Data protection**

The data obtained in the course of the trial will be treated pursuant to local regulatory requirements (eg, the European Union General Data Protection Regulation, ‘Datenschutzgrundverordnung’). During the clinical trial, patients will be identified solely by means of their individual identification code (ie, screening number, randomisation number). Trial findings stored on a computer will be handled in accordance with local data protection law and will be treated in strictest confidence. To prevent distribution of data to unauthorised persons organisational procedures are implemented and relevant stipulations of local data legislation will be strictly fulfilled in its entirety. The inspection of original data for monitoring purposes by health authorities and authorised persons (inspectors, clinical monitors, auditors) is permitted due to the patient’s written consent including the release of the investigator from his/her professional discretion. The investigator will maintain a patient identification list (screening numbers with the corresponding patient names) to enable records to be identified. Patients who did not consent to circulate their pseudonymised data will not be included into the trial.

**Data monitoring**

Monitoring will be done remotely and by personal visits from a clinical monitor according to SOP of the KKS Heidelberg. The monitor will review entries into the eCRF on the basis of source documents during on-site visits. Additionally, by remote monitoring and frequent communication (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements. Therefore, the investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor. Frequency and details of monitoring will be defined in the monitoring plan.

**Data Safety Monitoring Board and Steering Committee**

A Data Safety Monitoring Board (DSMB) has been set-up to ensure the clinical conduct of the trial and protect the rights and welfare of the patients. The DSMB consist of two medical doctors who are not involved in the trial and one independent methodological expert. DSMB meetings will take place on a regular basis at least once a year and once 30 patients have completed visit 6 within the trial. The study conduct, for example, recruitment and protocol adherence as well as safety issues will be reviewed by the DSMB. As a result the DSMB will make recommendations to the Steering Committee on the further conduct of the study regarding modification, continuation or closure. The data necessary for the DSMB to fulfill its function will be provided by the IMBI. The working procedures are described in detail in the DSMB charter.

**Patient and public involvement**

A Patient Committee composed of five volunteers, also members of the patient advisory board of the Study Center of the German Surgical Society located in Heidelberg, has been set-up to represent the patients’ needs and preferences throughout the entire trial. In accordance
with the patients’ concerns the study endpoints were defined. In particular, quality of life was considered a relevant outcome parameter and therefore involved as a secondary outcome parameter. The Patient Committee has the right to make recommendations to the investigator, the trial coordinators and the Steering Committee during the ongoing trial and will also play an important role in the interpretation of the trial results. The Patient Committee enables a close involvement of patients in all stages of the trial and gives them the power to influence the trial process. At the end of the trial patients will be asked to judge the relevance of the trial results from their perspective. The study is also supported by the Association ‘Deutsche Leberhilfe e.V.’ as well as by a patient advocate representing patient’s rights at the University Hospital Heidelberg.

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**Contributors** TH, MWB, AM, UK and CEM conceived the trial. TH is the sponsor’s representative and principal investigator of this trial. TH and UK applied for funding. TH and CEM drafted the study protocol and this manuscript. PS established the trial. LX and LB conceived the statistical analysis. EM represents the patient’s interests and rights. All authors read and approved the final manuscript.

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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.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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