PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic role of the "white test" with lipidic solution in the early intraoperative identification of open bile ducts for the prevention of bile leakage after liver resection: study protocol for a randomized controlled multicentric superiority trial (BiLe-Trial)
AUTHORS	Cristaudi, Alessandra; Tarantino, Ignazio; Scheiwiller, Andreas; Wiencierz, Andrea; Majno-Hurst, Pietro; Schmied, Bruno M.; Metzger, Juerg; Hartel, Mark; Kremer, Michael; Manzini, Giulia

VERSION 1 – REVIEW

REVIEWER	Jun Li University Medical Center Hamburg-Eppendorf, General, Visceral and Thorax Surgery
REVIEW RETURNED	21-Mar-2021

GENERAL COMMENTS	Well designed trial. Two factors can influence the sample size. Please pay attention: 1) The original "White test" study was performed in era of non-CUSA phase. Using CUSA or laparoscopic liver resection could reduce the rate of bile leak significantly. 2) The patients having a drainage or not could also affect the rate of bile leak defined by ISGLS.

REVIEWER	Pascal Probst University of Heidelberg, Department of General, Visceral and Transplantation Surgery
REVIEW RETURNED	23-Mar-2021

GENERAL COMMENTS	Cristaudi et al. present an RCT on the diagnostiic role of the white test in hepatic resection. The rationale to perform this trial is given. The introduction gives a good overview on the problem and existing literature. The methods are adequate (clear IC/EC, allocation, standardised and validated endpoints and sample size calculation). The discussion of the projected trial sufficient. I have a minor comment on reporting of blinding. Please see: Evidence-based recommendations for blinding in surgical trials. Langenbecks Arch Surg. 2019;404(3):273-284. What about blinding of data collectors and outcome assessors? I assume this is meant by ward doctors, however, it should be outlined explicitly who collects data for the trial and who grades the outcomes.

REVIEWER	G Martel Ottawa Hospital Research Institute
REVIEW RETURNED	02-Apr-2021

GENERAL COMMENTS	Thank you for asking me to review this manuscript by Cristaudi and

	colleagues. The authors present a clinical trial protocol (the BiLe-Trial) for a 5-site multi-center RCT to be conducted in Switzerland. The authors propose to randomize patients undergoing liver resections (2 or greater segments resected) to the white test vs usual care. Patients undergoing liver resection for any indication will be included, if a concomitant cholecystectomy is performed or if the surgeon deems it possible to access the cystic duct stump from the previous cholecystectomy site. Patients having a hepaticojejunostomy will be excluded. The primary outcome is 30-day postoperative bile leak based on ISGLS definition. Secondary outcomes include operative and postoperative complications, severity of bile leaks, ERCP rate, postoperative drain insertion, ICU stay and mortality. The trial has a superiority design and is powered to detect a difference in bile leak of 21% with usual care vs 7% with the white test (alpha 0.2, beta 0.05). A total of 210 patients will be randomized. I have the following comments and questions for the authors: -Has this trial been initiated? If so when? What is the expected completion date? -I understand that some study sites use the white test regularly, while others do not. The authors should specify whether there is any expected difficulty in achieving “buy-in” from those sites. The authors should state that all study sites are on board with the proposed protocol. -The authors should provide details of trial feasibility, including expected resection volumes at each study site. Do the authors have the option of including additional study sites, in the event of slow accrual? -The inclusion of liver resections with 2 or more segments is questionable. Some minor resections (particularly left lateral sectionectomies) have such a low risk of bile leak that this is likely to dilute the observed effect size. -Details of the cystic duct cannulation should be provided. What catheter will be used? How will it be secured in place (with a clip or with a balloon, etc.)? What happens if the surgeon is unable to cannulate the cystic stump due to the presence of valves? -Will laparoscopic resections be included? How will the protocol differ with laparoscopic resections, with respect to the technical aspects of the intervention? -It very questionable in my mind that the authors would include left lateral sectionectomies and carry out an unneeded cholecystectomy, simply for the purpose of accessing the cystic duct. Cholecystectomies are generally simple, but some are not. An element of unnecessary risk is introduced in those cases. -There is no description of patient consent for this trial. This should be added. Will consent be obtained? If so when? What happens when patients are consented but then do not get randomized? The authors should also specifically discuss consent with respect to the inclusion of resections where cholecystectomy is not needed for clinical purposes. -The authors propose to leave a drain for all patients included in the intervention arm. It is not formally stated, but I suspect they mean that this is the case for all control patients as well. I strongly question routine drainage in liver resection. Level 1 evidence has demonstrated that drains should not be used routinely after liver resection (Arita et al. Ann Surg 2021;273:224–231). What type of drains are the authors using? Is this standardized across the 5 institutions? If the authors do not want to eliminate this element of the trial, they should standardize it at a minimum. Perhaps more importantly, the routine use of drains is likely to strongly negatively

	affect the generalizability of this trial, even if positive. -Please describe the drain management protocol for this trial. -The choice of primary outcome of ISGLS bile leaks is perhaps the most debatable aspect of the proposed trial. The authors are including grade A leaks, which are essentially biochemical leaks that have no impact on clinical outcomes. Moreover, these are heavily driven by the presence of drains at the liver resection site. While this is very convenient for trial design and sample size calculations, it is unlikely that the proposed trial will be informative for liver surgeons given this major limitation. -The sample size calculation is very debatable. It includes all grades of bile leaks and is heavily driven by grade A leaks that are not clinically-significant. The proposed effect size of 21% to 7% is massive. More data should be provided to justify this, in light of the NSQIP data presented by Martin that were more conservative. Finally, I cannot be replicated the sample size calculation. I obtain 192 patients in total given the data provided by the authors and without adjusting for non-compliance. -The authors should include risk factors for bile leaks as part of their analysis. I do not believe that these have been described adequately. Numerous factors have been described (PVE, caudate resection, etc.). -The authors should consider conducting an interim analysis with stopping rules, particularly if the effect size is as large as anticipated. -How will the authors handle protocol deviations? Is the sample size adjusted for inability to cannulate the cystic duct and complete the intervention? I would recommend doing so.

REVIEWER	M Rizell University of Gothenburg
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	White test Abbreviations CI: correct to confidence HPB: correct the order hepatic-pancreato-biliary PTCD: is it more common to use cholangioduodenostomy?? Primary: Rate of 30d bile leakage If cholecystectomy has already taken place in a previous operation, the cystic stump will be explored and if this could be easily re-opened according to the experience of the operating surgeon the patient will be randomized, otherwise not. QUSA is a reg TM. Ultrasound aspirator? Sec endpotínts: Interventional drainage— clarify location: pleural effusion? Only for drainage of bile leakage? Re-operations: Definition- operations not planned before? Only addressing complications? Not whatsoever? How to handel two-stage resections etc Other outcomes: blood loss according to device….. no stratification for resection size.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments to Author:

Reviewer: 1
Dr. Jun Li, University Medical Center Hamburg-Eppendorf
Comments to the Author:
Well designed trial.
Two factors can influence the sample size. Please pay attention:
1) The original "White test" study was performed in era of non-CUSA phase. Using CUSA or laparoscopic liver resection could reduce the rate of bile leak significantly.

Thank you for this comment. The assumed rate of bile leakages used to perform the sample size calculation was obtained from the most recent publications, independently from the dissection method or device used. Even if it could be reasonable to think that CUSA could reduce the rate of bile leakages, and generally, that the instrument used to dissect the liver parenchyma can affect the postoperative rate of this complication, we could not find any evidence in literature for superiority of CUSA compared to clump-crush or other dissection technique concerning post-operative bile leak rate [1-4] . We would appreciate if you could indicate us any article that proved differently.

We completely agree that the question if different instruments correlate with different rate of postoperative bile leakages is of big clinical interest. This is one of our secondary endpoints. We reduced the number of instruments that can be used to perform the parenchymal dissection to three categories: 1. Diathermy i.e. Ultracision, LigaSure and Thunderbeat, 2. vascular stapler and 3. CUSA. We decided not to include the clamp-crush technique.

References

1 Vangelis G Alexiou. Technology-assisted versus clamp-crush liver resection: a systematic review and meta-analysis. Surg Innov 2013

2 Ioannis D Kostakis Impact of Ultrasonic Scalpels for Liver Parenchymal Transection on Postoperative Bleeding and Bile Leakage. In Vivo

3 John S Hammond. Comparison of liver parenchymal ablation and tissue necrosis in a cadaveric bovine model using the Harmonic Scalpel, the LigaSure, the Cavitron Ultrasonic Surgical Aspirator and the Aquamantys devices. HPB 2012

4 Allison N Martin. Clinical Factors and Postoperative Impact of Bile Leak After Liver Resection. J Gastrointest Surg 2018.

2) The patients having a drainage or not could also affect the rate of bile leak defined by ISGLS.

Thank you for this comment. Also another reviewer stressed the same. In fact this was not clear in our publication and is has been corrected (page 21). Both groups of patients, in the intervention as well as in the control group, will receive a surgical drain. This choice was driven by the need of uniformity, as some of the surgical teams would have not agree to avoid drains. Uniformity guarantees blinding. At day 3 bilirubin will be measured both in serum as well as in the drain, if negative the drain will be taken out.

Reviewer: 2
Dr. Pascal Probst, University of Heidelberg

Comments to the Author:
Cristaudi et al. present an RCT on the diagnostiic role of the white test in hepatic resection. The rationale to perform this trial is given. The introduction gives a good overview on the problem and existing literature. The methods are adequate (clear IC/EC, allocation, standardised and validated endpoints and sample size calculation). The discussion of the projected trial sufficient.

I have a minor comment on reporting of blinding. Please see: Evidence-based recommendations for blinding in surgical trials. Langenbecks Arch Surg. 2019;404(3):273-284. What about blinding of data collectors and outcome assessors? I assume this is meant by ward doctors, however, it should be outlined explicitly who collects data for the trial and who grades the outcomes.

Thank you very much for giving us the possibility to explain more in detail. In each clinic there are two teams, an unmasked team consisting of surgeons performing the operation and a masked team consisting of data collectors and outcome assessors. Documents are also physically stored separately in a "masked" and "unmasked" folder. The "unmasked" folder is stored by the operating surgeons and contains information about randomization group, batch number of SMOF lipid and NaCl which have also to be recorded. In the responsibility log stored in the Investigator Site File (both masked and unmasked), names of colleagues involved in the study are listed and it is clearly defined to which team each person belongs. For sure the surgeons who perform the operation will also visit the patients during the daily regular round but they don`t have access to SecuTrial and consequently they cannot entry data. They are only involved in performing the operation. In the operating report is written "the patient participates to the BiLe trial. He/she was intraoperatively randomized and treated accordingly". Both team members can screen patients and obtain the patient informed consent. This information is now included in the main manuscript (Page 12/13).

Reviewer: 3
Dr. G Martel, Ottawa Hospital Research Institute
Comments to the Author:
Thank you for asking me to review this manuscript by Cristaudi and colleagues. The authors present a clinical trial protocol (the BiLe-Trial) for a 5-site multi-center RCT to be conducted in Switzerland. The authors propose to randomize patients undergoing liver resections (2 or greater segments resected) to the white test vs usual care. Patients undergoing liver resection for any indication will be included, if a concomitant cholecystectomy is performed or if the surgeon deems it possible to access the cystic duct stump from the previous cholecystectomy site. Patients having a hepaticojejunostomy will be excluded. The primary outcome is 30-day postoperative bile leak based on ISGLS definition. Secondary outcomes include operative and postoperative complications, severity of bile leaks, ERCP rate, postoperative drain insertion, ICU stay and mortality. The trial has a superiority design and is powered to detect a difference in bile leak of 21% with usual care vs 7% with the white test (alpha 0.2, beta 0.05). A total of 210 patients will be randomized.

I have the following comments and questions for the authors:
-Has this trial been initiated? If so when? What is the expected completion date?

Yes, the trial initiated on March 1st 2021, the expected duration is 3 years according to the sample size calculation and to retrospective analysis provided to the sponsor by the participating centres about the expected number of patient that can be included. The estimated patients per year per center as reported from the principal investigators of each center that might qualify for inclusion in the study i.e. resection of at least 2 liver segments without necessity of hepatico-jejunostomy is as follows: Aarau: 12/year Lucerne: 8/year St. Gallen: 20-25/year Lugano: 30-35/year. This gives a total of 210 to 240 patients within 3 years.

-I understand that some study sites use the white test regularly, while others do not. The authors should specify whether there is any expected difficulty in achieving “buy-in” from those sites. The authors should state that all study sites are on board with the proposed protocol.

The technique is very simple and easily repeatable. A Standard Operating Procedure (SOP) written by the sponsor was provided to all centres in order to standardize the test. Additionally, Prof. Nadalin was contacted and asked about some technical information regarding the test in order to be sure to conduct it properly. As Prof. Nadalin said, when I asked him about the necessity to measure the injection pressure of SMOF lipid in the main biliary tract in order to standardize the test in all centres, he answered that the pressure measured in the infusion bag is not the same as in the cannula, so it is not possible to standardize it. So, as we aim to reproduce the test in its simple geniality, we think that the visual control of dilatation of main biliary duct gives us the information about enough pressure.

All operating surgeons could perform the test without problems from beginning of the study. The SOP is supplied as additional material. The choice to use SMOF lipid instead of Lipofundin was driven by the cheaper cost and minimal loss of product, as bottles are of 100ml instead of 250 ml. Additionally in a performed literature search, a “sterile lipid solution” is described without commercial name, only one study describes the use of diluted SMOF lipid 20% (Nage et al. 2018).

-The authors should provide details of trial feasibility, including expected resection volumes at each study site. Do the authors have the option of including additional study sites, in the event of slow accrual?

The estimated number patients per year per center which could be included (i.e. resection of at least 2 liver segments without hepatico-jejunostomy), as reported from the principal investigators of each center to the sponsor on the basis of a retrospective analysis in the 2-3 previous years was:

Aarau: 12/year

Lucerne: 8/year

St. Gallen: 20-25/year

Lugano: 30-35/year

This gives a total of 210 to 240 patients within 3 years. We decide to start the study with this 4 centres and to reevaluate after one year: if less than 70 patients will be included, we have the option to involve universitary centres (Basel, Genf or Lausanne) if needed.

-The inclusion of liver resections with 2 or more segments is questionable. Some minor resections (particularly left lateral sectionectomies) have such a low risk of bile leak that this is likely to dilute the observed effect size.

This is true, but a risk for bile leakage exist also with minor resections. Large series describe a rate of postoperative bile leakage up to 33% [5-9], including minor as well as major resections. Minor resections are reported to have bile leaks in up to 5.1% (Martin AN 2018). Statistically, the minor resections will be homogenously divided in both groups.

References

5 Yamashita Y, Hamatsu T, Rikimaru T et al. Bile leakage after hepatic resection. Annals of Surgery 2001. 233(1): 45-50

6 Nagano Y, Togo S, Tanaka K et al. Risk factors and management of bile leakage after hepatic resection. World J Surg 2003; 27(6):695-698

7 Terajima H, Ikai I, Hatano E et al. Effectiveness of endocopic nasobiliary drainage for postoperative bile leakage after hepatic resection. World J Surg 2004; 28(8): 782-786

8 Rudow DL, Brown RS jr, Emond JC et al. One-year morbidity after donor right hepatectomy. Liver Transpl. 2004; 10(11): 1428-1431

9 Capussotti L, Ferrero A, Vigano L et al. Bile leakage and liver resection: where is the risk? Arch Surg 2006; 141(7): 690-695

-Details of the cystic duct cannulation should be provided. What catheter will be used? How will it be secured in place (with a clip or with a balloon, etc.)? What happens if the surgeon is unable to cannulate the cystic stump due to the presence of valves?

Thank you for this comment. Because of space problems we could not describe everything in detail, but we have a SOP which describes the procedure, as mentioned above. We will submit it as supplementary material and refer to it in the main manuscript. For open surgery we use an olive-tip cannula as described by Nadalin et al. 2008, for laparoscopic surgery a standard cholangio-catheter according to the standard used in each clinic. Actually, the probability not to be able to cannulate the cystic stump is extremely low. If standard cannulation does not work, we will substitute the olive-tip cannula with a small i.v. access. In case this is also not possible, that patient, who was randomized to "intervention" will be treated as "control" because the test could not be performed. In this case, that patient belongs in the main analysis (ITT population) to the intervention group and in the per protocol analysis (PP analysis) to the control group. In the centres who routinely use the white test, there were no cases in which the cystic stump could not be cannulated in the last years. The catheter is secured in place in open surgery with fingers and in laparoscopic setting with a cholangiography forcep.

-Will laparoscopic resections be included? How will the protocol differ with laparoscopic resections, with respect to the technical aspects of the intervention?

Laparoscopic resections will be included if the resection will respect the inclusion criteria. The protocol for the white test will include a laparoscopic cholangiography catheter that will be used for injection through the cystic stump. The amount of solution and dilution will be the same as in open.

-It very questionable in my mind that the authors would include left lateral sectionectomies and carry out an unneeded cholecystectomy, simply for the purpose of accessing the cystic duct. Cholecystectomies are generally simple, but some are not. An element of unnecessary risk is introduced in those cases.

This is true, but the risk is small and the ethic committee and Swiss Medic already approved the study in this form. Patients are informed about if by signing the informed consent.

-There is no description of patient consent for this trial. This should be added. Will consent be obtained? If so when? What happens when patients are consented but then do not get randomized? The authors should also specifically discuss consent with respect to the inclusion of resections where cholecystectomy is not needed for clinical purposes.

This is a randomized controlled trial classified from the swiss authorities as risk B (as we use a substance in a different dosage and indication as that approved). The informed consent is mandatory

and obtained from all subjects. The informed consent as well as the list of all required documents from the swiss authorities are attached as supplemental material (BiLe trial is classified as clinical trial on medicinal products, risk category B).

-The authors propose to leave a drain for all patients included in the intervention arm. It is not formally stated, but I suspect they mean that this is the case for all control patients as well. I strongly question routine drainage in liver resection. Level 1 evidence has demonstrated that drains should not be used routinely after liver resection (Arita et al. Ann Surg 2021;273:224–231). What type of drains are the authors using? Is this standardized across the 5 institutions? If the authors do not want to eliminate this element of the trial, they should standardize it at a minimum. Perhaps more importantly, the routine use of drains is likely to strongly negatively affect the generalizability of this trial, even if positive.

Thank you for the commentary. To standardize we need a drainage, because we can not force the surgeons not to use a drainage (this would be more difficult, especially after major liver resections). So, in order to achieve uniformity, we decide to put drainage in all patients. This is made clearer in the main manuscript at page 11. We could not be too restrictive with type of drainage or fixation, also because of generalisability. We will record the type of drainage (passive or active) as well as if the drainage was fixed only externally or both externally and intrabdominal to the peritoneum near the resection surface. In the exploratory analysis we will investigate if a difference in detection of bile leakage is observed according to the type and fixation of the draiange.

The cited study Arita et. al. suffers from a selection bias, as patients with high risk for bile leak or bleeding have been excluded from randomisation. Therefore, we can not conclude in general to omit the usage of drainage in liver surgery, maybe only in uncomplicated cases. In our study, all patients independent of their risk to develop complications, are randomized.

-Please describe the drain management protocol for this trial.

At the end of the operation a drainage is put at the resection surface of the liver. The type of drainage is according to the internal standard of the clinic (active or passive) as well as the internal fixation of the drainage. The drainage remains in place at least until the 3rd postoperative day. At this time Bilirubin is measured in the drainage and in serum and the presence or absence of a bile leakage is recorded. If no bile leakage is found, the drainage is removed the same day. Otherwise, it remains as long as needed and according to the internal standard of the clinic.

-The choice of primary outcome of ISGLS bile leaks is perhaps the most debatable aspect of the proposed trial. The authors are including grade A leaks, which are essentially biochemical leaks that have no impact on clinical outcomes. Moreover, these are heavily driven by the presence of drains at the liver resection site. While this is very convenient for trial design and sample size calculations, it is unlikely that the proposed trial will be informative for liver surgeons given this major limitation.

We partially agree, but, as written before, we wanted to achieve a uniformity in the use of drainage, as some of the surgical teams will not agree to avoid completely drain use after liver resection. The definition of the ISGLS is easy to assess. Studies demonstrate that complicated end points make difficult for study personal to conduct right the study. Up to now, the ISGLS is routinely used to document bile leaks, also in the studies cited by this reviewer (Martin AN 2018). Although clinically not critically relevant, the rate of grade A bile leaks still can give information to our question, if the white test can influence this rate.

-The sample size calculation is very debatable. It includes all grades of bile leaks and is heavily driven by grade A leaks that are not clinically-significant. The proposed effect size of 21% to 7% is massive. More data should be provided to justify this, in light of the NSQIP data presented by Martin that were more conservative.

As pointed out before, the rate of grade A bile leaks -although clinically not critically relevant- still can give information to our question, if the white test can influence this rate. In the study of Martin AN et. al. no information is given, if any test for bile leakage has been performed in their study population. Furthermore, this study is a retrospective cohort study, based on datasets provided by participating hospitals.
The 21% bile leakage rate in the control group of our study has been obtained from retrospective data of our own centers and published data.

-Finally, I cannot be replicated the sample size calculation. I obtain 192 patients in total given the data provided by the authors and without adjusting for non-compliance.

We complemented the corresponding section (pag. 15-16). We determined the sample size via simulations, where we generated 1111 synthetic data sets for a range of sample sizes. With each of the synthetic data sets, we performed the intended primary analysis (i.e. a chi-squared test with continuity correction). The power associated with each sample size is then estimated as the percentage of rejected tests (out of the 1111 corresponding hypothetical experiments).

Using simulations instead of using the power derived directly from the asymptotic chi-squared distribution of the test, has the advantage of taking sampling uncertainty into account and being able to use the test with continuity correction. That is why we obtain a slightly larger number of participants.

All details about sample size calculation are described in the statistical analysis plan.

-The authors should include risk factors for bile leaks as part of their analysis. I do not believe that these have been described adequately. Numerous factors have been described (PVE, caudate resection, etc.).

This is a very good point, it is planned in the exploratory analysis (for example, type of resection and presence liver cirrhosis is recorded as it is known that patients with liver cirrhosis have less bile leakage). Portal Vein embolization is a very good factor, we will record also this and see if a correlation can be found in the exploratory analysis.

-The authors should consider conducting an interim analysis with stopping rules, particularly if the effect size is as large as anticipated.

Thank you for your suggestion. We had considered the possibility of an interim analysis with stopping rules during the planning phase, but we preferred not to do it due to the risk of stopping early because the data are too optimistic by chance. Moreover, there are uncertainties implied for study conduct (cost, time). Therefore, we opted for increasing our research efforts to find realistic assumptions for a fixed sample design instead.

-How will the authors handle protocol deviations? Is the sample size adjusted for inability to cannulate the cystic duct and complete the intervention? I would recommend doing so.

The study is professionally monitored by clinical trial unit (CTU) of the university of Basel as well as government authorities. Therefore, all protocol deviations are recorded and analyzed.
Sample size was not adjusted for inability to cannulate the cystic duct. As previously stated, the probability is extremely low. In this case, that patient belongs in the main analysis (ITT population) to the intervention group and in the per protocol analysis (PP analysis) to the control group.

Reviewer: 4
Dr. M Rizell, University of Gothenburg
Comments to the Author:
White test

- Abbreviations:
CI: correct to confidence
HPB: correct the order hepatic-pancreato-biliary

Thank you very much for this correction. The abbreviations have been corrected in the main manuscript.

- PTCD: is it more common to use cholangioduodenostomy??

This abbreviation refers to a percutaneous transhepatic biliary drain and can be changed in PTBD which is a largely known abbreviation term. We changed accordingly throughout the publication.

- QUSA is a reg TM. Ultrasound aspirator?

CUSA: Cavitron Ultrasonic Surgical Aspirator

-Secondary endpoints:
Interventional drainage— clarify location: pleural effusion? Only for drainage of bile leakage?

Interventional drainages are considered only as an abdominal drainage. An eventual drainage of pleural effusions will be considered in overall morbidity (Clavien IIIa)

-Re-operations:
Definition- operations not planned before? Only addressing complications? Not whatsoever? How to handel two-stage resections etc

Re-operation are considered only as emergency/urgent re-operation for complications. Furthermore, in patients with planned two staged procedures, the first step will often not qualify for the inclusion criteria as it would be mostly a clearing with wedge resections, so these patients will be eligible only in the second step of the procedure, when they will benefit of a larger hepatectomy. In case the first stage also qualifies for the study, the same patients will be included two times in the study and be randomized twice. Consequently he/she will receive two different study IDs.

- Other outcomes: blood loss according to device….. no stratification for resection size.

During descriptive analysis, we will describe and stratify for type of dissection technique and device.

VERSION 2 – REVIEW

REVIEWER	Jun Li University Medical Center Hamburg-Eppendorf, General, Visceral and Thorax Surgery

REVIEW RETURNED	31-May-2021

GENERAL COMMENTS	The study is well designed. The following comments might be helpful before performing the trial. 1) The sample size is based on bile leak rate from the publication in 2009. Two factors are different from that. One is Li et al only included major hepatectomy, in which the bile leak incidence should be higher than in BiLe-Trial (including minor hepatectomy). The other is Li et al used Crash-clamp technique instead of moderate technique such as CUSA. So the bile leak incidence could be much lower in the BiLe-Trial. These two factors impact the sample size calculation. 2) Currently, laparoscopic or robotic liver resection is increasingly performed. The incidence of bile leak has been reported lower than in open surgery. Moreover, the condition to perform white test in laparoscopic setting would be different from the open surgery. The authors should give a clear definition in the including criteria, such as only open resection is considered.

REVIEWER	Pascal Probst University of Heidelberg, Department of General, Visceral and Transplantation Surgery
REVIEW RETURNED	27-May-2021

GENERAL COMMENTS	All queries are resolved

REVIEWER	G Martel Ottawa Hospital Research Institute
REVIEW RETURNED	21-Jun-2021

GENERAL COMMENTS	I thank the authors for adequately addressing my comments and questions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Jun Li, University Medical Center Hamburg-Eppendorf

Comments to the Author:

The study is well designed. The following comments might be helpful before performing the trial.

1) The sample size is based on bile leak rate from the publication in 2009. Two factors are different from that. One is Li et al only included major hepatectomy, in which the bile leak incidence should be higher than in BiLe-Trial (including minor hepatectomy). The other is Li et al used Crash-clamp technique instead of moderate technique such as CUSA. So the bile leak incidence could be much lower in the BiLe-Trial. These two factors impact the sample size calculation.

Thank you very much for this comment. The study is already running in the described form since March 2021. The assumed postoperative bile leakage rate of 21% in the control group relies not only on the literature but on the postoperative bile leakage rate (including Grad A) of the participating centres in previous years. The 4 participating centres are not high volume centres, all performing less than 50 liver resection of at least 2 segments/year, being this the reason for a higher rate than in high volume centres.

So, to use a lower rate in the control group only based on reported rates of high volume centers will unfortunately not reflect our situation and lead to an optimistic scenario which is not reflecting the rate.

2) Currently, laparoscopic or robotic liver resection is increasingly performed. The incidence of bile leak has been reported lower than in open surgery. Moreover, the condition to perform white test in laparoscopic setting would be different from the open surgery. The authors should give a clear definition in the including criteria, such as only open resection is considered.

This is true, but also according to the comment mentioned before, this rate is reported by mainly high volume centers. Considering our 4 centres, less than 10% of the resections are expected to be laparoscopic, so these resections will affect only slighly the biliary leakage rate. A SOP for the performance of the white test in the laparoscopic setting has been established.

Reviewer: 3

Dr. G Martel, Ottawa Hospital Research Institute

Comments to the Author:

I thank the authors for adequately addressing my comments and questions.

We are happy that you feel that our answers are appropriate. Thank you very much.