BMJ Open

Surgical mapping with advanced 3D-reconstruction in minimally invasive liver surgery (SMART-MILS): protocol for a prospective randomised controlled trial

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To cite: Laurenz N, Bilge A, DeTemple D, *et al*. Surgical mapping with advanced 3D-reconstruction in minimally invasive liver surgery (SMART-MILS): protocol for a prospective randomised controlled trial. *BMJ Open* 2026;**16**:e120110. doi:10.1136/bmjopen-2026-120110

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2026-120110)

Received 25 March 2026
Accepted 09 July 2026

Check for updates

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ABSTRACT

Introduction Liver resection is a technically demanding procedure due to the complex and highly variable anatomy of the liver. Conventional preoperative planning relies on two-dimensional imaging, which requires mental reconstruction of three-dimensional anatomical relationships and may increase cognitive workload and intraoperative decision-making time. Patient-specific three-dimensional (3D) liver mapping has been shown to improve anatomical understanding and planning accuracy; however its impact on intraoperative efficiency has not been adequately investigated.

Methods and analysis This is a prospective, randomised, controlled, open-label superiority trial with a 1:1 allocation ratio, stratified by planned resection type (extent of resection according to highest applicable Iwate difficulty score). Adult patients (≥18 years) scheduled for elective minimally invasive liver resection at the University Hospital RWTH Aachen will be enrolled. The control arm will receive standard preoperative planning using conventional two-dimensional CT and/or MRI. The intervention arm will receive additional patient-specific 3D liver mapping generated using CE-approved software (MeVis Liver Suite), available preoperatively and intraoperatively. The primary endpoint will be the operative time (minutes from the first cutaneous incision to the final suture). Secondary endpoints will include intraoperative blood loss, rate of R0 resection in oncological cases, length of stay in the hospital and intensive care unit, surgeon task load, surgeons' salivary cortisol levels and cost-effectiveness. A total of 126 patients (63 per arm) will be enrolled to achieve 120 evaluable datasets.

Ethics and dissemination Ethics approval has been obtained from the Ethics Committee of the Medical Faculty, University Hospital RWTH Aachen (Ref. No. 26–050). Written informed consent will be obtained from all patients and participating surgeons. Results will be disseminated through peer-reviewed publications and scientific conferences, independent of study outcomes.

Trial registration number DRKS00039587.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, randomised controlled superiority trial with 1:1 allocation, stratified by resection complexity using the validated Iwate difficulty score, reducing confounding by case-mix variation.
⇒ The primary endpoint (operative time) is an objective, continuously measured variable extracted directly from operative records, minimising the risk of measurement bias despite the open-label design.
⇒ Surgeon stress is assessed using two independent methods—the validated surgeon task load questionnaire and biochemical measurement of salivary cortisol—providing both subjective and objective measures of intraoperative workload.
⇒ The sample size calculation is based on a single retrospective study and may overestimate the true effect; a pre-specified conditional adaptive extension to 340 patients is included to safeguard adequate power if the observed difference falls below the planned estimate.
⇒ The monocentric design at a single tertiary referral centre may limit generalisability, and blinding of the operating surgeon is not feasible given the visible nature of the three-dimensional models used in the intervention arm.

BACKGROUND

Liver resection remains one of the most technically demanding procedures in abdominal surgery owing to the organ's complex and highly variable anatomy.[1] In particular, interindividual variations in portal and hepatic venous branching, biliary anatomy and the spatial relationship between tumours and vascular structures pose significant challenges for safe and efficient surgical planning and execution.[2] Precise preoperative planning is therefore essential to ensure oncological radicality while preserving an adequate

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future liver remnant (FLR) to prevent postoperative liver failure.[2]

Conventional preoperative planning is primarily based on two-dimensional (2D) CT or MRI.[3] Although these modalities provide high-resolution anatomical information, surgeons must mentally reconstruct three-dimensional (3D) relationships from a series of 2D image slices. This cognitive process is highly dependent on experience and may be associated with increased mental workload, particularly in complex resections or in the presence of atypical vascular anatomy.[2 4] These limitations may contribute to prolonged intraoperative decision-making and, consequently, longer operative times.[4]

Recent advances in medical image processing have enabled the generation of patient-specific 3D reconstructions from standard CT datasets. These reconstructions can be visualised on conventional screens, explored interactively in virtual reality (VR) or materialised as physical 3D-printed models.[5–7] Such 3D-mapping techniques allow an intuitive and spatially accurate representation of hepatic parenchyma, tumours and intrahepatic vessels, potentially reducing the need for mental transformation of imaging data.[1 6 8]

Several studies have demonstrated that 3D-based planning improves the understanding of individual liver anatomy and supports more accurate estimation of resection volumes and FLR compared with conventional 2D planning.[2 4] Moreover, immersive visualisation techniques such as VR have been shown to enhance spatial orientation and subjective confidence during surgical planning, particularly for complex liver resections.[8] Most data published on 3D-based planning of liver surgery was collected retrospectively and are gathered in the systematic reviews of Banchini *et al* and Rossi *et al*.[7 9] Both review papers validated the safety and efficacy of 3D-based surgical planning.[7 9] Two of the larger retrospective cohort trials by Wang *et al* and Nakayama et al have demonstrated the safety of 3D-based surgical planning as well as reductions of operation time ranging from 11.6 to 43 min.[1 10]

A current prospective randomised controlled trial by Huber *et al* (with a published protocol in 2022) is planning to analyse the effects of preoperative 3D mapping before liver surgery on postoperative outcomes such as remaining liver volume and planned resection volume.[2] Their hypothesis is based on an improved preoperative orientation and assessment of liver anatomy.[2] However, the trial was not designed to assess short-term surgical outcomes such as operative time, intraoperative blood loss, rates of R0 resection in oncological procedures or the cost-effectiveness of the intervention. Furthermore, it was not restricted to minimally invasive liver resections, which are increasingly becoming the international standard of care and particularly depend on three-dimensional navigation due to the lack of tactile feedback.

Despite recent findings, evidence regarding the impact of preoperative 3D mapping on intraoperative efficiency remains limited. In particular, the effect of 3D-based planning on operative time has not been sufficiently investigated in a systematic and controlled manner. Given that operative duration is a key determinant of perioperative risk, resource utilisation and healthcare costs, evaluating whether preoperative 3D mapping can shorten liver resection procedures is of high clinical relevance.

Objectives

The primary objective of this study is to evaluate whether additional patient-specific preoperative and intraoperative 3D liver mapping reduces operative time in elective minimally invasive liver resections compared with solely conventional 2D imaging-based planning. Operative time is chosen as the primary endpoint, as it represents an objective and clinically relevant measure of intraoperative efficiency, resource utilisation and perioperative risk.

Secondary objectives are to assess the impact of preoperative and intraoperative 3D mapping on additional intraoperative and postoperative outcomes, intraoperative blood loss, rate of R0 resection, extent of resection of healthy liver tissue beyond oncologically required margins and cost-effectiveness. Furthermore, the study aims to evaluate the perioperative course of patients using perioperative 3D mapping by relating additional planning. The impact of improved overview and improved anatomical understanding on the surgeons' stress level will also be evaluated.

Together, these objectives seek to determine whether the improved anatomical understanding facilitated by 3D mapping translates into measurable clinical and economic benefits beyond enhanced perioperative planning accuracy.

METHODS

Trial design

This trial is designed as a randomised, controlled, open-label, superiority trial. Allocation will be performed as 1:1 allocation into the two trial arms (standard procedure/perioperative 3D mapping). Allocation will be stratified by planned resection procedure (extent of minimally invasive resection according to the highest applicable Iwate difficulty score) to further protect the analysis from bias due to high variation in operation times. The study design and procedure are illustrated as a flowchart (online supplemental figure S1).

Study setting

This monocentric trial will be conducted at the Department for General, Visceral, Paediatric and Transplant Surgery of the University Hospital RWTH Aachen (Director: Univ.-Prof. Dr. med. Florian W. R. Vondran), a tertiary referral centre with an annual volume of approximately 100 liver resections. The principal coordinating investigator is Prof. Dr. med. Oliver Beetz, MHBA. All surgeons participating in the study have each performed at least 50 minimally invasive liver resections.

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Participants

Inclusion criteria

- Age ≥18 years
- Indication for elective minimally invasive (laparoscopic or robotic) liver resection for benign or malignant disease
- Availability of contrast-enhanced preoperative CT and/or MRI suitable for 3D reconstruction
- Written informed consent

Exclusion criteria

- Emergency liver surgery
- Liver transplantation or living-donor hepatectomy
- Previous major liver resection
- Preoperative known necessity of further extrahepatic resections or extensive adhesolysis
- Inability to provide informed consent
- Current institutionalisation on court or official order
- Current or planned pregnancy preoperatively

Interventions

Control arm

Standard preoperative planning and intraoperative navigation using conventional 2D CT and/or MRI, consistent with the current institutional standard of care.

Intervention arm

Standard 2D preoperative planning plus additional patient-specific 3D liver mapping derived from CT and/or MRI, available preoperatively and intraoperatively. 3D reconstructions will be generated using the CE-approved medical device software MeVis Liver Suite and made available to the operating surgeon preoperatively on screen as 3D models, as well as via VR glasses if required. The software will be used strictly within the boundaries of its instructions for use and intended use as published by the manufacturer.

Based on the assumptions of the dissertation of Dr. Ing. V. Chheang from 2022, the estimated planning time for 3D reconstruction will be comparable to the time a surgeon needs to reconstruct a patient's anatomy from 2D CT/MR images.[11] However, possible prolongation of surgical planning time due to 3D-based mapping will be assessed as a secondary endpoint of this trial.

The surgical procedure will be performed according to the respective preoperative planning as per randomisation. If intraoperative findings indicate the need to deviate from the planned procedure, the surgeon will act on the intraoperative findings. The statistical analysis of these cases will still be performed as an intention-to-treat (ITT) analysis, based on the assumption that operation time will still be shortened due to improved 3D understanding of liver anatomy by the surgeon. Patients with preoperative known necessity of extensive adhesions or requirement for further extrahepatic resections will be excluded from the trial, as these factors extend operation time irrespective of 2D or 3D preoperative planning. Patients requiring intraoperative conversion to open surgery will be recorded as secondary endpoint of this study, as conversion time is in most cases unrelated to preoperative anatomical planning of the liver itself and should therefore have an equal impact on both study arms.

Outcomes

Primary endpoint

Operative time, defined as the time from the first cutaneous incision to the final suture, measured in minutes.

Secondary endpoints

- Blood loss (mL)
- Rate of R0 resection (in oncological cases)
- Length of hospital stay
- Length of stay in the intensive care unit (ICU)
- Rate of intraoperative conversion to open surgery
- Volumetric tumour-to-normal liver tissue ratio determined by synchrotron-based phase-contrast imaging (exploratory)
- Usage of disposable and/or DaVinci robot-related instruments
- Estimated time frame of 2D-supported and 3D-supported surgery planning
- Surgeon stress and anxiety level through the Surgeon Task Load Index (SURG-TLX) and biochemical analyses (salivary cortisol sample and saliva-cortisol analysis of the surgeon)

Participant timeline

The individual study participation duration corresponds to the perioperative hospital stay, including surgery and postoperative follow-up until discharge. No further follow-up visits will be necessary.

Sample size

Sample size determination was performed with G*Power (v3.1.9.7) in the form of an a priori computation. The expected mean difference was based on the retrospectively measured differences in operation time published by Nakayama *et al*.[1] The operation time reduction was retrospectively reported to be approximately 43 min with a conservatively estimated SD of ±95 min. Therefore, a 43 min mean difference in operation time was estimated for power analysis, resulting in an effect size (d) of 0.453. The significance level for this trial is set to α=0.05. Calculating for a power (1-β) of 0.8, the minimal sample size is estimated at 120 patients (60 per group). Accounting for drop-out due to unforeseen events or changes in disease severity, the recruitment goal of the trial is set to 126 patients with 1:1 allocation to both groups in stratification according to planned surgical procedures (extent of resection according to the highest applicable Iwate difficulty score). A recruitment period of 3 years is anticipated, based on an annual volume of approximately 80–100 liver resections at the participating department and accounting for the inclusion and exclusion criteria.

As the assumed effect size originates from a single retrospective study and may therefore be overestimated,

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Table 1 Sensitivity table of estimated sample size, measured differences and effects

Estimated true difference	Effect size D	Power at n=120 patients	Clinical classification/interpretation
43 min (Nakayama *et al*[1])	0.453	80%	Planned sample size
35 min	0.368	63%	Moderate effect leading to continuation
30 min (MCID)	0.316	41%	Lower clinical significance threshold
25 min	0.263	36%	Lower MCID, no continuation of recruitment
20 min	0.211	24%	Of questionable clinical relevance, primary hypothesis refuted, no continuation

MCID, minimal clinically important difference.

we define a minimum clinically important difference (MCID) of 30 min, representing the threshold below which, in authors' perspective, a reduction in operative time would not translate into meaningful clinical or resource benefits in routine practice. As shown in table 1, the study achieves 41% power to detect an effect at the MCID level with the primary sample size. The MCID therefore also represents a statistical threshold below which the statistical power falls to <50% of the assumed power of the primary analysis.

To address this limitation, we prospectively specify the following conditional adaptive extension: on completion of the primary analysis (n=120 evaluable patients), if the observed mean difference falls within the range of ≥30 and <43 min, recruitment will be continued until a total of 320 evaluable patients are enrolled (160 per group), which provides ≥80% power to detect a true difference of 30 min at the given SD. This extension will be implemented as a protocol amendment, subject to approval by the ethics committee of the University Hospital RWTH Aachen.

To control the family-wise type I error rate across both analyses, a Bonferroni–Holm correction will be applied: the primary analysis will be conducted at α_1=0.025 (two-sided) and the final analysis following extension at α_2=0.025 (two-sided), maintaining an overall $\alpha \leq 0.05$. The decision to initiate the extension phase will be made by the principal investigator and trial biostatistician based on the observed point estimate only, without unblinding of group-specific results to trial personnel, to preserve the integrity of the ongoing study.

If the observed difference in the primary analysis is ≥43 or <30 min, the trial will be concluded without extension. In the former case, the primary hypothesis is considered confirmed. In the latter, the effect is deemed below the pre-specified MCID, and the trial is concluded.

Recruitment

Patients aged ≥18 years with an indication for elective liver resection at the participating centre will be screened for eligibility during routine preoperative evaluation. Eligible patients will be informed about the study, utilising the EC-approved informed consent form in the attachment, by a member of the study team and invited to participate. Recruitment will continue until the required sample size is reached.

Randomisation and blinding

Randomisation will be performed in a 1:1 ratio using the embedded randomisation tool of the electronic Case Report Form (eCRF) database, stratified by planned resection type (extent of resection according to the highest applicable Iwate difficulty score: ≤6 vs >6).

This is an open-label trial. Blinding of the operating surgeon is not possible because of the visible nature of the 3D models used in the intervention arm. Patients will be informed about the study and their group allocation as part of the informed consent process and cannot be blinded to treatment assignment.

However, patient awareness of group allocation is not expected to introduce relevant bias for the primary endpoint (operative time), which is an objective measure extracted directly from operative records and not susceptible to patient-reported or behavioural influence. To further mitigate performance bias, data extraction for all endpoints will be performed by personnel blinded to treatment allocation. The statistical analysis will be conducted by a designated analyst who will receive a blinded dataset (with group labels concealed) until the analysis is complete and the primary endpoint results are locked.

Data collection

The following data will be collected:

- Demographic data (age, sex, height, weight and body mass index)
- Diagnosis and indication for surgery
- Type of liver resection
- Operative time
- Intraoperative blood loss
- Time required for 2D and 3D surgery planning
- Postoperative morbidity and mortality
- Length of ICU and hospital stay postoperatively
- Surgeon stress level and SURG-TLX

The digital medical records of the surgical department of the University Hospital RWTH Aachen will be used exclusively. All medical records relevant to the trial will be printed, validated by investigator signature and stored in a closed storage cabinet within the clinical trial centre of the clinic.

Data from participating surgeons will be limited to the SURG-TLX questionnaires and the salivary cortisol

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Table 2 Time schedule of the study

First patient in	Q3 2026
Recruitment of 50% of patients	Q1 2028–Q2 2028
Last patient in	Q3 2029
Last patient out	Q4 2029
Data Lock	Q4 2029
Statistical analysis	Q1 2030

Q, quarter.

analysis before and after surgery. All participating surgeons will be included as study investigators and will receive written and personal information about the data collection from the principal investigator. All investigators are required to provide informed consent for data collection to participate in the study. The study schedule and key milestones are clearly set out in table 2.

Surgeon workload assessment

Subjective intraoperative workload of the surgeon will be assessed immediately after surgery using the SURG-TLX questionnaire, which comprises six dimensions (mental demand, physical demand, temporal demand, task complexity, situational stress and distractions), each rated on a 20-point scale. The unweighted mean score will be used for analysis, with higher values indicating greater workload.[12] For objective comparison, an additional saliva sampling for cortisol level will be performed within 30 min before the first incision of the surgery as well as within 15 min after the final suture to evaluate the increase/decrease in the surgeon's cortisol level throughout the procedure. Weekly saliva samples are collected from participating surgeons on days when they are not performing surgery to serve as a baseline for monitoring the progression and changes in cortisol levels during the preoperative and intraoperative periods.

Perioperative medical treatment

Perioperative and postoperative medical treatments, including antibiotics and heparins, will be administered according to institutional standards. No deviations from routine clinical care are required.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study. The results of the study will be made available to participants on request.

STATISTICAL METHODS

Primary endpoint analysis

All statistical analyses will be performed according to the ITT principle. A per-protocol analysis will be conducted as a sensitivity analysis. Statistical tests will be two-sided with a significance level of α=0.05. Continuous variables will be summarised as mean (SD) or median (IQR) and categorical variables as absolute and relative frequencies.

The primary endpoint is operative time, defined as the time from the first cutaneous incision to the final suture in minutes. The primary analysis will compare operative time between the two study groups using a linear regression model, with treatment group (3D mapping vs standard planning) as the main independent variable and planned resection type (extent of resection according to the highest applicable Iwate difficulty score: ≤6 vs >6) as a covariate to account for stratified randomisation. The treatment effect will be reported as an adjusted mean difference with a 95% CI and corresponding p-value. If substantial deviations from normality or homoscedasticity are observed, appropriate transformations or robust statistical methods will be applied. An unadjusted comparison using a two-sample t-test (or Mann–Whitney U test, if applicable) will be performed as a sensitivity analysis.

The primary ITT analysis will include all randomised patients regardless of intraoperative events, including those requiring intraoperative conversion to open surgery or unplanned additional extrahepatic resection. For patients requiring conversion, operative time will be recorded in full as the time from the first cutaneous incision to the final suture, irrespective of the surgical approach ultimately used. This approach preserves the benefits of randomisation and avoids selection bias.

Secondary endpoint analyses

Secondary endpoints will be analysed in an exploratory manner. Intraoperative blood loss will be analysed as a continuous variable using linear regression adjusted for resection type. If the distribution is markedly skewed, non-parametric or generalised linear models will be used. The rate of R0 resection (oncological cases only) will be compared between groups using logistic regression adjusted for resection type; results will be reported as ORs with 95% CIs. Exploratory volumetric assessment of tumour-to-normal liver tissue ratio using synchrotron-based phase-contrast imaging will be analysed as a continuous outcome using linear regression adjusted for resection type. No formal adjustment for multiple testing will be applied for secondary endpoints. Results will be interpreted descriptively. The secondary endpoint of surgeons' stress level will be evaluated using preoperative and postoperative salivary cortisol levels as well as the validated SURG-TLX.[12] The proportion of patients requiring unplanned conversion to open surgery will be compared between treatment arms using logistic regression, with treatment group as the primary predictor and resection complexity (Iwate score ≤6vs > 6) as a covariate. Results will be reported as ORs with 95% CIs. Absolute conversion rates per arm will be reported with Wilson score 95% CIs, and the absolute risk difference will be estimated using the Newcombe method. If the total number of conversion events is <10, Fisher's exact test will be substituted for logistic regression, as pre-specified. This endpoint is

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exploratory; no multiplicity adjustment will be applied, and no confirmatory claims will be made.

Statistical analysis personnel

Statistical analyses will be performed by Bengt Arne Wiemann, MD (sub-investigator, not involved in the direct treatment of the patients and blinded to group allocation) using a blinded dataset. Group allocation labels will be revealed to the analyst only after completion of the primary analysis and prior to the preparation of the final results table (blinded analysis approach).

Missing data

Missing data for the primary endpoint is expected to be minimal. Analyses will be based on available data; sensitivity analyses may be performed if relevant missingness occurs.

Methods for minimisation and prevention of bias

The following measures are implemented to minimise bias:

- Stratified randomisation: randomisation is stratified by planned resection type (extent of resection according to the highest applicable Iwate difficulty score) to ensure a balanced distribution of a major determinant of operative time across study arms.
- Standardised surgical and perioperative protocols: surgical procedures and perioperative management will be performed according to standardised institutional protocols to reduce performance bias related to variations in the operative technique or postoperative care.
- Objective definition of the primary endpoint: operative time is defined using a clear and objective time interval (from the first cutaneous incision to the final suture), minimising measurement bias.
- Blinded Outcome Assessment Where Feasible: Although blinding of the operating surgeon is not possible, data extraction of operative time, blood loss, and length of stay will be performed by personnel blinded to treatment allocation whenever feasible.
- Use of routinely documented data sources: primary and secondary endpoints are derived from routinely documented operative and clinical records, reducing the risk of observer and recall bias.
- ITT analysis: primary analyses will follow the ITT principle, preserving the benefits of randomisation and reducing attrition bias.
- Restriction of co-interventions: no study-specific co-interventions are introduced beyond routine clinical care, minimising confounding due to differential perioperative management.
- Training and familiarisation with 3D mapping tools: surgeons involved in the trial will receive standardised training in the use of 3D-mapping tools prior to study initiation, reducing learning-curve effects and performance bias.
- Monitoring of protocol deviations: protocol deviations will be prospectively documented and reported. Sensitivity analyses excluding major deviations will be performed to assess the robustness of results.

ETHICS AND DISSEMINATION

Ethics approval

Ethics approval has been granted by the Ethics Committee of the Medical Faculty of the University Hospital RWTH Aachen (Reference No. 26–050). The study will be conducted in full conformity with Good Clinical Practice standards, Declaration of Helsinki and applicable national and European regulations.

Consent

Eligible patients will receive verbal and written information about the study objectives, procedures, potential risks and benefits using the attached informed consent form in online supplemental file 3. Adequate time will be provided to consider participation. Written informed consent will be obtained prior to randomisation and any study-specific procedures. All participating surgeons and investigators will be provided with written information regarding the collection of salivary cortisol levels and data collection for stress assessment. Investigators will be required to provide a signed informed consent form for participation in this study. Participants may withdraw their consent at any time. In the event of withdrawal, data handling and deletion will be carried out in accordance with applicable legal and regulatory requirements.

Confidentiality and data protection

Data will be collected and processed in pseudonymised form (traceability possible via a code list). No directly identifying personal data will be used for analysis. All data will be collected and saved in the form of an eCRF using a validated and specialised system in accordance with the standards of the European Clinical Trials Regulation and German data protection regulations. In the event of publication, only anonymised data not connected to patients' private data will be used. The patients' identification list will be kept in the central study binder within the trial centre and will not leave the centre.

Benefit–risk assessment

The intervention under investigation consists solely of an additional perioperative planning tool and does not alter the surgical procedure itself. No additional risks for participants are anticipated. Potential benefits include improved surgical efficiency and reduced operative time. The overall risk–benefit ratio is considered favourable.

As standard surgical planning requires either CT, MRI or both modalities, no additional imaging is needed for trial participation or trial performance. Therefore, no additional radiation exposure is anticipated. The software used for 3D reconstruction (MeVis Liver Suite) can work with either CT, MRI or both modalities for model creation. All imaging will be performed within the clinical standard

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procedure, under oversight of an experienced radiologist and within medical guideline recommendations.

Safety reporting and medical device vigilance

Adverse events (AEs) and serious adverse events (SAEs) related to the surgical procedure are not systematically collected within this study, as all patients undergo routine clinical treatment in accordance with established standards of care. However, if a serious clinical event occurs for which a causal relationship with the use of the medical device software cannot be excluded, such an event will be documented and assessed as a potential device-related incident in accordance with applicable vigilance requirements.

CE-marked medical device software (MeVis Liver Suite) for 3D preoperative planning will be used in this clinical study exclusively as a decision-support tool during the preoperative planning process. The software does not have direct contact with the patient and does not interact with the patient's body or intraoperative instrumentation. Conventional 2D imaging remains available to the surgical team at all times and represents the standard basis for operative decision-making.

As this study is a monocentric investigator-initiated trial, the study centre acts as sponsor and is responsible for the identification, documentation and causality assessment of any suspected device-related incident. In cases where a causal relationship between device use and a SAE cannot be excluded, the sponsor will ensure reporting to the competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) in accordance with applicable provisions of Regulation (EU) 2017/745 (MDR).

Handling of biomaterial

As part of the assessment of intraoperative stress among participating surgeons, saliva samples will be collected for the determination of cortisol levels as a physiological stress marker. Saliva samples will be obtained from participating surgeons at pre-defined time points in the perioperative period using non-invasive collection methods. All participating surgeons will provide written informed consent prior to inclusion in the biomaterial collection. Each sample will be pseudonymised immediately after collection using a study-specific identification code. No directly identifying personal data will be linked to the biomaterial during laboratory analysis. Samples will be transferred to the central laboratory of the University Hospital RWTH Aachen for a one-time determination of salivary cortisol concentration. No genetic analyses or additional biochemical assessments will be performed. Following analysis, all saliva samples will be discarded. No storage, freezing or biobanking of biomaterial will take place, and no further analyses beyond the pre-defined cortisol measurement are planned.

Publication policy

In case of publication, only anonymised data will be made available. The publication of the main outcomes of this study is aimed to be submitted to a leading international journal. Secondary outcomes arising primarily from secondary endpoints will be published in international, English-language medical journals. Publication of data is in no way related to the outcome of the study. Data will be published independent of the resulting statements.

Protocol amendments

Should any significant changes or amendments to this study protocol occur during study conduct, the ethics committee of the University Hospital RWTH Aachen will be informed immediately, and all significant changes will be published at the trial registration website.

DISCUSSION

The SMART-MILS trial is designed to address a critical evidence gap in minimally invasive liver surgery: the impact of patient-specific 3D liver mapping on operative efficiency. Further details of the study design and rationale can be found in the online supplemental file 2. While prior retrospective studies and systematic reviews have demonstrated improved anatomical understanding and planning accuracy using 3D visualisation, no prospective randomised controlled trial has been specifically designed to investigate the effect of 3D mapping on operative time as a primary endpoint in the setting of minimally invasive liver resection.

The choice of the operative time as the primary endpoint is justified by its objectivity, clinical relevance and direct relationship to perioperative risk, resource utilisation and healthcare costs. Minimally invasive liver resections are particularly suited for this investigation, as laparoscopic and robotic approaches inherently lack tactile feedback, making 3D spatial orientation more dependent on preoperative (and intraoperative) imaging navigation than open procedures.

The trial uses CE-approved software (MeVis Liver Suite), ensuring regulatory compliance and clinical applicability of the intervention. The use of a validated, commercially available tool rather than an experimental prototype increases the external validity of the results and facilitates potential clinical translation.

Stratified randomisation by resection type (extent of resection according to the highest applicable Iwate difficulty score: ≤6 vs >6) accounts for a major source of variability in operative time, strengthening the internal validity of the trial. The use of salivary cortisol sampling in combination with the validated SURG-TLX questionnaire provides a dual objective–subjective assessment of surgeon workload, which has not previously been investigated in the context of 3D surgical planning. The cortisol sampling protocol includes three time points (T1, 30 min before the first incision; T2, 15 min after the final suture; baseline levels on non-operational days), enabling assessment of the intraoperative cortisol stress trajectory and diurnal individual comparison to baseline levels rather than a simple pre-to-post comparison. The

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primary cortisol analysis will use the pre-to-post change (ΔCortisol=T2 − T1) as the dependent variable, as well as ΔCortisol=T2 – baseline and ΔCortisol=T1 – baseline adjusted for the time of day of surgery to partially account for diurnal variation.

The exclusion criteria have been designed to apply exclusively to conditions that are documented and known prior to randomisation. Patients with preoperatively known extensive adhesions or a preoperative indication for additional extrahepatic resection are excluded before enrolment; however, patients in whom such findings arise unexpectedly during surgery are retained in the primary ITT analysis, with their full operative time recorded as observed. This design is specifically chosen to fully preserve the benefit of randomisation and avoid selection bias. Furthermore, unplanned intraoperative conversion to open surgery will be recorded as an exploratory secondary endpoint and will be analysed using logistic regression with the randomisation stratification variable as a covariate, enabling assessment of whether 3D planning influences the need for conversion.

The effect size of 43 min used for sample size calculation is based on a single retrospective cohort study, which represents the best available evidence at the time of trial design. We have accounted for the possibility of a smaller true effect through the adaptive sample size re-estimation built into the protocol. A sensitivity analysis demonstrated that the trial achieves only 41% power to detect a difference at the pre-specified MCID of 30 min with the primary sample size. To mitigate the risk of an underpowered result, a pre-specified conditional adaptive extension has been incorporated into the protocol: if the primary analysis yields an observed difference between and at 43 min, recruitment will continue to a maximum of 320 patients under a protocol amendment, controlled by a Bonferroni–Holm correction to maintain the family-wise type I error rate at α=0.05 across both analyses. This design provides a prospective pathway to achieve adequate power if the true effect size is smaller than assumed while preserving the integrity of the primary analysis.

To address limitations in the pre-specification of the primary statistical model, a decision rule for distributional assumptions has been formalised: operative time, which characteristically follows a right-skewed distribution, will be formally assessed for normality prior to analysis. If substantial right-skewness is observed, the primary analysis will use linear regression on log-transformed operative time, with results back-transformed and reported as geometric mean ratios. As a pre-specified sensitivity analysis independent of distributional assessment, a generalised linear model with gamma distribution and log link function will be fitted to untransformed operative time data. This pre-specification eliminates the risk of post-hoc model selection.

Secondary endpoints have been stratified into confirmatory and exploratory tiers to address the risk of false-positive findings arising from multiple comparisons. Intraoperative blood loss and surgeon task load (SURG-TLX) are designated as tier 1 confirmatory secondary endpoints to be tested using a sequential Holm–Bonferroni procedure applied only after the primary endpoint has achieved statistical significance. All remaining secondary endpoints are designated as exploratory and will be reported descriptively with 95% CIs; no confirmatory claims will be made from these analyses.

The tumour-to-resection volume ratio, assessed using virtual pathology based on non-destructive synchrotron phase-contrast micro-CT, serves as a surrogate measure of resection precision. A higher ratio indicates a more tumour-focused resection with less unnecessary removal of healthy hepatic parenchyma. We hypothesise that the superior 3D anatomical understanding afforded by preoperative 3D planning will facilitate more precise resection margins, resulting in a higher tumour-to-resection volume ratio in the intervention arm. However, due to the exploratory nature and design of this secondary endpoint, no confirmatory claims will be made from this analysis.

No independent Data Safety and Monitoring Board has been established for this trial. This decision is justified by the nature of the intervention, which consists solely of an additional preoperative planning tool that does not alter the surgical procedure or introduce additional invasive elements, and by the monocentric investigator-initiated design without external commercial sponsorship. Ongoing safety oversight is the responsibility of the principal investigator, who will review accumulating safety-relevant data at 3-monthly intervals and report to the ethics committee in accordance with applicable regulations. No interim efficacy analyses are planned; the trial will not be stopped early for benefit.

Limitations of this trial include its monocentric setting at a single tertiary referral centre, which may limit generalisability across centres with different case volumes, surgical teams and institutional cultures. As blinding of the operating surgeon is not feasible given the visible nature of the 3D models, performance bias cannot be entirely excluded; this is mitigated through standardised pre-trial training in 3D-mapping tools, adherence to institutional protocols, blinded data extraction by personnel unaware of group allocation and a blinded statistical analysis. Patient blinding is also not feasible and unnecessary in this open-label design, as the informed consent process may disclose the use of 3D reconstruction in the intervention arm. However, this limitation has negligible impact on the primary endpoint, which is an objective measure extracted directly from operative records and not susceptible to patient knowledge or behaviour. Likewise, it has no impact on the relevant confirmatory secondary endpoints of the study. The assumed effect size is derived from a single retrospective study and may be overestimated; this limitation is addressed by the pre-specified conditional adaptive extension described above. Salivary cortisol measurements are subject to inter-individual circadian variation; without a same-time-of-day control on a non-surgical day, absolute cortisol levels cannot be fully corrected for individual baseline differences, and results

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will therefore be interpreted primarily as within-subject pre-to-post changes rather than absolute values.

The results of this trial may contribute to the growing evidence base supporting the routine adoption of 3D surgical mapping in minimally invasive liver surgery, with implications for surgical training, resource allocation and patient outcomes. If the primary hypothesis is confirmed, the findings will provide prospective randomised evidence for the integration of patient-specific 3D planning as a standard element of preoperative workup in minimally invasive hepatobiliary surgery. Should the primary analysis yield a clinically relevant but statistically non-significant trend, the pre-specified adaptive extension mechanism ensures that the trial retains the capacity to generate definitive evidence without compromising statistical integrity.

Trial status

Protocol Version 1.1, dated 3 March 2026. The trial has received ethics approval (Ref. No. 26–050, Ethics Committee of the Medical Faculty, University Hospital RWTH Aachen) and is registered in the German Clinical Trials Register (DRKS00039587). Recruitment is planned to commence in Q3 2026.

Protocol Version 2.0 dated 08 June 2026 has been filed with the Ethics Committee of the Medical Faculty, University Hospital RWTH Aachen), and all significant changes have been registered in the German Clinical Trials Register (DRKS00039587).

Contributors NL and OB conceived and designed the study protocol and manuscript. BAW will perform the blinded statistical analysis. NL drafted the manuscript. OB, FO, MvW and TV critically revised the manuscript for important intellectual content. OB and FWV supervised the protocol design. All authors have read and approved the final version. OB is the guarantor of this work and, as such, had full access to all documents and materials and takes responsibility for the integrity of the trial protocol and manuscript. Claude.ai was used for structuring of clinical trial protocol to manuscript transfer. Further, Claude.ai was used to optimise the text in terms of language and grammar without altering the content. During protocol creation and writing, ChatGPT was used for language and grammar optimisation.

Funding As this is a routine, guideline-compliant therapy, the surgical procedure is covered by standard health care reimbursement. All additional costs are covered by the hospital's internal budget. There are no external sponsors. Since the study intervention consists exclusively of diagnostic and planning procedures that are part of routine clinical care, no reimbursement of expenses or financial compensation for participants is planned.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design or conduct or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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