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Intraoperative visualisation of pancreatic leakage (ViP): study protocol for an IDEAL Stage I Post Market Clinical Study

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ABSTRACT

Introduction Pancreatic resections are an important field of surgery worldwide to treat a variety of benign and malignant diseases. Postoperative pancreatic fistula (POPF) remains a frequent and critical complication after partial pancreatectomy and affects up to 50% of patients. POPF increases mortality, prolongs the postoperative hospital stay and is associated with a significant economic burden. Despite various scientific approaches and clinical strategies, it has not yet been possible to develop an effective preventive tool. The SmartPAN indicator is the first surgery-ready medical device for direct visualisation of pancreatic leakage already during the operation. Applied to the surface of pancreatic tissue, it detects sites of biochemical leak via colour reaction, thereby guiding effective closure and potentially mitigating POPF development.

Methods and analysis The ViP trial is a prospective single-arm, single-centre first in human study to collect data on usability and confirm safety of SmartPAN. A total of 35 patients with planned partial pancreatectomy will be included in the trial with a follow-up of 30 days after the index surgery. Usability endpoints such as adherence to protocol and evaluation by the operating surgeon as well as safety parameters including major intraoperative and postoperative complications, especially POPF development, will be analysed.

Ethics and dissemination Following the IDEAL-D (Idea, Development, Exploration, Assessment, and Long term study of Device development and surgical innovation) framework of medical device development preclinical in vitro, porcine in vivo, and human ex vivo studies have proven feasibility, efficacy and safety of SmartPAN. After market approval, the ViP trial is the IDEAL Stage I trial to investigate SmartPAN in a clinical setting. The study has been approved by the local ethics committee as the device is used exclusively within its intended purpose. Results will be published in a peer-reviewed journal. The study will provide a basis for a future randomised controlled interventional trial to confirm clinical efficacy of SmartPAN.

Trial registration number German Clinical Trial Register DRKS00027559, registered on 4 March 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ SmartPAN medical device development has been fully conducted in accordance with IDEAL-D framework and after preclinical proof of feasibility, efficacy and safety the Visualisation of pancreatic leakage trial represents a derisked translation to clinical stage (stage I).
⇒ By design, trial participants receive unaltered state-of-the art pancreatic surgery plus additional intraoperative indication of pancreatic biochemical leakage and potentially effective targeted leak closure.
⇒ Limitation of the trial is its single-arm single-centre exploratory design with focus on usability and safety that will require a subsequent randomised controlled trial to confirm SmartPAN's clinical efficacy.

INTRODUCTION

Context

Pancreatic surgery is the only curative therapeutic approach in many benign and especially malignant pathologies. Despite the fact, that advanced surgical techniques, perioperative care improvements and centralisation in specialised high-volume centres have led to mortality rates of under 5%,[1–4] pancreatic surgery is still complex with a considerable risk for complications and an overall morbidity of more than 50%.[3 5 6] One of the most frequent and critical complications after partial pancreatectomy is postoperative pancreatic fistula (POPF).[7] A leakage of enzyme-rich pancreatic fluid either from the pancreatic remnant, for example after distal pancreatectomy or pancreatic enucleation, or from the pancreatic anastomosis, for example after partial pancreatoduodenectomy, can lead to severe consequences such as sepsis or postpancreatectomy haemorrhage.[8] POPF affects up to 50% of patients following pancreatic surgery and is associated

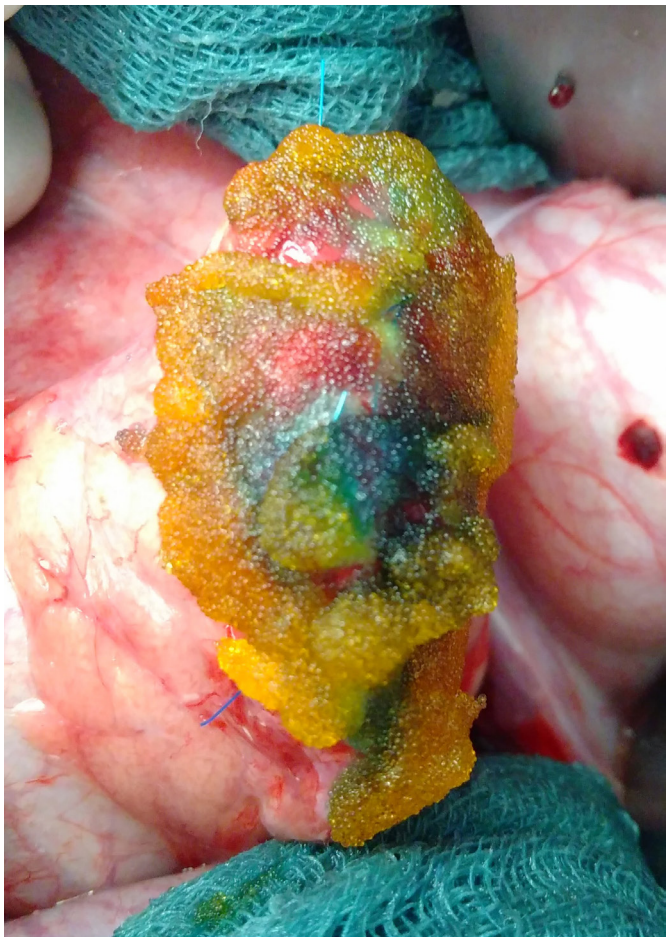

Figure 1 Representative image of SmartPAN blue colour reaction to leakage at the pancreatic remnant after distal pancreatectomy in porcine animal trial. Photo credit: TMP.

with a prolonged hospital stay and a significant economic burden.[5 9–12] Furthermore, in-hospital mortality due to POPF or subsequent complications reaches up to 33% in high-risk subgroups.[2 9]

Current knowledge

Many attempts have been made to reduce the POPF occurrence such as development of different techniques for pancreatic dissection,[13] application of drugs like somatostatin analogues[14] or intraoperative usage of sealants such as fibrin glue or haemostyptics[15] without ground-breaking success. An auspicious chance would be to detect the leakage of pancreatic fluid during surgery, as high concentrations of pancreatic enzymes in intraoperatively derived abdominal fluid are highly predictive for POPF.[16] An intraoperative indicator visualising leakage could enable immediate targeted closure of the detected leakage sites, optimised drain placement and postoperative care and thus lead to a reduction of clinically relevant POPF. However, since pancreatic fluid is physiologically invisible no suitable tool has been developed before to identify leakage sites in routine clinical use.[17–21] Recently, a novel indicator for pancreatic leakage called SmartPAN has been developed according to the IDEAL-D framework for surgical innovation and medical devices.[22–24] SmartPAN contains the pH-indicator bromothymol blue (BTB) bound to an active biodegradable polysaccharide-microsphere matrix to detect alkali pancreatic fluid and phosphate buffered saline. It is applied to the pancreatic surface in the surgical area in one continuous layer. Appearing orange when applied, it locally turns green bluish over pancreatic leakage (figure 1). During development, one superior indicator for pancreatic fluid was selected for further evaluation.[25] This prototype was assessed in vivo using a porcine model (Sus scrofa domesticus) for usability, effectiveness and reliability. Treatment groups were defined by SmartPAN-reaction at initial pancreatic resection: indicator positive or negative. Indicator-positive individuals randomly received either targeted closure of leakage sites or no further closure. SmartPAN's reliability and effectiveness were assessed by monitoring abdominal drainage for pancreatic enzymes and with relaparotomy after 48 hours. SmartPAN responses were consistent between both surgical procedures and conformed to amylase measurements. In a consecutive preclinical randomised efficacy trial, SmartPAN was capable of precisely detecting sites associated with biochemical leak and subsequent clinical POPF-symptoms with high sensitivity and specificity, thereby guiding effective closure.[26] Preclinical safety assessments did not show cytotoxicity at concentrations used in practise.[27] It was shown that SmartPAN consists of components that are either biocompatible or quickly neutralised by dilution and drainage. Therefore, the preclinical IDEAL stage 0 has been completed[28] with proof of efficacy and safety providing a derisked translation to first-in-human studies.

METHODS AND ANALYSIS

Objective

According to the IDEAL-D framework the visualisation of pancreatic leakage (ViP) trial represents a stage I first in human trial.[22–24] Hence, this post-market clinical follow-up (PMCF) trial aims to confirm the usability and safety of the indicator application in the clinical environment of elective pancreatic resections when used according to the instructions for use. Usability, safety and previously unknown side-effects or contraindications of the indicator in the clinical environment of elective pancreatic resection will be assessed.

Trial design

ViP is a prospective investigator-initiated single-arm single-centre study.

Patient and public involvement

Establishing SmartPAN in clinical routine could be a big step towards the best complication treatment after pancreatic surgery, a goal which we have shown to be a research priority of utmost relevance identified by patients, caregivers and professional stakeholders in our

priority setting partnership project[29] (also see Ethics and dissemination section). Trial results will be discussed with the patient advisory board of the SDGC for interpretation and for preparation of subsequent trials.

Study population

The study will be conducted at the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital. Annually, more than 700 pancreatic surgeries are conducted at this high-volume centre. Enrolment of patients was started on 27 June 2022 and completion of the trial is expected in February 2023. Accounting for interfering trials, conservatively 5 patients per month are expected to be included and completion of recruitment is feasible within 7 months. All patients with planned partial pancreatectomy will be screened consecutively for eligibility. They will be informed about the ViP-trial during a pretreatment visit or on the day of hospitalisation. Eligible for participation are (1) all patients with diseases of the pancreas which necessitate partial pancreatectomy with open or minimally invasive surgical approach. Additionally, (2) age≥18 years and (3) the capability to understand the subject and individual consequences of the clinical trial have been chosen as inclusion criteria. Exclusion criteria are defined as follows: (1) American Society of Anesthesiologists (ASA) Score>3, (2) pregnancy or lactation, (3) known allergy or intolerability to BTB or potato starch, (4) participation in another intervention trial with interference of intervention and outcome of this study, (5) any condition which could result in an undue risk for the patient in the opinion of the clinical investigator, (6) expected lack of compliance or language problems. Patients may withdraw from the trial at their own request at any time without giving reasons. If no partial pancreatic resection is performed (e.g., because of technical irresectability or metastatic disease) or if the investigator stops the trial intervention due to expected harm to the patient's well-being, the respective patient will leave the trial early (see Sample size calculation section). This will be detailed in the final report of the trial to ensure complete transparency.

Intervention

All participating surgeons will be experienced in pancreatic surgery. To ensure recognition of experience as well as device usage, a self-categorisation will be performed by the surgeons (online supplemental file 1). Surgeons will be trained regarding study-specific handling instructions for the investigational device by the principal investigator prior to the study initiation. Laparoscopic or open partial pancreatectomy is performed according to local standard operating procedures. In case of distal pancreatectomy, a stapler will be used for closure of the remnant pancreas and no additional covering (e.g., teres ligament patch) will be conducted. In case of partial pancreatoduodenectomy, reconstruction includes a pancreaticojejunostomy, a hepaticojejunostomy and a duodenojejunostomy or gastrojejunostomy. Somatostatin or analogues will not be given postoperatively as a matter of routine. However, if applied usage must be documented and justified. After accomplished resection and reconstruction phase and haemostasis, the SmartPAN indicator is applied in a standardised procedure as specified in the instructions for use of the device: prior to application, the operative field is gently rinsed and dabbed to ensure complete blood dryness which could possibly reduce effectiveness of the indicator. The target area is maintained in a horizontal position and approximately 4 mL of the indicator hydrogel is applied rapidly and uniformly to the cut surface/pancreatic anastomosis, taking care to cover the whole tissue of interest and to prevent overspill. Depending on the surgeon's preference, application can be performed solely with the original syringe or with additional surgical standard application devices. The surrounding area will be covered with sterile surgical gauzes to guarantee contact of the indicator only to the tissue of interest. Colour change only appears close to relevant pancreatic leakage (figure 1). The observation time for any colour change is defined as up to 3 min after application. In case of subsequent localised colour change, extra single stiches may be applied to close pancreatic leakage depending on the operating surgeon's preference and SmartPAN may be reapplied to confirm closure tightness. Nature of colour change (speed of appearance, number and size of spots, optical discrimination, durability) and subsequent targeted closure will be reported (online supplemental file 1). After usage, the surgical site is rinsed with sterile isotone saline and drainage or suctioning of the fluid is assured to avoid accumulation of the product in the abdominal cavity.

To investigate concentration of BTB in patients, venous blood samples will be taken from central venous catheter 15 min after indicator application. This timepoint takes into account the maximum intra-abdominal BTB concentration known from preclinical studies at approximately 5 min plus a latency for potential systemic absorption. According to standard surgical procedure, a drainage is inserted into abdominal cavity or drainage omission is documented if not inserted. Easy-flow drainages in case of open surgery and Robinson drainages in case of minimally invasive surgery are placed next to the remnant of the pancreas before the abdominal wall is closed. A sample from the intraperitoneal drain fluid will be taken for the assessment of BTB and amylase/lipase concentrations at the end of surgery. At the second postoperative day, drain fluid is checked for amylase/lipase and BTB. If enzyme concentrations are <3 times institutional normal serum values, the drain is typically removed on day 2 or 3. If values are high, the drain is kept longer, and enzyme concentrations will be rechecked until drain removal according to standard clinical procedure.

Outcome parameters

The chosen endpoints cover important usability endpoints as well as safety endpoints represented by clinical intraoperative and postoperative parameters including

Table 1 Definition of outcome parameters

Endpoint	Definition
Usability endpoints	
Adherence to study protocol including SmartPAN instructions for use	Recording of all deviations from the study protocol with justification.
Usability evaluation of SmartPAN by operating surgeon	Surgeon's usability score with six dimensions (experience, ease of use, usefulness, ease of learning, intention to use, safety; see online supplemental file 1).
Safety and efficacy endpoints	
Major intraoperative and postoperative complication and relation to SmartPAN usage	Complications classified according to Clavien-Dindo[30] grade III-V within 30 days after the index surgery including information on potential relation to usage of SmartPAN.
Duration of surgery (min)	Time from the beginning of skin incision to the end of skin closure.
Intraoperative blood loss (mL)	Volume of blood loss as recorded in the anesthesiology report.
Postoperative pancreatic fistula (%)	Rate of postoperative biochemical leak and grade B and C POPF within 30 days after the index surgery as defined by the ISGPS.[7]
Non-surgical reinterventions	Occurrence of non-surgical reinterventions within 30 days after the index operation (eg, image-guided drain placement, angiography with stenting/ other interventions, endoscopy).
Reoperations	Occurrence of reoperations within 30 days after the index surgery.
Mortality (%)	Rate of deaths within 30 days after the index surgery.
Health-related quality of life (HRQoL)	Differences in health-related quality of life measured by the SF-36 at baseline and at the 30th day after the index surgery.[31]
Concentration of bromothymol blue (degradation product of SmartPAN) in central venous blood and in abdominal fluid (ng/mL)	Measured in central venous blood 15 min after SmartPAN application and at the second day after the index surgery. Measured in abdominal drainage fluid at the end of surgery and at the second day after the index surgery.

patient-reported outcome and laboratory outcomes. For a detailed list of all measured outcome parameters, see table 1.

Participant timeline

Patients will undergo follow-up within 30 days after the index surgery. Preoperative and postoperative data collection will be performed at six visits which will be conducted by clinical investigators and study nurses as mentioned in table 2. During the screening visit (visit 1, 1–7 days prior surgery), patients will be included in the trial if they fulfil all inclusion criteria and do not meet any exclusion criteria. Baseline demographic and clinical data will be collected during visit 1. Intraoperative data will be recorded during visit 2 including the indicator usability score (online supplemental file 1), collection of one central venous blood sample and of one drain fluid

Table 2 Trial visits

	1	2	3	4	5	6
	Screening	Day of surgery	POD 2	POD 7	Day of discharge	POD 30
Visit	Outpatient/ inpatient	Inpatient				Outpatient/ telephone
Eligibility criteria	X					
Informed consent	X					
Baseline demographics and clinical data	X					
Surgical intervention		X				
Assessment of usability		X				
Assessment of safety		X	X	X	X	X
Assessment of efficacy		X	X	X	X	X

POD, postoperative day

sample. During the follow-up visits 3–5 on postoperative day 2, 7 and the day of discharge safety and efficacy data items and information about their potential relation to use the trial device are documented, like the occurrence of POPF[7] or other major postoperative complications (classified as Clavien-Dindo grade III to V[30]), non-surgical reinterventions or reoperations. Additionally, at visit 3 on postoperative day 2, central venous blood and abdominal drain fluid will be examined for BTB concentration and for amylase and lipase. Visit 6 will take place as a telephone interview at postoperative day 30 and includes a survey of health-related quality of life measured by the SF-36 questionnaire.[31]

Safety aspects

All Clavien-Dindo grade III–V complications will undergo further assessment and the potential relationship to the use of the trial device will be investigated. If immediate action is required concerning the continuation of the trial, the principal investigator and the steering committee will be informed and will decide if any modifications or precautions regarding the trial procedure are needed. Serious incidents will be reported to the device manufacturer Magle Chemoswed AB Holding (Malmö, Sweden) within 24 hours. These include Clavien-Dindo grade III–V events that are considered to be medical device related. Device malfunction incidents and other serious events such as the death of a patient or other person, the temporary or permanent serious deterioration of a patient's, user's or other person's state of health or a serious public health threat will be reported as well.

Sample size calculation

Due to the fact that this is an exploratory trial, no formal sample size calculation was performed. Analysis of 30 patients was judged sufficient for a preliminary evaluation of usability and safety of the SmartPAN device. Considering that approximately 5 patients will be excluded due to inoperability or the implementation of another type of pancreatectomy, an overall number of 35 patients will be allocated to the trial (figure 2). From previous randomised controlled trials on distal pancreatectomy and partial pancreatectomy and from a review of the literature, there is good evidence that the rate of POPF after distal pancreatectomy is 40%[6 13] and 20% after partial pancreatoduodenectomy.[5 32] Accordingly, we expect about 10 patients to develop a POPF and SmartPAN-driven closure attempts by the operating surgeon will be described and compared with literature controls as basis for subsequent interventional trials.

Statistical analysis

Endpoints are described as mean values along with SD, median values, and quartiles, minimum and maximum for continuous, and relative and absolute frequencies for categorical endpoints. Regarding the use of SmartPAN, adherence and usability will be analysed qualitatively and quantitatively in the whole study group and in the subgroups of the two most common types of surgery, respectively. The safety analysis includes calculation of frequencies and rates of major complications (Clavien-Dindo grade III–V) together with 95% CI. Statistical analyses will be fully specified in a statistical analysis plan that is written prior to database closure. All analyses will be exploratory, having only descriptive character and will be done using SAS (SAS Institute) V.9.4 or higher.

Data collection and data management

Study data will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Study Center of the German Society of Surgery at Heidelberg University Hospital. REDCap is a secure, web-based software platform designed to support data capture for research studies.[33 34] An electronic case report form (eCRF) will be used for data collection. All information collected during the trial will be entered in the eCRF by the study investigators or study nurses. The eCRF pages will be completed as soon as possible, preferably on the same day that a trial participant is undergoing trial procedure step. Any outstanding entries will be completed immediately after the final visit. An explanation should be given for all missing data. To assure a safe and secure environment for acquired data, transmission is encrypted with secure socket layer technology. Only authorised users are able to enter or edit data. Changes to data are logged with a computerised timestamp in an audit trail. All data will be pseudonymised. To guarantee high data quality, data validation rules will be defined in a separate data validation plan. Completeness, validity and plausibility of data will be checked in time of data entry (edit checks) and using validating programmes, which will generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or by a designated subinvestigator. The investigator or the designated representatives are obliged to clarify or explain queries. If no further corrections are to be made in the database, eCRF data will be locked. Data will finally be downloaded and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures that guarantee an efficient conduct complying with good clinical practice (GCP). At the end of the trial, the data will be transformed into different data formats (eg, csv-files) for archiving.

Methods for minimising bias

The study protocol has been drafted in adherence to SPIRIT (Standard Protocol Items for Randomized Trials) statement (online supplemental file 2).[35] To reduce performance bias, the patients will be blinded for all endpoints but HRQol and safety issues that would need to be communicated outside of the study due to ethical reasons. By design, the operating surgeons cannot be blinded to usability endpoints. However, they will not be involved in data contribution of any endpoint after the operation. Data collectors, outcome assessors and data

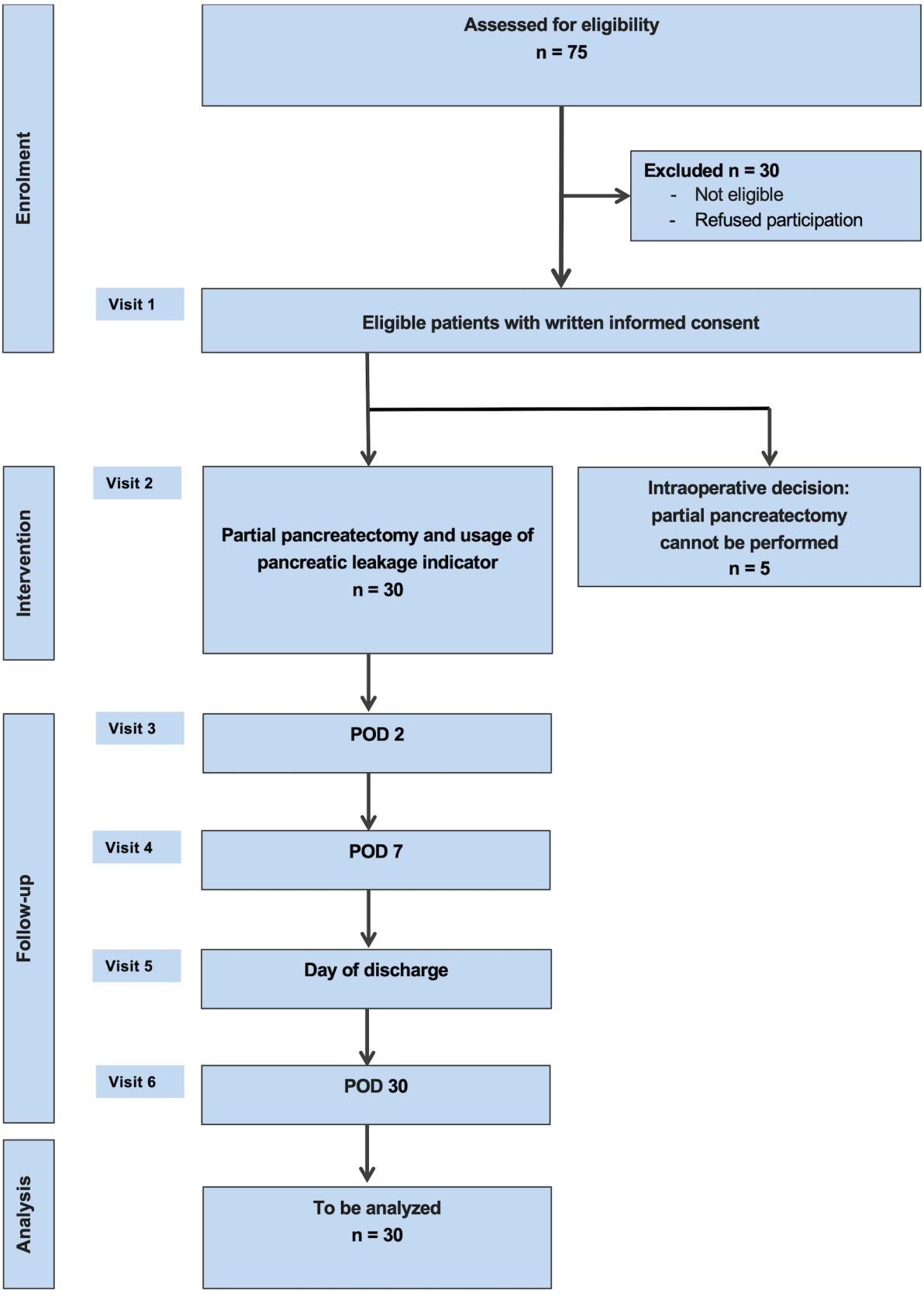

Figure 2 Flow chart of the visualisation of pancreatic leakage (ViP) trial. POD, postoperative day.

analysts will not be blinded, but endpoints are assumed to be robust against their unconscious or intentional influence and therefore detection bias can be avoided.[36]

To avoid the risk of selective reporting, the trial protocol is hereby fully published. The patient flow and the CONSORT (Consolidated Standards of Reporting Trials)

flow chart will be reported with the final analysis. The number of patients screened, included and analysed will be reported, and differences will be explained.

ETHICS AND DISSEMINATION

Study registration, ethics and consent

This trial protocol was approved by the ethics committee of the University of Heidelberg (Medizinische Fakultät Heidelberg, S-043/2022, 4 February 2022). It was registered at the German clinical trial register (DRKS, DRKS00027559, 4 March 2022) before inclusion of the first patient. The ethics committee will be informed of all subsequent protocol amendments in order to determine whether formal approval needs to be sought and whether the informed consent document should also be revised. The study is designed according to the Medical Association's professional code (Berufsordnung der Landesärztekammer Baden-Württemberg) §15 (non-AMG/non-MPG trials). It will be conducted at the Clinical Trial Centre (KSC) of the Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital and the principal investigator will ensure that the implementation will take place in the context of GCP (ICH E6) and in accordance with the Declaration of Helsinki (latest amendment Fortaleza, Brazil, October 2013). All patients will be informed orally. Study aims, consequences and possible risks and benefits will be exposed in detail. It is the responsibility of the study physician to explain patients their duties within the trial and it will be emphasised that participation is voluntary and that the patient is allowed to withdraw further participation in the trial at any time without giving reasons. This will not prejudice the patient's subsequent care. In this case, patients will be asked whether the data recorded up to that date may be used in the analysis of the trial or if it should be discarded. The written informed consent form will be signed and personally dated by the patient after sufficient time to decide on participation (online supplemental file 3). Data collection is performed by the KSC. Statistical analysis will be performed independently by the Institute of Medical Biometry of Heidelberg University Hospital.

Confidentiality

All patient-related information is subject to medical confidentiality according to the European General Data Protection Regulation (Datenschutzgrundverordnung, DSGVO), the Federal Data Protection Act (Bundesdatenschutzgesetz) and the State Data Protection Act (Landesdatenschutzgesetz). Trial-specific documents will be stored in accordance with local data protection law/ICH-GCP Guidelines and will be handled in strictest confidence. For protection of these data, organisational procedures are implemented to prevent distribution of data to unauthorised persons. Original patient data will be pseudonymised immediately before data management and recording. The trial site will maintain a personal subject identification list to enable records to be identified. Third parties have no access to original documents. At the end of the study, all patient data will be anonymised, and the sponsor Magle Chemoswed will receive a data copy including case report forms and raw technical data but excluding any personal patient information. This data copy will be exclusively used for device development and manufacturing as well as for marketing purposes. All data collected during the study will be kept on file for 10 years after completion of the trial.

Access to data

Original data access will be restricted to electronic database manager (MW), study project manager (TP, TH, RK) and study nurses, scientific physicians and a medical doctoral student (FER), all employees of the KSC.

Benefits and risks of trial intervention

All patients receive state-of-the art pancreatic surgery. The study benefit for the patient is the potentially effective indication of biochemical leakage of pancreatic enzymes during surgery, enabling targeted leak closure and prevent POPF development. A risk might be an allergic reaction to one of the SmartPAN components. This risk is estimated to be very low and does not exceed the risk of any allergic reaction to other biomaterials routinely applied intracorporally, i.e., haemostatic glue.[37–40] During product development biocompatibility and toxicity evaluations were conducted according to the international standard guideline (ISO 10993-1:2009.-06[41]; ISO 10993-12018: 2018-08[42]). Degradable starch microspheres are routinely used as haemostatic (Arista by BD, NJ, USA) and embolic agents (EmboCept S by PharmaCept, Berlin, Germany or EmboLog S by Serumwerk Bernburg, Germany). Pharmacokinetic measurements demonstrated that BTB was not detectable in abdominal drainage 2 days after surgery and it could not be detected in the bloodstream.[27] Overall, the components of SmartPAN are either biocompatible or quickly neutralised by dilution and drainage. Usage of SmartPAN in this study is fully aligned to its field of application according to CE-approved market-registration. The ViP-trial will be closely monitored to ensure the identification, documentation and analysis of potential major complications and compliance with the protocol.

Dissemination policy

After completion of the trial, the data obtained will be analysed according to this protocol and published in a peer-reviewed journal. Furthermore, dissemination will be carried out via online media in lay language to ensure accessibility to any healthcare professional or member of the public. The study protocol is available on request. An anonymised minimal data set laying out the results of the trial will be made available on publication of the final results as a supplement in line with data protection rules. The statistical analysis plan will be available on request after publication of the final results.

DISCUSSION

Despite numerous attempts to reduce POPF rates, it is still a frequent and dangerous complication after pancreatic surgery.[7] Since decades POPF has been counted most often among the causes of problems and death.[43] Recently, a root cause analysis has highlighted the typical complication-sequence pattern, which runs from POPF over subsequent complications such as postpancreatectomy haemorrhage[8] or sepsis and following reoperation, eventually to death.[44] Accordingly, there is an urgent need for further innovation in order to lower the risk of clinically relevant POPF. Development of POPF has been attributed to hospital/surgeon-related and to patient-related causes.[45] Mechanisms to control the first group have undergone constant optimization.[1 2 4] Mitigation of the latter group has been limited mainly to patient selection, which from a certain point has limits again. A major patient-related factor which is difficult to predict is the intraoperative nature of the pancreatic gland. Texture of the pancreatic parenchyma and anatomy of pancreatic ducts, two crucial determinants of POPF development,[45] often cannot be ascertained without doubt or auxiliary devices. The development of an indicator of pancreatic leakage that mitigates POPF development by targeted closure or precise drain placement already during surgery is promising. In 1998, the benefit of red litmus paper to visualise alkali pancreatic fluid on the resection margin of human pancreas was explored.[20] However, this method was too crude to be clinically useful. More recent studies relied on a fluorescent chymotrypsin probe activated by enzymes present in pancreatic fluid.[18 19 21] At least their method was successful to visualise pancreatic leaks intraoperatively, but its costs and effort were too high to implement the technique into routine clinical usage. Finally, a Förster resonance energy transfer heat-shock protein probe was developed,[17] but this technique requires specialist equipment not available in most operating theatres. SmartPAN is simple for intraoperative use and provides clear, localised and rapid responses to identify leakage sites related to POPF pathogenesis. Previous studies have proven effective SmartPAN-driven closure of the pancreatic remnant and adoption of appropriate postoperative management in order to reduce the risk of POPF.[26] SmartPAN visualises leakage of alkali pancreatic fluid via colour change of its active component the pH-indicator BTB. In a randomised preclinical trial indicator reaction has been shown to be consistent over a 1 week timeframe.[26] SmartPAN aims to reduce the incidence and severity of POPF which in turn could decrease the rate of postoperative major complications, prolonged hospital-stay and mortality. ViP is the first in-human clinical trial to collect data on the safety and usability of the SmartPAN indicator after preclinical stage 0 has been passed. According to market approval, this PMCF study will evaluate clinical data from the use of SmartPAN in humans within its intended purpose. Exploration of device application in all variants of partial pancreatectomy has been chosen to conclude optimal patient selection for subsequential trials. Additionally, SmartPAN needs careful confirmation of its usability and safety to medical staff and patients in order to introduce this new device to clinical routine successfully. Limitation of the trial is its single-arm single-centre exploratory design. Nevertheless, it generates the conditions of a following exploratory study focused on device performance in the optimal target population. Together these explorations will provide the basis for a high-quality randomised controlled interventional multicentre trial that will investigate the efficacy of the indicator. To this end, several aspects need to be elucidated in our exploratory trial: (1) it is unclear whether and how patients planned for partial pancreatic resection are willing to undergo inclusion to this trial. (2) The results and subgroup analyses from our exploratory trial will help to define the target population of future trials. (3) high-quality data will be collected in our trial to enable sound sample size calculation. Future trials will answer the question of whether the intraoperative visualisation of a potential leakage will lead to clinical superiority in terms of a lower overall morbidity. And they will indicate whether and in which patient SmartPAN should be used within clinical routine.

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Contributors TMP, IR, MW, AS, ST, JL, PP, TH and RK are responsible for the study design, definition of endpoints and preparation of the protocol. BG is responsible for preparation of the protocol and its publication. TH provided a clinical perspective as an expert in the field. MB provided expertise in the conduct of toxicological studies. MH, FER and FP provided support with protocol publication. Furthermore, all coauthors revised and approved the final manuscript critically.

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Competing interests TMP reports financial support provided by Heidelberger Stiftung Chirurgie. BG reports a relationship with Magle Chemoswed that includes employment. TMP and TH have patent Body Fluid Leakage Detection Aqueous Composition (Pausch T, Hackert T, Johansson H, et al. European Patent Office, Germany. 2018) licensed to Magle Chemoswed Holding AB and University of Heidelberg.

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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