Trials

STUDY PROTOCOL

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Standard versus Pre-emptive Antibiotic Treatment to Reduce the Rate of Infectious Outcomes after Whipple resection (SPARROW): a study protocol for a multicentre, open-label, randomised controlled trial

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Abstract

Background Consensus and evidence on the impact of pre-emptive antibiotic treatment after pancreatoduodenectomy is lacking, which is reflected by contradictory recommendations in (inter)national guidelines and current clinical practice. Pre-emptive antibiotic treatment may reduce the risk of abdominal surgical site infections in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. This pertains mostly patients with preoperative biliary drainage or an ampullary malignancy. The SPARROW trial will evaluate the effect of pre-emptive antibiotic treatment in patients with preoperative biliary drainage or an ampullary malignancy undergoing pancreatoduodenectomy.

Methods The SPARROW trial is a multicentre, open-label, randomised controlled trial evaluating the effect of pre-emptive antibiotic treatment in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. A total of 366 evaluable patients will be included in twelve centres in the Netherlands. Patients will be randomly allocated to either the perioperative antibiotic prophylaxis and pre-emptive antibiotic treatment (intervention) arm and the perioperative antibiotic prophylaxis (control) arm. In both study arms, the perioperative antibiotic prophylaxis consists of cefazolin, metronidazole and a single-dose of gentamicin, which is discontinued after surgery. In the pre-emptive antibiotic treatment arm, an additional antibiotic course of 5 days of cefuroxime and metronidazole is started postoperatively. The primary outcome is a clinically relevant organ/space surgical site infection (OSI) up to 90 days after surgery. Secondary outcomes include other clinically relevant complications (such as isolated OSI, superficial

Sponsor: the Leiden University Medical Centre is the sponsor of the SPARROW trial as an investigator-initiated study. The sponsor as an institute and the funder have no active role in the study design or performance, neither in the interpretation of the data, article writing or publication.

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incisional surgical site infections, postoperative pancreatic fistula, ICU admission, readmission, and in-hospital and 90-day mortality), use of therapeutic antibiotics, and concordance between perioperative obtained bile cultures and cultures obtained from infectious complications.

Discussion The SPARROW trial will provide evidence on the effect of pre-emptive antibiotic treatment in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy to provide recommendations for an improved and standardised antimicrobial policy.

Trial registration ClinicalTrials.gov NCT0578431. Registered on March 23, 2023.

Keywords Antibiotic prophylaxis, Pre-emptive antibiotic treatment, Extended antibiotic prophylaxis, Antimicrobial policy, Pancreatoduodenectomy, Whipple, Contaminated bile, Biliary drainage, Intraoperative obtained bile cultures, Pancreatic ductal adenocarcinoma, Ampullary carcinoma

Background

Abdominal surgical site infections, often defined as organ/space surgical site infections (OSI), and postoperative pancreatic fistula (POPF) account for the majority of the postoperative morbidity after pancreatoduodenectomy [1, 2]. POPF correlates with 72–80% of the OSI after pancreatoduodenectomy, whereas isolated (non-POPF) OSI occur in 7–18% of the patients [2, 3]. Contaminated bile during pancreatoduodenectomy is present in the vast majority of patients with preoperative biliary drainage (± 95%) or an ampullary malignancy (± 90%) [3, 4]. As contaminated bile is associated with OSI and clinically relevant (grade B/C) POPF following pancreatoduodenectomy, appropriate antibiotic prophylaxis is presumed to reduce OSI and grade B/C POPF in these patients [1, 4–6].

The updated Enhanced Recovery After Surgery protocol recommends considering pre-emptive antibiotic treatment in patients that have contaminated bile [7]. In a survey amongst all surgical centres of the Dutch Pancreatic Cancer Group ($n = 15$, 100% response rate), we found that seven centres (47%) only used perioperative antibiotic prophylaxis for pancreatoduodenectomy, and eight centres (53%) used perioperative and pre-emptive antibiotic treatment following pancreatoduodenectomy (Fig. 1A). Pre-emptive antibiotic treatment was indicated for all patients undergoing pancreatoduodenectomy in three centres (37.5%) and only for patients after preoperative biliary drainage in five centres (62.5%, Fig. 1A). The antibiotic agents used as pre-emptive antibiotic treatment varied substantially (Fig. 1B). Also, the duration of pre-emptive antibiotic course ranged from 48 h in one centre (12.5%), 72 h in three centres (33.3%) to 5 days in four centres (50%, Fig. 1C). Altogether, the antibiotic prophylactic regimes for pancreatoduodenectomy vary remarkably between Dutch centres, and a clinical equipoise exists regarding the evidence and consensus on the effectiveness of pre-emptive antibiotic treatment.

The effect of pre-emptive antibiotic treatment for pancreatoduodenectomy was evaluated in a meta-analysis demonstrating a 42 to 21% decrease in both abdominal and wound infections in patients receiving antibiotic prophylaxis based on previously obtained bile cultures [8]. As bile culture results are not immediately available after surgery, pre-emptive antibiotic treatment would be a feasible alternative for personalised antibiotic prophylaxis [9–12]. However, the effect of pre-emptive antibiotic treatment after pancreatoduodenectomy is still under debate as most studies were observational and the two randomised controlled trials reported conflicting results [13].

The objective of the SPARROW trial is to evaluate the effect of pre-emptive antibiotic prophylaxis on clinically relevant OSI in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. The results of the SPARROW trial will provide recommendations for a standardised antimicrobial policy for these patients undergoing pancreatoduodenectomy.

Methods

Design

The SPARROW trial is a multicentre, open-label, randomised controlled, superiority trial comparing perioperative antibiotic prophylaxis versus pre-emptive antibiotic treatment in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. Patients will be recruited in twelve Dutch participating centres. Patients will be randomised with a 1:1 allocation into the intervention (pre-emptive antibiotic treatment) or control (perioperative antibiotic prophylaxis) group.

Study population

Adult patients with a high risk of contaminated bile undergoing elective pancreatoduodenectomy will be assessed for eligibility to participate in the SPARROW

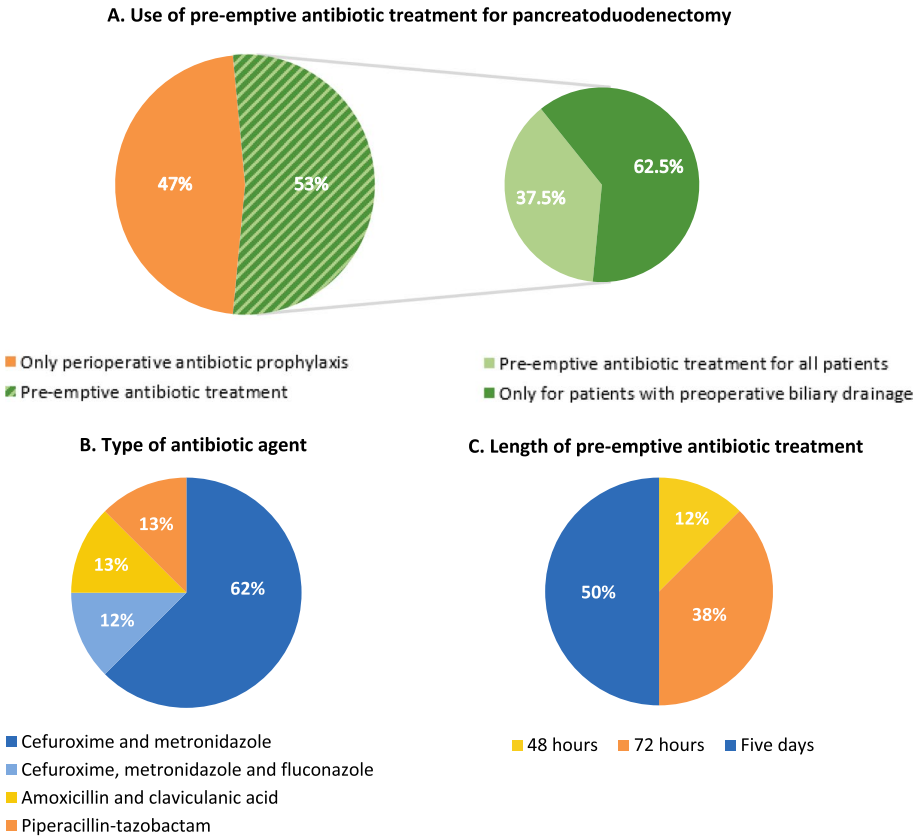

Fig. 1 Pre-emptive antibiotic treatment after pancreaticoduodenectomy in 15 Dutch pancreatic surgery centres. The use of pre-emptive treatment for pancreatoduodenectomy in the Netherlands. **A** Use of only perioperative antibiotic prophylaxis versus pre-emptive antibiotic treatment in centres and the indication for pre-emptive antibiotic treatment. **B** Type of antibiotic agent used as pre-emptive antibiotic treatment. **C** Duration of pre-emptive antibiotic treatment

trial. A high risk of contaminated bile is defined as the performance of preoperative biliary drainage or the presence of an ampullary malignancy [1, 3–5].

Inclusion criteria

Eligible patients must meet all of the following criteria:

- Age of at least 18 years
- Undergoing elective pancreatoduodenectomy
- Preoperative biliary drainage and/or an ampullary malignancy

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

- Pregnancy
- Contraindication for the study antibiotics (e.g. allergy or intolerance)
- Indication for endocarditis prophylaxis
- Preoperative planned therapeutic antibiotic treatment after surgery
- Participation in another study with interference of the primary outcome
- A reduced renal function, defined as an eGFR of < 60 ml/min/1.73 m^2 measured on the closest timepoint prior to pancreatoduodenectomy

Randomisation

Patients will be recruited in the outpatient clinic. After obtaining written informed consent by the attending physician or study coordinator, patients will be enrolled and randomised by the study coordinator via the computer controlled data management system Castor EDC (CIWIT B.V., Amsterdam, the Netherlands). Patients will be randomly allocated to either the control arm (perioperative antibiotic prophylaxis) or intervention arm (pre-emptive antibiotic treatment). The randomisation

process is stratified for participating centre and open or minimally invasive procedure. The study antibiotics will be prescribed by the surgeon or attending physician. The treatment allocation is blinded for participants until surgery, but not for treating physicians and data managers. However, members of the adjudication committee for assessment of the primary outcome will be completely blinded for treatment allocation.

Antibiotic prophylaxis

The perioperative antibiotic prophylaxis during the surgical procedure in the SPARROW trial adheres to the guidelines of the Dutch Foundation for Antimicrobial Policies (Dutch acronym: SWAB). These guidelines recommend the use of 2 g of intravenous cefazolin and 500 g of intravenous metronidazole during abdominal surgical procedures, which is repeated every 4 h during surgery. Additionally, a single dose of gentamicin (5–7 mg/kg) is administered within 1 h before incision. Patients in the intervention group receive perioperative antibiotic prophylaxis as described above, followed by the pre-emptive antibiotic treatment of 5 days of 1500 mg IV cefuroxime and 500 mg IV metronidazole thrice daily. Patients in the control group receive similar perioperative antibiotic prophylaxis, which will be discontinued directly after surgery.

The choice for these antibiotic agents is based on two Dutch studies demonstrating low rates of acquired bacterial resistance for cefazolin and metronidazole in the intraoperative obtained bile cultures [3, 5]. However, it was suggested that an additional dose of gentamicin during surgery would provide a 99% coverage of microorganisms cultured from intraoperative obtained bile cultures [5]. To provide a complete coverage of microorganisms, we added a single dose of gentamicin to the perioperative antibiotic prophylaxis. As gentamicin has a wide therapeutic range, but also contains a substantial risk for ototoxicity and nephrotoxicity after repeated doses, a single dose of gentamicin was considered sufficient as perioperative antibiotic prophylaxis and preferred over repeated dosages after surgery.

The study antibiotics will not be modified during the trial. If patients are allergic or intolerant to the study antibiotics (cefazolin, metronidazole, cefuroxime or gentamicin), patients will not be able to participate in the trial. In case of discontinuation of the pre-emptive antibiotic treatment in the intervention group, patients will be analysed according to the intention-to-treat principles. The reason for adjustments or discontinuation of the antibiotic regimen will be collected both in the control as in the intervention group.

Surgical procedure

Pancreatoduodenectomy will be performed according to the local standard surgical procedures and may be performed open or minimally invasive. The study protocol does not provide details on surgical procedures. However, patients are stratified for participating centre to account for local variance in surgical techniques. As the effect of minimally invasive pancreatoduodenectomy on postoperative morbidity was under investigation in the DIPLOMA-2 trial at time of the design of the SPARROW trial, patients are stratified for open or minimally invasive pancreatoduodenectomy [14]. Bile duct clamping during the procedure will be performed depending on surgeon's preference but will be registered and stratified for during the analysis, as described in the statistical analysis.

Bile culture analysis

Perioperative cultures of bile will be obtained during pancreatoduodenectomy in all participating patients. The samples will be performed by a sterile swab or syringe directly after transection of the common bile duct. The samples will be analysed in the laboratory of the centre in which the surgery is performed. Bile cultures analysis is performed according to the standard operating procedure in all participating centres including the following aspects:

- Culture plates for aerobic incubation @ ± 35 °C (minimum incubation 2 days): blood agar, Cystine Lactose Electrolyte Deficient agar (CLED) and Columbia Nalidixic Acid agar (CNA), or comparable selective gram-negative and gram-positive culture media.
- Culture plates for anaerobic incubation @ ± 35 °C (minimum incubation 3 days): blood agar with gentamicin or comparable selective anaerobic culture media.
- Identification of microorganisms in case of ≤ 2 species, including aerobic species.
- Identification of all bacteria cultured from selective media for isolation of multi-drug resistant organism plates.
- Identification of colonies suspect for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, β-haemolytic *Streptococcus* species and *Clostridium perfringens*.
- Identification of colonies suspect for fungal species (e.g. *Candida* species).
- Reporting of resistance patterns should include susceptibility for cefuroxime and metronidazole, unless intrinsically resistant.

Bile culture results will not result into the start, prolongation or adjustments of pre-emptive antibiotic

treatment, unless antibiotics are required therapeutically for clinical infection.

Postoperative care

Postoperative care is performed according to local protocol. In all participating centres, standard postoperative care includes frequent blood tests on infectious parameters (blood count and CRP) and the performance of blood cultures and fluid cultures from surgical sites in case of infections, fever or clinical deterioration. Other postoperative regimes, such as drain management, antithrombotic prophylaxis, pain management, nutrition, mobilisation, fluid balance and glycaemic control, will follow the local standard of care [15, 16]. Postoperative cultures will be performed after radiological or surgical abdominal drainage for OSIs, by obtained a swab from the surgical incision for superficial SSIs, and by a blood culture for cholangitis, fever of suspected sepsis.

Primary outcome

The primary outcome is the occurrence of a clinically relevant OSI up to 90 days after surgery. The definition of a clinically relevant OSI is based on the Centre for Disease Control definition for an OSI [17]. A clinically relevant OSI is defined as (1) a deep surgical site infection involving any part of the abdomen (e.g. organs and/or spaces) other than the surgical incision, (2) requirement of a radiological, endoscopic or surgical intervention, or therapeutic antibiotics for an episode of sepsis (defined as two or more SIRS criteria [18]) and (3) organisms isolated from an aseptically obtained culture.

Secondary outcomes

Secondary outcomes include the rate of OSI [17] and isolated OSI defined as an OSI without concurrent anastomotic leak (pancreatojejunostomy, hepaticojejunostomy or gastrojejunostomy, Table 1). The concept of an isolated OSI is used to separately classify abdominal infections without concurrent anastomotic leak [2, 3]. Other secondary outcomes are wound infections defined as superficial incisional SSI [16], clinically relevant (grade B/C) POPF [19], bile and enteric leak [20], post pancreatectomy haemorrhage (PPH) [21], delayed gastric emptying (DGE) [22], chyle leak [23], postoperative bacteraemia (defined as a positive blood culture), *Clostridium difficile* infection, major complications (defined as a Clavien-Dindo [24] score of ≥ III), reintervention during admission (either radiological, surgical or endoscopic), ICU admission within 90 days after surgery, length of hospital stay, readmission, in-hospital and 90-day mortality, switch of postoperative antibiotics (including reason for the deviation), antibiotic sensitivity patterns in bile cultures and cultures from surgical sites, and the concordance of microorganisms in bile and surgical site cultures.

Data collection

Data on baseline characteristics (age, body mass index, sex, ASA score, medical history, previous abdominal surgery, preoperative imaging and endoscopic or radiologic interventions, preoperative histopathological diagnosis and staging), surgical details (type of procedure and techniques, blood loss, duration of surgery, performance of bile culture and bile clamping), primary and secondary outcomes (as described previously) will be collected by the local study coordinators up to 90 days after surgery (Table 2). The local study coordinators will be trained by the coordinating investigator, particularly on the primary outcome (clinically relevant OSI). The data will be cross-checked by a central data manager and the coordinating investigator, and all data on the primary outcome will be double-checked by the coordinating investigator. Missing data will be limited as the data will be collected prospectively. The data will be registered and stored in a highly secured online database system Castor EDC. Castor EDC

Table 1 Overview of the definitions of surgical site infections

Type surgical site infection (SSI)	Description
Superficial incisional SSI	Wound infection defined according to the CDC definition [17]
Organ/space SSI (OSI)	A deep SSI involving any part of the abdomen (e.g. organs and/or spaces) other than the surgical incision [17]
Isolated OSI	Isolated (non-pancreatic fistula) OSI: absence of concurrent anastomotic leak (pancreatojejunostomy, defined as postoperative pancreatic fistula (POPF), hepaticojejunostomy or gastrojejunostomy)
Non-isolated OSI	Not-isolated OSI: concurrent anastomotic leak (at time of OSI diagnosis)
Clinically relevant OSI (primary outcome)	An isolated or non-isolated OSI is clinically relevant in case of: - Requirement of a radiological, endoscopic or surgical intervention, or therapeutic antibiotics for an episode of sepsis (defined as two or more SIRS criteria) and - Organisms isolated from an aseptically obtained culture

Table 2 Participant timeline

	STUDY PERIOD					
	Enrolment	Allocation	Surgery	Post-allocation		Close-out
TIMEPOINT	0		0	+5d	+3m	+3m
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Pre-emptive antibiotic treatment: intervention arm			X			
Peroperative antibiotic prophylaxis: control arm			◆—	—◆		
Baseline characteristics	X					
Surgical variables			X			X
Outcomes				X	X	X

Table 2. Study schedule including enrolment, intervention and assessments according to the SPIRIT guidance

is a validated system and approved by external auditors that complies with the applicable laws and regulations: Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US) ISO 9001 and ISO 27001, and is a validated system and approved by external auditors (www.castoredc.com/gcp/). The handling of the data complies with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

After obtaining written informed consent, patients will be enrolled in the Castor EDC database and assigned to a unique patient code. The key of the sequential patient code, which is based on a combination of country, institute code, study code and sequential patient number, is safeguarded by the participating centre in an identification, screening and enrolment log. Study data and documents (e.g. CRFs, informed consent documents, identification and enrolment logs) will be stored for 25 years. Bile culture samples will not be stored for future use, as the bile culture results will be analysed as presented in the medical electronical records of the patients.

Adjudication committee

In this trial, we propose a new definition for a clinically relevant OSI after pancreatoduodenectomy (Table 1). To ensure the data quality, data on the primary outcome and several secondary outcomes (OSI, superficial incisional SSI, POPF, bile leakage, PPH, DGE, cholangitis and bacteraemia) will be double-checked by the coordinating investigator team. Hereafter, an adjudication committee, consisting of pancreatic surgeons, microbiologists, infectiologists and radiologists, will have scheduled meetings during the trial to assess the primary outcome based on a blinded clinical presentation to assure the data accuracy of the primary outcome.

Sample size calculation

The sample size is calculated for superiority to achieve a clinically relevant OSI difference of 12.8% (31.4% vs 18.6%). These percentages are based on previous research that showed a 15% (40% vs 25%) OSI difference [3, 9–11]. Based on the assumption that a maximum of 80% of the OSI is clinically relevant and by maintaining a comparable odds ratio regarding the initial 15% OSI difference, the sample size was calculated based on a 12.8% (31.4% vs 18.6%) clinically relevant OSI difference. With 80% power $(1-\beta)$, a two-sided significance level (α) of 5.0%, a sample

of 366 evaluable patients is required to confirm superiority. Assuming a 12% non-resection rate due to metastatic or locally advanced disease and a 3% loss-of-follow-up rate, 421 patients are expected to have to be included to reach the sample size of 366 evaluable patients. Twelve Dutch centres performing pancreatoduodenectomy will participate in the SPARROW trial to ensure an adequate inclusion rate to reach the calculated sample size.

Statistical analysis

Intention-to-treat analysis will be performed on the primary and secondary outcomes as primary analysis. In the intention-to-treat analysis, all eligible patients will be analysed as randomised and will be included in the data analyses with multiple imputation of missing data after assessment of their randomness. Patients will be excluded if they did not undergo pancreatoduodenectomy after randomisation, for instance due to locally advanced disease or metastasis, or appeared not eligible for other reasons. Secondary, a per-protocol will be performed in patients without major violations of the antimicrobial treatment protocol (either regarding the perioperative prophylaxis or pre-emptive antibiotic treatment).

The primary hypothesis of superiority will be analysed primarily by an intention-to-treat analysis. Results will be represented as absolute numbers and percentages. Comparisons on the primary outcome will be made using the Mantel–Haenszel test, stratifying for participating centre and open or minimally invasive procedure. Missing data on the primary outcome are not expected. In case of missing data on the primary outcomes, additional analyses will be performed by the involved statistician using multiple imputation. A potential effect of bile duct clamping on OSIs is expected to be covered by stratification for centre. Therefore, a subanalysis will be performed on the primary outcome, stratified for bile duct camping.

Secondary outcomes will be analysed comparably to the primary outcome, although missing data will be left out of analyses. The independent *t*-test or Mann–Whitney *U* test will be used for continuous data based on a normal or non-normal distribution and expressed as mean (SD) or median (interquartile range). The chi-square test or Fisher's exact test (in case of small groups) will be used for categorical data and expressed as absolute numbers and percentages. Bile culture results will be analysed for exploratory reasons and represented as positive (yes/no, single of multiple microorganisms) or negative. Sensitivity and resistance patterns will be represented as acquired resistance for the received type of antibiotics (yes/no). The incidence of cultured and resistant microorganisms will be represented as percentages. Additional analyses will be performed on secondary outcomes stratified for relevant variables, such as bile culture clamping. Potential predicting variables will be identified using univariate analysis and included in a multivariate analysis to assess predictors for primary and secondary outcomes, such as clinically relevant and isolated OSI.

Interim analysis

A Data Safety Monitoring Board (DSMB) will assess safety aspects. The DSMB includes three independent, voting members: a HPB surgeon, a clinical infectiologist and statistician. The DSMB will assess the safety of the study based on reported data on the primary outcome, relevant secondary outcomes (major morbidity, ICU admission, mortality and adverse effects of the study antibiotics) and reported serious adverse events. The assessment of the DSMB will be based on a data report after completion of the follow-up of the 150th randomised patient. The report will focus on the primary outcome, relevant secondary outcomes and serious adverse events in order to assess safety aspects of the trial. The data will be presented in line with the statistical section. No formal interim analysis will be performed as the DSMB will primarily monitor the safety of the trial participants. The DSMB can either advise to continue the study or to terminate the study for safety concerns or because continuing the study is not feasible. The complete DSMB charter is available upon request to the corresponding author.

Safety

All complications are reported up to 90 days after surgery. In accordance with approval of the medical ethical committee, only serious adverse events were reported through an web portal (www.toetsingonline.nl) in case of a complication requiring surgical intervention, intensive care admission, readmission or mortality within 90 days after surgery, and are recorded in an annual safety report which is submitted to the medical ethical committee. Safety aspect will be assessed by the DSMB based on the interim analysis.

This trial is considered a low-risk intervention trial as both the control and the intervention arm is considered standard-of-care in several centres in the Netherlands. Therefore, the risk of harm for the participants is negligible. However, the sponsor has a liability insurance to provide coverage for damage to participate through death or injury in accordance to article 7 of WMO.

Monitoring

The SPARROW trial is conducted in accordance to the principles of the Declaration of Helsinki and the Dutch regulations, as approved by the medical ethical committee Leiden Den Haag Delft (METC LDD). This RCT will be reported according to the CONSORT statement

for clinical trials [25]. Progress reports will be provided to the accredited medical ethical committee annually. Protocol amendments will be sent to the participating centres and independent monitor after approval by the medical ethical committee.

Every participating centre will be monitored as agreed upon in the monitoring plan. The monitoring visits will be executed by an independent monitor of the Leiden University Medical Centre. During the monitoring visits, the participating centres will be audited on the study procedures, including the patient recruitment and randomisation process, the treatment allocation and data collection. The complete monitoring plan is available upon reasonable request to the corresponding author.

Dissemination policy

The results of the SPARROW trial are intended to be published in a high-impact peer-reviewed medical journal, regardless of the study outcome. The results are expected to change and harmonise the use of pre-emptive antibiotic treatment and the performance of intraoperative bile cultures amongst (inter)national centres. As twelve out of the fifteen centres of the Dutch Pancreatic Cancer Group will participate in the trial, implementation of results as a standard-of-care policy in the Netherlands is plausible and expected. The results of the trial will be presented at international congresses and shared with several international organisations, such as the European Society of Surgical Oncology (ESSO) and the European-African Hepato-Pancreato-Biliary Association (E-AHPBA), to provide recommendations for international protocols or provide advice for future trials.

Discussion

The SPARROW trial is a multicentre, open-label, randomised controlled trial in which the effect of 5 days of pre-emptive antibiotic treatment is compared to only perioperative antibiotic prophylaxis in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. This trial is initiated by the Dutch Pancreatic Cancer Group and aims to provide recommendations for improved antibiotic prophylaxis for pancreatoduodenectomy.

Antibiotic prophylaxis in abdominal surgery is generally limited to perioperative prophylaxis to prevent the development of superficial SSI [7]. However, antimicrobial regimes for pancreatoduodenectomy vary remarkably between (inter)national centres regarding type and duration of the antibiotic prophylaxis [13]. Antibiotic prophylaxis for abdominal surgery generally consists of a combination of cephalosporin and metronidazole to cover a wide range of, respectively, gram-negative and several gram-positive bacteria and anaerobic bacteria. A recent randomised trial from the USA demonstrated that the use of perioperative piperacillin-tazobactam compared to only perioperative cefoxitin reduces both the rates of SSI and POPF after pancreatoduodenectomy, suggesting that *Enterococcus* species, which are intrinsically resistant to cefoxitin, mediate in the development of OSI and POPF [26, 27]. However, it remains unclear to what extend the benefit can be attributed to additional coverage of some *Enterococcus* species or additional coverage of anaerobic bacteria and gram-negative bacteria with depression of AmpC β-lactamase production. Specifically, *Enterococcus* species are considered low-virulence microorganisms and were not associated with postoperative complications after pancreatoduodenectomy in other studies [12, 28]. Furthermore, piperacillin-tazobactam is generally used as a back-up antibiotic agent for severe infections with multi-drug resistant microorganisms and has a significant selecting effect on the remaining microorganisms. The use of a second- or third-generation cephalosporin combined with metronidazole is expected to provide an adequate coverage of virulent microorganisms in regions with low cephalosporin-resistance rates [29]. The antibiotic protocol of the SPARROW trial includes an additional dose of gentamicin to optimise coverage of the remaining gram-negative bacteria [5]. Hence, a perioperative antibiotic combination of cefazolin, metronidazole and gentamicin (a single dose for toxicity concerns) is used as perioperative antibiotic prophylaxis in the SPARROW trial to provide an adequate coverage of contaminated bile during pancreatoduodenectomy.

The use of pre-emptive antibiotic treatment after pancreatoduodenectomy has been suggested to reduce postoperative morbidity as contaminated bile during pancreatoduodenectomy has been associated with OSI and POPF [1, 6]. As patients with preoperative biliary drainage or an ampullary malignancy have contaminated bile in more than 95%, a potential effect of pre-emptive antibiotic treatment is expected in these patients [3, 4]. Several observational studies demonstrated a promising effect of pre-emptive antibiotic in patient with preoperative biliary drainage, although two randomised controlled trials reported conflicting results [13]. Despite the absence of solid recommendations by international guidelines, the observation of a positive effect in several observational studies currently leads to expanding and largely varying antibiotic prophylactic regimes between international centres. As effective pre-emptive antibiotic treatment is hypothesised to prevent OSI, the need for antibiotic treatment after pancreatoduodenectomy is assumed to decrease. However, with regard to antibiotic stewardship and expanding international antibiotic resistance rates [30, 31], the absolute effect of

pre-emptive antibiotic treatment on postoperative morbidity, use of antimicrobial therapy and microbiology resistance rates should be carefully evaluated in an adequately randomised controlled trial before (inter)national implementation.

Conclusion

This multicentre, randomised controlled trial aims to evaluate pre-emptive antibiotic treatment compared to only perioperative antibiotic prophylaxis in patients with a high risk of contaminated bile undergoing pancreatoduodenectomy. This trial will guide future recommendations on the use of pre-emptive antibiotic treatment after pancreatoduodenectomy in order to improve and harmonise the antimicrobial policy amongst centres performing pancreatoduodenectomy.

Trial status

Ethical approval for the SPARROW trial was received by the medical ethical review committee METC LDD on February 23, 2023. The trial was registered in ClincialTrails.gov on March 23, 2023 with identification number NCT05784311. The first included patients underwent surgery in April 2023. All twelve participating centres are currently open for patient accrual. During submission of this trial protocol for publication in July 2024, 202 out of the 366 patients (55%) were included. Completion of the inclusion is expected in the summer of 2025. The results of the trial are expected in 2026.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08574-z.

Additional file 1: SPIRIT checklist.

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Authors' contributions
DHMD, MGJdB, JvP, HP, BKG, HCvS, MGB, ALV and JSDM contributed to the design of the study and protocol development. DHMD drafted the manuscript, with assistance of MGJdB, JvP and HP on specific topics. DHMD, HP and JSDM performed the sample size calculation and statistical methods of the trial. DHMD, JvP, JPBMB and JSDM are primarily coordinating the trial. All authors gathered in several meeting on the trial design and protocol development, critically reviewed the manuscript and provided approval for the final version of the manuscript.

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Data availability
Study documents and the database are or will be available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval for the SPARROW trial was received by the medical ethical review committee Leiden Den Haag Delft (METC LDD, identification number NL82304.058.22). Patients are only able to participate in the SPARROW trial after providing written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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