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# Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a multicentre, open-label, single-arm, phase II study (CRC-PIPAC).



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**Title**

Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a multicentre, open-label, single-arm, phase II study (CRC-PIPAC).

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**Abstract**

*Introduction:* Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) is offered as a palliative treatment option for patients with isolated unresectable colorectal peritoneal metastases (PM) in several centres worldwide. However, little is known about its feasibility, safety, tolerability, efficacy, costs, and pharmacokinetics in this setting. This study aims to explore these parameters in patients with isolated unresectable colorectal PM who receive repetitive ePIPAC-OX as a palliative monotherapy.

*Methods and analysis:* This multicentre, open-label, single-arm, phase II study is performed in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM. Eligible patients are adults who have histologically or cytologically proven isolated unresectable PM of a colorectal or appendiceal carcinoma, a good performance status, adequate organ functions, and no symptoms of gastrointestinal obstruction. Instead of standard palliative treatment, enrolled patients receive laparoscopy-controlled ePIPAC-OX (92 mg/m$^2$ body-surface area [BSA]) with intravenous leucovorin (20 mg/m$^2$ BSA) and bolus 5-fluorouracil (400 mg/m$^2$ BSA) every six weeks. Four weeks after each procedure, patients undergo clinical, radiological, and biochemical evaluation. ePIPAC-OX is repeated until disease progression, after which standard palliative treatment is (re)considered. The primary outcome is the number of patients with major toxicity (grade ≥3 according to the Common Terminology Criteria for Adverse Events v4.0) up to four weeks after the last ePIPAC-OX. Secondary outcomes are the environmental safety of ePIPAC-OX, procedure-related characteristics, minor toxicity, organ-specific toxicity, postoperative complications, hospital stay, readmissions, quality of life, costs, pharmacokinetics of oxaliplatin, progression-free survival, overall survival, and the radiological, histopathological, cytological, biochemical, and macroscopic tumour response.

*Ethics and dissemination:* This study is approved by an ethics committee, the Dutch competent authority, and the institutional review boards of both study centres. Results are intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders.

*Registration:* ClinicalTrials.gov/NCT03246321, ISRCTN/ISRCTN89947480, NTR/NTR6603, EudraCT/2017-000927-29.

**Keywords**

Colorectal surgery (from list); gastrointestinal tumours (from list); colorectal cancer (not from list); peritoneal metastases (not from list); PIPAC (not from list); intraperitoneal chemotherapy (not from list).

**Strengths and limitations of this study**

- This is the first study that prospectively explores predefined endpoints regarding the feasibility, safety, and efficacy of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.
- Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy, thereby minimising the influence of concurrent palliative systemic therapy on study outcomes.
- Apart from exploring clinical outcomes such as feasibility, safety, and efficacy, this study includes assessment of quality of life and costs as well as pharmacokinetic and translational side studies.
- The broad eligibility criteria could lead to enrolment of prognostically heterogeneous patients in different lines of palliative treatment, which could impede the interpretation of efficacy outcomes.

## INTRODUCTION

After the liver, the peritoneum is the second most common isolated metastatic site of colorectal cancer.[1,2] The majority of patients with isolated colorectal peritoneal metastases (PM) does not qualify for curative intent surgical treatment,[3] mostly due to insufficient condition or unresectable disease. Palliative systemic therapy is the standard treatment for patients with isolated unresectable colorectal PM.[4] Although its increasing use has improved the outcomes of these patients,[3] palliative systemic therapy appears less effective for isolated colorectal PM than for isolated non-peritoneal colorectal metastases.[5] This phenomenon may be explained by a relatively low intraperitoneal concentration of systemically administered chemotherapy.[6] Moreover, a relatively high systemic concentration could cause systemic toxicity. Intraperitoneal administration of chemotherapy is thought to increase locoregional efficacy and decrease systemic toxicity through a favourable peritoneum-plasma concentration ratio.[6-8] However, intraperitoneal chemotherapy seems to have three major limitations: a poor direct tissue penetration, an inhomogeneous intraperitoneal drug distribution, and dose-limiting local toxicity.[9,10] This has encouraged development of new intraperitoneal drug delivery systems that aim to overcome these limitations.

Currently, pressurised intraperitoneal aerosol chemotherapy (PIPAC) is one of these systems that internationally gains the most attention.

**Pressurised intraperitoneal aerosol chemotherapy (PIPAC)**

PIPAC is a laparoscopy-controlled repetitive intraperitoneal administration of low-dose chemotherapy as a pressurised aerosol.[11,12] It combines the theoretical pharmacokinetic advantages of low-dose intraperitoneal chemotherapy (i.e. low toxicity, high intraperitoneal concentration, low systemic concentration) with the principles of an aerosol (homogeneous intraperitoneal distribution) and intra-abdominal pressure (deep tissue penetration).[13-20] Two groups systematically reviewed results of non-comparative clinical studies that assessed the feasibility, safety, tolerability, and preliminary efficacy of PIPAC with various drugs for PM of various origins.[21,22] They concluded that PIPAC is a safe, feasible, and well tolerated treatment with good preliminary response rates.[21,22] These preliminary conclusions have led to an increasing acceptance of PIPAC as a palliative treatment option for PM in several centres worldwide.[23] In these centres, patients with isolated unresectable colorectal PM usually receive PIPAC with oxaliplatin (PIPAC-OX) in an empirically chosen dosage of 92 mg/m$^2$ body-surface area (BSA) every four to six weeks.[23] Some centres use electrostatic precipitation of the aerosol during PIPAC-OX (ePIPAC-OX),[24,25] since this could increase tissue penetration of oxaliplatin.[26]

**PIPAC for colorectal PM**

Several clinical studies included patients who received repetitive PIPAC-OX for colorectal PM.[27-36] However, the vast majority of these studies reported outcomes of entire cohorts that received repetitive PIPAC with various drugs for PM of various origins without presenting subgroup analyses of patients who received PIPAC-OX for colorectal PM.[27-34] Only two studies reported separate outcomes of repetitive PIPAC-OX for colorectal PM.[35,36] By using a prospectively maintained database, Teixeira-Farinha *et al* retrospectively included 20 patients with isolated colorectal PM who received 37 procedures.[35] They concluded that repetitive PIPAC-OX causes a modest and transitory inflammatory response without haematological, renal, or hepatic toxicity.[35] Demtröder *et al.* retrospectively included 17 patients with isolated colorectal PM who received 48 procedures within an off-label program.[36] They concluded that repetitive PIPAC-OX induces regression of pretreated colorectal PM and that the toxicity seems to be low.[36] Both studies have a retrospective design without predefined eligibility criteria and endpoints. Moreover, both studies included patients who receive repetitive PIPAC-OX as a monotherapy as well as patients who receive PIPAC-OX in combination with palliative systemic therapy. These shortcomings strongly impede the interpretation

of these studies. Besides, recently published case reports suggested that PIPAC-OX could lead to severe hypersensitivity reactions and peritoneal sclerosis.[37,38]

**Rationale for this study**

In conclusion, little is known about the safety, tolerability, and efficacy of repetitive PIPAC-OX in patients with isolated unresectable colorectal PM, whereas nothing is known about its costs and pharmacokinetics. Specifically for repetitive ePIPAC-OX, all these outcomes have never been reported. This questions the current use of repetitive (e)PIPAC-OX as a palliative treatment option for isolated unresectable colorectal PM outside the framework of clinical study protocols. Ideally, these patients are included in prospective studies with predefined eligibility criteria, interventions, and endpoints. However, by the knowledge of the investigators, such studies are currently lacking and not ongoing.[39] Therefore, this study aims to prospectively explore the safety, tolerability, preliminary efficacy, costs, and pharmacokinetics of repetitive ePIPAC-OX as a palliative treatment for isolated unresectable colorectal PM. Although implementation of PIPAC appears feasible and occupationally safe,[21,22,24,40-43] there is no experience with PIPAC in the Netherlands. Hence, this study also aims to assess the feasibility of implementation of ePIPAC-OX in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM.

**Rationale for intervention**

Repetitive ePIPAC-OX may be administered as part of a bidirectional therapy with palliative systemic therapy or as a monotherapy. When administered as a bidirectional therapy, the main objective is maximising tumour response, probably at the cost of an increased treatment burden that could interfere with quality of life. When administered as a monotherapy, the main objective is temporary intraperitoneal disease stabilisation with minimal treatment burden and preservation of quality of life. For this study, the investigators decided to administer repetitive ePIPAC-OX as a palliative monotherapy with (re)consideration of standard palliative treatment upon progression. According to internationally used protocols, ePIPAC-OX is administered in a dosage of 92 mg/m$^2$ at six-weekly intervals.[23] The investigators actively followed two ongoing phase I studies in which repetitive PIPAC-OX is administered in various pre-planned dosage levels to evaluate whether the dosage of oxaliplatin in this study needs to be modified.[44,45] Before administration of ePIPAC-OX, patients receive intravenous low-dose leucovorin with bolus 5-fluorouracil, since this is thought to potentiate the effect of intraperitoneal oxaliplatin.[46,47]

## METHODS AND ANALYSIS

**Design and setting**

This prospective, open-label, single-arm, phase II study is performed in two Dutch teaching hospitals qualified as tertiary referral hospitals for the surgical treatment of colorectal PM.

**Eligibility criteria**

Eligible patients are adults who have:

- a World Health Organisation (WHO) performance status of ≤1;
- histological or cytological proof of PM of a colorectal or appendiceal carcinoma;
- unresectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy or laparotomy;
- adequate organ functions (haemoglobin ≥5.0 mmol/L, neutrophils ≥1.5 x $10^9$/L, platelets ≥100 x $10^9$/L, serum creatinine <1.5 x ULN, creatinine clearance ≥30 ml/min, and liver transaminsases <5 x ULN);
- no symptoms of gastrointestinal obstruction;
- no radiological evidence of systemic metastases;
- no contraindications for oxaliplatin or 5-fluorouracil/leucovorin;
- no contraindications for a laparoscopy;
- no previous PIPAC-procedures.

Importantly, enrolment is allowed for patients with an unresected primary tumour (if asymptomatic) and for patients in various lines of palliative treatment, including patients who refuse, have not had, or do not qualify for first-line palliative systemic therapy. All potentially eligible patients are discussed by a multidisciplinary team. Enrolled patients are informed about the potential consequences of postponing or discontinuing standard palliative treatment by a medical oncologist prior to enrolment.

**Interventions and procedures**

*Figure 1* shows a flow chart of the study. *Table 1* presents a schedule of enrolment, interventions, and assessments.

**Table 1.** Schedule of enrolment, interventions, and assessments.

| | Study period | | | | |
|---|---|---|---|---|---|
| | Enrolment/allocation | Post-enrolment | | | |
| | Outpatient clinics | Baseline radiology | Each ePIPAC-OX | 1 week after each ePIPAC-OX | 4 weeks after each ePIPAC-OX |
| ENROLMENT/ALLOCATION | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| INTERVENTIONS | | | | | |
| ePIPAC-OX | | | X | | |
| Blood (organ functions, tumour markers) | X | | X[A] | | X |
| Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)[B] | | | X | | |
| Translational research (blood, ascites, PM) | | | X[C] | | |
| Thoracoabdominal computed tomography | | X | | | X |
| Diffusion-weighted magnetic resonance imaging | | X | | | X |
| Cytology (ascites or peritoneal washing) | | | X | | |
| Histopathology (peritoneal biopsies) | | | X | | |
| Questionnaires: quality of life | | X | | X | X |
| Questionnaires: costs[D] | | X | | | X |
| ASSESSMENTS | | | | | |
| Baseline characteristics | X | X | X | | |
| Toxicity | | | X | X | X |
| Environmental safety of ePIPAC-OX[E] | | | X | | |
| Procedure-related characteristics | | | X | | |
| Number of procedures in each patient, reasons for discontinuation | | | X | X | X |
| Organ-specific toxicity | | | X | | X |
| Postoperative complications | | | X | X | X |
| Hospital stay | | | X | | |
| Readmissions | | | | X | X |
| Clinical evaluation | | | X | X | X |
| Radiological tumour response | | X | | | X |
| Histopathological tumour response | | | X | | |
| Cytological tumour response | | | X | | |
| Macroscopic tumour response | | | X | | |
| Biochemical tumour response | | | X | | X |
| Quality of life | | X | | X | X |
| Costs | | X | | | X |
| Progression-free survival | | | X | X | X |
| Overall survival | | | X | X | X |

ePIPAC-OX electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin; PM peritoneal metastases; [A]drawn on each postoperative day; [B]blood is drawn before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after oxaliplatin injection during/after the first three procedures, urine is collected before ePIPAC-OX and on postoperative days 1, 3, 5, and 7, ascites/PM/normal peritoneum are collected directly after oxaliplatin injection; [C]blood is drawn before ePIPAC-OX; [D]MCQ 4 weeks after each procedure, PCQ 4 weeks after each second procedure; [E]only during the first three procedures in the study.

ePIPAC-OX

The procedure-related principles of (e)PIPAC have been extensively described by Willaert *et al* and Giger-Pabst *et al*.[24,48] In this study, ePIPAC-OX is performed at six-weekly intervals by at least one PIPAC-qualified surgeon in a standard operating room with laminar airflow. In both study centres, the operating personnel attended procedures in experienced PIPAC centres before performing their first procedure. All procedures are performed under general anaesthesia without antibiotic prophylaxis or venous thromboembolism prophylaxis. Before each procedure, a checklist is used to ensure all

materials are available. The operating personnel wears appropriate chemotherapy-protective clothes according to existing HIPEC protocols.

The Hasson technique is used to insert a 10 mm blunt tip balloon trocar through the abdominal wall. After obtaining a normothermic 12 mmHg capnoperitoneum, a second 10 mm blunt tip balloon trocar is inserted under direct vision and explorative laparoscopy is performed. Only if needed, careful adhesiolysis may be performed to create sufficient working space. In case of an iatrogenic bowel lesion, the procedure is ended after closure of the lesion, and ePIPAC-OX may be postponed by two to four weeks. If the procedure is considered feasible, leucovorin (20 mg/m$^2$ BSA in 10 minutes) and bolus 5-fluorouracil (400 mg/m$^2$ BSA in 15 minutes) are administered intravenously. In the meantime, ascites (or injected saline if ascites is not present) is completely evacuated, sent for cytology and translational research, and the ascites volume is documented. The Zühlke score and the peritoneal cancer index (PCI) are registered and photographs are taken throughout the peritoneal cavity.[49,50] A piece of normal peritoneum and three peritoneal metastases, preferably from different areas, are biopsied, sent for histopathology and translational research, and their locations are documented and marked with clips to enable biopsies of the same locations during subsequent procedures.

Then, the ePIPAC setup is installed. A stainless steel brush electrode (Ionwand®, Alesi Surgical, Cardiff, United Kingdom) is inserted through a mini-trocar under direct vision, secured with its tip at least 2 cm away from other structures, and connected to its generator (Ultravision®, Alesi Surgical, Cardiff, United Kingdom). A nebuliser (CapnoPen®, Capnomed GmbH, Villingendorf, Germany) is inserted through one of the trocars and secured with its nozzle just inside the peritoneal cavity at a safe distance from visceral organs. The camera, inserted through the other trocar, is secured by a laparoscope holder in a way it permanently visualises the electrode and the nebuliser. The valve of the trocar connected to the $CO_2$ insufflation remains opened, whereas the other trocar is connected to a closed aerosol waste system (CAWS) with its valve closed. The CAWS consecutively consists of a smoke evacuation filter, a water seal drainage system, an infant-paediatric electrostatic microparticle filter, and the air waste system of the hospital. The preoperatively prepared syringe with oxaliplatin (92 mg/m$^2$ BSA diluted in a total volume of 150 ml 5% dextrose) is vented, placed in a standard angiographic injector, and connected to the nebuliser with a saline-flushed high-pressure line protected by a plastic camera cover. A leak-free capnoperitoneum is ensured by zero-flow of $CO_2$. If necessary, incisions may be additionally sutured and Luer lock caps may be placed on balloon valves of trocars. The angiographic injector is installed at a flow rate of 30 ml/min and a maximum pressure of 200 pounds per square inch. Protective films are placed on the floor below the angiographic injector and around the patient. The angiographic injector is positioned above a chemotherapy waste bin. The peripheral venous line of the patient is connected to a 60 ml saline-containing syringe outside the operating room. Vital parameters of the patient, real-time videolaparoscopy, and a patient-aimed

camera are displayed on three screens outside the operating room. The screen of the angiographic injector is positioned in front of the window of the operating room. General anaesthesia is ensured for at least another 40 minutes. A checklist is used to confirm that all aforementioned steps have been adequately taken. After completion of the checklist, the entire operating personnel leaves the operating room.

Oxaliplatin is injected through the nebuliser by remote controlled activation of the angiographic injector from outside the operating room. After complete formation of the oxaliplatin-containing aerosol in 5 minutes, the surgeon enters the operating room and turns on the Ultravision® generator, which results in electrostatic precipitation of the aerosol. The electrostatic field and the capnoperitoneum are maintained for another 25 minutes. During this phase, the patient and the procedure are monitored through the three screens and the window of the operating room. Drugs may be administered to the patient through the intravenous access outside the operating room if necessary.

After 25 minutes, the surgeon enters the operating room, turns off the Ultravision® generator, closes the trocar valve connected to the $CO_2$ insufflation, and opens the trocar valve connected to the CAWS. After complete evacuation of the aerosol, the electrode and the nebuliser are removed, the entire operating personnel enters the operating room, and a new capnoperitoneum is obtained. Ascites and peritoneal biopsies are collected for pharmacokinetic purposes. In case no bleeding or perforations are observed, instruments are removed and incisions are closed with absorbable sutures. All instruments and materials are directly disposed in chemotherapy waste bins and the operating room is cleaned according to existing HIPEC protocols.

After ePIPAC-OX, patients are admitted to the general surgical ward. To relieve postoperative pain, patients receive paracetamol (1 g, four times daily), on-demand morphine, and 1 g of metamizole directly after the procedure. To minimise postoperative nausea and vomiting, patients receive perioperative dexamethasone and on-demand granisetron (1 mg, three times daily). Standard post-surgical clinical evaluations are performed a few hours after the procedure and on every postoperative day. Blood is drawn for bone marrow, liver, and kidney functions, albumin, and C-reactive protein on every postoperative day. If the postoperative period is uneventful, patients are discharged on the first postoperative day. All body excretes are considered oxaliplatin-contaminated for up to five days after the procedure.

Dose reduction, prohibited and permitted concomitant care, and strategies to improve adherence are not specified *a priori*, but left to the discretion of the treating physician. ePIPAC-OX is repeated until clinical, radiological, or macroscopic (i.e. ascites, PCI) progression, unacceptable toxicity, physician's decision to discontinue, or at patient's request to discontinue. In patients who develop

systemic metastases, continuation of ePIPAC-OX can only be considered if the patient has no systemic palliative treatment options and stable peritoneal disease.

Outpatient evaluations

One week after each ePIPAC-OX, patients undergo clinical evaluation by phone. Four weeks after each ePIPAC-OX, patients undergo radiological evaluation (i.e. thoracoabdominal CT, diffusion-weighted magnetic resonance imaging [DW-MRI]), biochemical evaluation (i.e. bone marrow, liver, and kidney functions, albumin, C-reactive protein, tumour markers), and clinical evaluation.

Questionnaires

Patients are asked to complete EQ-5D-5L, QLQ-C30, and QLQ-CR29 at baseline and one and four weeks after each ePIPAC-OX.[51-53] iMTA Productivity Cost Questionnaire (PCQ) and iMTA Medical Consumption Questionnaire (MCQ) are sent to the patients at baseline and four weeks after each ePIPAC-OX (PCQ) and each second ePIPAC-OX (MCQ).[54,55]

Pharmacokinetics

Blood is collected during and after the first three procedures in each patient. Four ml of whole blood is drawn and collected in heparin tubes before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after injection of oxaliplatin. After immediate centrifuging, an aliquot of plasma is stored at -80°C until analysis. Another aliquot of 1 ml of plasma is centrifuged through an ultrafiltration membrane and stored at -80°C until analysis. Urine, ascites, peritoneal metastases, and normal peritoneum are collected during and after all procedures. Four ml of urine is collected in urinalysis tubes before ePIPAC-OX and on the first postoperative day. These are stored at -20°C until analysis. After discharge, patients are asked to collect four ml of urine in urinalysis tubes on the third, fifth, and seventh postoperative day, and to store these specimens at their home address at -20°C until analysis. After electrostatic precipitation of the aerosol, the surgeon aspirates a few ml of ascites and biopsies two peritoneal metastases and two pieces of normal peritoneum, preferably from different locations. These are collected in aliquots and directly stored at -80°C until analysis. Concentrations of oxaliplatin are measured by using atomic absorption spectrophotometry.

Translational research

Before each ePIPAC-OX, 20 ml of blood is drawn and collected in 10 ml Cell-free DNA BCT tubes (Streck, La Vista, NE, USA). According to the manufacturer's instructions, these tubes are sent to a central lab for isolation and storage (-80°C) of plasma and cell pellet. Collected ascites or saline is centrifuged twice (5 minutes, 420 g, zero break) under sterile conditions. The supernatant is snap frozen and stored

at -80°C for further analysis on soluble components. The cell pellet is suspended in organoid culture medium at 4°C for transport and further work up. Of each collected PM, three parts are snap frozen and stored at -80°C for sequencing analysis.

**Outcomes**

An assessment schedule is presented in *Table 1*. The primary outcome is the number of patients with major toxicity, defined as grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0,[56] up to four weeks after the last ePIPAC-OX. Secondary outcomes are:

- the environmental safety of ePIPAC-OX, based on air and surface concentrations of oxaliplatin during the first three procedures, measured by atomic absorption spectrophotometry;
- procedure-related characteristics of ePIPAC-OX (e.g. intraoperative complications, amount of adhesions, technical difficulties, operating time);
- the number of procedures in each patient and reasons for discontinuation;
- minor toxicity, defined as grade ≤2 according to CTCAE v4.0,[56] up to four weeks after the last ePIPAC-OX;
- organ-specific toxicity, based on bone marrow, liver, and kidney functions measured at different time points (Table 1);
- major and minor postoperative complications, defined as grade ≥3 and grade ≤2 according to Clavien-Dindo,[57] respectively, up to four weeks after the last ePIPAC-OX;
- hospital stay, defined as the number of days between ePIPAC-OX and initial discharge;
- readmissions, defined as any hospital admission after initial discharge, up to four weeks after the last ePIPAC-OX;
- radiological tumour response, based on central review of thoracoabdominal CT and DW-MRI at baseline and four weeks after each ePIPAC-OX, performed by two independent radiologists (JN, MLH) blinded to clinical outcomes (classification is not defined *a priori*);
- histopathological tumour response, based on central review of collected peritoneal biopsies during each ePIPAC-OX, performed by two independent pathologists (e.g. CJRH) blinded to clinical outcomes by using the Peritoneal Regression Grading Score;[58]
- macroscopic tumour response, based on PCI and ascites volume during each ePIPAC-OX;
- biochemical tumour response, based on tumour markers measured at different time points (Table 1);
- cytological tumour response, based on collected ascites or peritoneal washing cytology during each ePIPAC-OX;

- quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different time points (Table 1);
- costs, derived from the Dutch costing guidelines for health care research at the time of analysis, based on case report forms, hospital information systems, and questionnaires (iMTA PCQ, iMTA MCQ) at different time points (Table 1);
- progression-free survival, defined as the time between enrolment and clinical, radiological, or macroscopic progression, or death;
- overall survival, defined as the time between enrolment and death;
- the pharmacokinetics of oxaliplatin during and after ePIPAC-OX.

**Sample size**

Given the absence of evident clinical endpoint in this patient category, the investigators pragmatically determined the sample size of this exploratory study. The investigators agreed that 60 procedures are required to explore the feasibility, safety, tolerability, and preliminary efficacy of repetitive ePIPAC-OX in this setting. Since the expected mean number of procedures is three per patient,[36] the initial sample size is determined at 20 patients. This pragmatically determined sample size is approved by the central ethics committee. Enrolled patients who do not undergo a first ePIPAC-OX (e.g. systemic metastases on baseline radiology, non-access, resectable disease) are replaced to enrol 20 patients who receive at least one ePIPAC-OX.

**Recruitment**

The study started in October 2017 and is currently enrolling patients. The investigators anticipate that 20 patients will be enrolled within a maximum of three years. Strategies for achieving adequate participant enrolment are not defined *a priori.*

**Data collection and data management**

Outcomes are collected in all patients who receive at least one ePIPAC-OX. All baseline characteristics and clinical outcomes are prospectively collected and entered in an ISO 27001 certified central study database (De Research Manager, Deventer, Netherlands) with study-specific electronic case report forms by a local investigator in each study centre (RJL, ECEW). This ISO 27001 certified system ensures adequate data integrity, including data coding, security, and storage. Questionnaires (quality of life, costs), peritoneal biopsies (histopathological response), and radiological examinations (radiological response) are collected by the coordinating investigator (KPR) throughout the study and centrally analysed after study completion. Plans to promote data quality, participant retention, and complete follow-up are not specified *a priori.*

**Statistical methods**

Repetitive continuous outcomes (e.g. organ toxicity, quality of life, operating time) are analysed by using the Wilcoxon signed-rank test, the paired samples t-test, the Friedman test, or repeated measurements analysis of variance where appropriate. Repetitive categorical outcomes (e.g. intraoperative complications, postoperative complications) are analysed by using the McNemar test, the Wilcoxon signed-rank test, the Cochran's Q test, or generalised estimating equations where appropriate. Time-to-event variables (i.e. overall and progression-free survival) are analysed and displayed by using the Kaplan-Meier method. Other outcomes are analysed by using descriptive statistics. All statistical tests are two-sided and $p<0.05$ is considered statistically significant.

**Data monitoring**

Interim analyses are performed after 8 and 20 procedures. The study is terminated after these interim analyses if CTCAE grade ≥3 toxicity, directly related to ePIPAC-OX, is observed after ≥4 and ≥10 procedures. Furthermore, the study is directly terminated if more than one CTCAE grade 5 toxicity, directly related to ePIPAC-OX, occurs during the study. The coordinating investigator and the principal investigator (IHJTH) have access to these interim results. The principal investigator makes the decision to terminate or continue the study. The investigators decided that a data monitoring committee is not needed given the clear stopping rules and the low expected toxicity of repetitive ePIPAC-OX.

**Harms**

Local investigators report all serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) to the coordinating investigator within 24 hours. The coordinating investigator reports SAEs/SUSARs to the ethics committee within seven days of first knowledge for lethal or life threatening SAEs/SUSARs, and within fifteen days for other SAEs/SUSARs. The time window for reporting SAEs/SUSARs is from enrolment up to four weeks after the last ePIPAC-OX.

**Auditing**

The study is audited by independent qualified monitors of Clinical Trial Centre Maastricht (Maastricht, Netherlands) as a high-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centres. This means that study centres are audited at least three times per year, depending on enrolment, with 100% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification, and SAEs/SUSARs.

**Patient and public involvement**

Patients were not involved in the study design before the start of the study. Shortly after the start of the study, the investigators presented the study design to a patient advisory group. Majors topics of discussion were the rationale for the study, outcome parameters, recruitment strategies, the patient information sheet, dissemination strategies, and the potential risks, benefits, and burden of participation from the patient's perspective. The patient advisory group supported the presented study design. Although the patient advisory group is not involved in the recruitment and the conduct of the study, they will be involved in plans to disseminate the study results to relevant patient groups.

## ETHICS AND DISSEMINATION

**Research ethics approval**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, number R17.038), the Dutch competent authority, and the institutional review boards of both study centres.

**Protocol amendments**

Important protocol modifications are communicated to the ethics committee, the Dutch competent authority, the institutional review boards of both study centres, all investigators, and trial registries.

**Consent or assent**

Written informed consent is obtained by local investigators at the outpatient clinic of the study centres. Patients are given the possibility to give separate permission for undergoing DW-MRI and for storage of specimens for translational research.

**Confidentiality**

Personal information about potential and enrolled patients is collected, shared, and maintained according to the Dutch law (Wet Bescherming Persoonsgegevens).

**Declaration of interests**

The investigators declare no competing interests. The funders have no role in the study design, in writing the report, or in the decision to submit the report for publication.

**Access to data**

All investigators have access to the final datasets, without contractual agreements that limit such access.

**Ancillary and post-study care**

The sponsor (Catharina Hospital, Eindhoven, Netherlands) is insured to provide cover for patients who suffer harm from study participation. After discontinuation of ePIPAC-OX, patients receive standard palliative treatment for unresectable metastatic colorectal cancer according to Dutch guidelines.[4]

**Dissemination policy**

Results of the study are personally communicated to participants and intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders. Authorship eligibility guidelines for the main manuscript and manuscript of side studies are not defined *a priori*. The full protocol and Dutch informed consent forms are, or will become, available upon reasonable request.

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None.

**AUTHORS' CONTRIBUTIONS**

KPR is the coordinating investigator. RJL, AMJT, GMC, JWAB, SWN are the local investigators of the first study centre. ECEW, and TJMK, ML, MJW, and DB are the local investigators of the second study centre. RT performs the pharmacokinetic analyses. MJD is the study pharmacologist supervising the pharmacokinetic analyses. JN and MJL are the study radiologists performing the central radiological review. CJRH is the study pathologist performing the central histopathological review. IE and RJAF are responsible for translational research on blood. AC and OK are responsible for translational research on ascites and PM. IHJTH is the principal investigator. KPR, RJL, and IHJTH made substantial contributions to conception and design of the study, drafted the protocol, and drafted the manuscript. The other authors made substantial contributions to conception and design of the study and critically

revised the protocol and the manuscript for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

**FUNDING**

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**COMPETING INTERESTS**

None declared.

**ETHICAL APPROVAL**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, number R17.038), the Dutch competent authority (CCMO, The Hague, Netherlands), and the institutional review boards of both study centres.

**DATA SHARING**

Not applicable.

**PATIENT CONSENT**

Not applicable.

**PROTOCOL VERSION**

Version 6, 10 January 2019

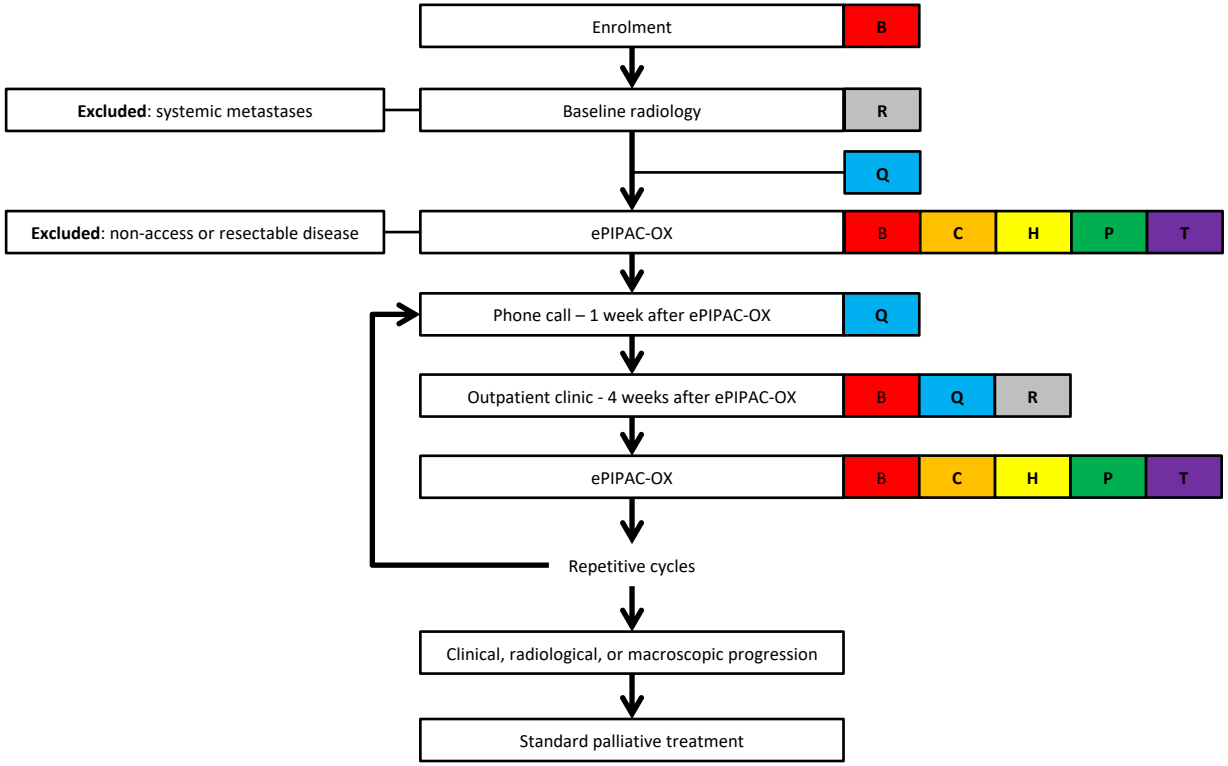
**FIGURE TITLES**

**Figure 1**. Flow chart of the CRC-PIPAC study

**FIGURE LEGENDS**

Figure 1. *ePIPAC-OX* electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin;

- B Bloods (organ toxicity, tumour markers)
- C Cytology (ascites or peritoneal washing with saline)
- H Histopathology (peritoneal biopsies)
- P Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)
- Q Questionnaires (quality of life, costs)
- R Radiology (thoracoabdominal CT, diffusion-weighted MRI)
- T Translational research (blood, ascites, PM)


Enrolment
B
Excluded: systemic metastases
Baseline radiology
R
Q
Excluded: non-access or resectable disease
ePIPAC-OX
B
C
H
P
T
Phone call – 1 week after ePIPAC-OX
Q
Outpatient clinic - 4 weeks after ePIPAC-OX
B
Q
R
ePIPAC-OX
B
C
H
P
T
Repetitive cycles
Clinical, radiological, or macroscopic progression
Standard palliative treatment

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | **1** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | **2** |
| | 2b | All items from the World Health Organization Trial Registration Data Set | **Entire manuscript** |
| Protocol version | 3 | Date and version identifier | **20** |
| Funding | 4 | Sources and types of financial, material, and other support | **20** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | **1-2, 19-20** |
| | 5b | Name and contact information for the trial sponsor | **1** |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | **14** |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | **Entire manuscript** |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | **3-5** |
| | 6b | Explanation for choice of comparators | **Not applicable** |
| Objectives | 7 | Specific objectives or hypotheses | **5** |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | **6** |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | **6** |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | **6** |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | **6-11** |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | **9** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | **9** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | **9** |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | **11-12** |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | **Table 1, Figure 1** |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | **12** |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | **12** |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | **Not applicable** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | **Not applicable** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | **Not applicable** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | **Not applicable** |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | **Not applicable** |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | **12** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | **12** |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | **12** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | **13** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | **Not applicable** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | **12** |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | **13** |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | **13** |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | **13** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | **13** |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | **14** |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | **14** |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | **14** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | **14** |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | **14** |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | **14** |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | **14** |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | **15** |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | **15** |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | **15** |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | **15** |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | **Available upon request** |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | **10** |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC).

| | |
|---|---|
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**Title**

Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC).

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**Abstract**

*Introduction:* Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) is offered as a palliative treatment option for patients with isolated unresectable colorectal peritoneal metastases (PM) in several centres worldwide. However, little is known about its feasibility, safety, tolerability, efficacy, costs, and pharmacokinetics in this setting. This study aims to explore these parameters in patients with isolated unresectable colorectal PM who receive repetitive ePIPAC-OX as a palliative monotherapy.

*Methods and analysis:* This multicentre, open-label, single-arm, phase II study is performed in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM. Eligible patients are adults who have histologically or cytologically proven isolated unresectable PM of a colorectal or appendiceal carcinoma, a good performance status, adequate organ functions, and no symptoms of gastrointestinal obstruction. Instead of standard palliative treatment, enrolled patients receive laparoscopy-controlled ePIPAC-OX (92 mg/m$^2$ body-surface area [BSA]) with intravenous leucovorin (20 mg/m$^2$ BSA) and bolus 5-fluorouracil (400 mg/m$^2$ BSA) every six weeks. Four weeks after each procedure, patients undergo clinical, radiological, and biochemical evaluation. ePIPAC-OX is repeated until disease progression, after which standard palliative treatment is (re)considered. The primary outcome is the number of patients with major toxicity (grade ≥3 according to the Common Terminology Criteria for Adverse Events v4.0) up to four weeks after the last ePIPAC-OX. Secondary outcomes are the environmental safety of ePIPAC-OX, procedure-related characteristics, minor toxicity, postoperative complications, hospital stay, readmissions, quality of life, costs, pharmacokinetics of oxaliplatin, progression-free survival, overall survival, and the radiological, histopathological, cytological, biochemical, and macroscopic tumour response.

*Ethics and dissemination:* This study is approved by an ethics committee, the Dutch competent authority, and the institutional review boards of both study centres. Results are intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders.

*Registration:* ClinicalTrials.gov/NCT03246321, ISRCTN/ISRCTN89947480, NTR/NTR6603, EudraCT/2017-000927-29.

**Keywords**

Colorectal surgery (from list); gastrointestinal tumours (from list); colorectal cancer (not from list); peritoneal metastases (not from list); PIPAC (not from list); intraperitoneal chemotherapy (not from list).

**Strengths and limitations of this study**

- This is the first study that prospectively explores predefined endpoints regarding the feasibility, safety, and efficacy of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.
- Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy, thereby minimising the influence of concurrent palliative systemic therapy on study outcomes.
- Apart from exploring clinical outcomes such as feasibility, safety, and efficacy, this study includes assessment of quality of life and costs as well as pharmacokinetic and translational side studies.
- The broad eligibility criteria could lead to enrolment of prognostically heterogeneous patients in different lines of palliative treatment, which could impede the interpretation of efficacy outcomes.

## INTRODUCTION

After the liver, the peritoneum is the second most common isolated metastatic site of colorectal cancer.[1,2] The majority of patients with isolated colorectal peritoneal metastases (PM) does not qualify for curative intent surgical treatment,[3] mostly due to insufficient condition or unresectable disease. Palliative systemic therapy is the standard treatment for patients with isolated unresectable colorectal PM.[4] Although its increasing use has improved the outcomes of these patients,[3] palliative systemic therapy appears less effective for isolated colorectal PM than for isolated non-peritoneal colorectal metastases.[5] This phenomenon may be explained by a relatively low intraperitoneal concentration of systemically administered chemotherapy.[6] Moreover, a relatively high systemic concentration could cause systemic toxicity. Intraperitoneal administration of chemotherapy is thought to increase locoregional efficacy and decrease systemic toxicity through a favourable peritoneum-plasma concentration ratio.[6-8] However, intraperitoneal chemotherapy seems to have three major limitations: a poor direct tissue penetration, an inhomogeneous intraperitoneal drug distribution, and dose-limiting local toxicity.[9,10] This has encouraged development of new intraperitoneal drug delivery systems that aim to overcome these limitations.

Currently, pressurised intraperitoneal aerosol chemotherapy (PIPAC) is one of these systems that internationally gains the most attention.

**Pressurised intraperitoneal aerosol chemotherapy (PIPAC)**

PIPAC is a laparoscopy-controlled repetitive intraperitoneal administration of low-dose chemotherapy as a pressurised aerosol.[11,12] It combines the theoretical pharmacokinetic advantages of low-dose intraperitoneal chemotherapy (i.e. low toxicity, high intraperitoneal concentration, low systemic concentration) with the principles of an aerosol (homogeneous intraperitoneal distribution) and intra-abdominal pressure (deep tissue penetration).[13-20] Two groups systematically reviewed results of non-comparative clinical studies that assessed the feasibility, safety, tolerability, and preliminary efficacy of PIPAC with various drugs for PM of various origins.[21,22] They concluded that PIPAC is a safe, feasible, and well tolerated treatment with good preliminary response rates.[21,22] These preliminary conclusions have led to an increasing acceptance of PIPAC as a palliative treatment option for PM in several centres worldwide.[23] In these centres, patients with isolated unresectable colorectal PM usually receive PIPAC with oxaliplatin (PIPAC-OX) in an empirically chosen dosage of 92 mg/m$^2$ body-surface area (BSA) every four to six weeks.[23] Some centres use electrostatic precipitation of the aerosol during PIPAC-OX (ePIPAC-OX),[24,25] since this could increase tissue penetration of oxaliplatin.[26]

**PIPAC for colorectal PM**

Several clinical studies included patients who received repetitive PIPAC-OX for colorectal PM.[27-36] However, the vast majority of these studies reported outcomes of entire cohorts that received repetitive PIPAC with various drugs for PM of various origins without presenting subgroup analyses of patients who received PIPAC-OX for colorectal PM.[27-34] Only two studies reported separate outcomes of repetitive PIPAC-OX for colorectal PM.[35,36] By using a prospectively maintained database, Teixeira-Farinha *et al* retrospectively included 20 patients with isolated colorectal PM who received 37 procedures.[35] They concluded that repetitive PIPAC-OX causes a modest and transitory inflammatory response without haematological, renal, or hepatic toxicity.[35] Demtröder *et al.* retrospectively included 17 patients with isolated colorectal PM who received 48 procedures within an off-label program.[36] They concluded that repetitive PIPAC-OX induces regression of pretreated colorectal PM and that the toxicity seems to be low.[36] Both studies have a retrospective design without predefined eligibility criteria and endpoints. Moreover, both studies included patients who received repetitive PIPAC-OX as a monotherapy as well as patients who received PIPAC-OX in combination with palliative systemic therapy. These shortcomings strongly impede the interpretation

of these studies. Besides, recently published case reports suggested that PIPAC-OX could lead to severe hypersensitivity reactions and peritoneal sclerosis.[37,38]

**Rationale for this study**

In conclusion, little is known about the safety, tolerability, and efficacy of repetitive PIPAC-OX in patients with isolated unresectable colorectal PM, whereas nothing is known about its costs and pharmacokinetics. Specifically for repetitive ePIPAC-OX, all these outcomes have never been reported. This questions the current use of repetitive ePIPAC-OX as a palliative treatment option for isolated unresectable colorectal PM outside the framework of clinical study protocols. Ideally, these patients are included in prospective studies with predefined eligibility criteria, interventions, and endpoints. However, by the knowledge of the investigators, such studies are currently lacking and not ongoing.[39] Therefore, this study aims to prospectively explore the safety, tolerability, preliminary efficacy, costs, and pharmacokinetics of repetitive ePIPAC-OX as a palliative treatment for isolated unresectable colorectal PM. Although implementation of PIPAC appears feasible and occupationally safe,[21,22,24,40-43] there is no experience with PIPAC in the Netherlands. Hence, this study also aims to assess the feasibility of implementation of ePIPAC-OX in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM.

**Rationale for intervention**

Repetitive ePIPAC-OX may be administered as part of a bidirectional therapy with palliative systemic therapy or as a monotherapy. The bidirectional therapy hypothetically maximises tumour response, probably at the cost of an increased treatment burden that could interfere with quality of life. Repetitive ePIPAC-OX as a monotherapy hypothetically temporarily stabilises the intraperitoneal disease burden with minimal toxicity and preservation of quality of life. For this study, the investigators decided to administer repetitive ePIPAC-OX as a palliative monotherapy with (re)consideration of standard palliative treatment upon progression. According to internationally used protocols, ePIPAC-OX is administered in a dosage of 92 mg/m$^2$ at six-weekly intervals.[23] The investigators actively followed two ongoing phase I studies in which repetitive PIPAC-OX is administered in various pre-planned dosage levels to evaluate whether the dosage of oxaliplatin in this study needs to be modified.[44,45] Before administration of ePIPAC-OX, patients receive intravenous low-dose leucovorin with bolus 5-fluorouracil, since this is thought to potentiate the effect of intraperitoneal oxaliplatin.[46,47]

## METHODS AND ANALYSIS

**Design and setting**

This prospective, open-label, single-arm, phase II study is performed in two Dutch teaching hospitals qualified as tertiary referral hospitals for the surgical treatment of colorectal PM.

**Eligibility criteria**

Eligible patients are adults who have:

- a World Health Organisation (WHO) performance status of ≤1;
- histological or cytological proof of PM of a colorectal or appendiceal carcinoma;
- unresectable disease determined by the treating physician, based on abdominal computed tomography (CT) and a diagnostic laparoscopy or laparotomy;
- adequate organ functions (haemoglobin ≥5.0 mmol/L, neutrophils ≥1.5 x $10^9$/L, platelets ≥100 x $10^9$/L, serum creatinine <1.5 x upper limit of normal [ULN], creatinine clearance ≥30 ml/min, and liver transaminsases <5 x ULN);
- no symptoms of gastrointestinal obstruction;
- no radiological evidence of systemic metastases;
- no contraindications for oxaliplatin or 5-fluorouracil/leucovorin;
- no contraindications for a laparoscopy;
- no previous PIPAC-procedures.

Importantly, enrolment is allowed for patients with an unresected primary tumour (if asymptomatic) and for patients in various lines of palliative treatment, including patients who refuse, have not had, or do not qualify for first-line palliative systemic therapy. All potentially eligible patients are discussed by a multidisciplinary team. Enrolled patients are informed about the potential consequences of postponing or discontinuing standard palliative treatment by a medical oncologist prior to enrolment.

**Interventions and procedures**

*Figure 1* shows a flow chart of the study. *Table 1* presents a schedule of enrolment, interventions, and assessments.

**Table 1.** Schedule of enrolment, interventions, and assessments.

| | Study period | | | | |
|---|---|---|---|---|---|
| | Enrolment/allocation | Post-enrolment | | | |
| | Outpatient clinics | Baseline radiology | Each ePIPAC-OX | 1 week after each ePIPAC-OX | 4 weeks after each ePIPAC-OX |
| ENROLMENT/ALLOCATION | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| INTERVENTIONS | | | | | |
| ePIPAC-OX | | | X | | |
| Blood (organ functions, tumour markers) | X | | X[A] | | X |
| Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)[B] | | | X | | |
| Translational research (blood, ascites, PM) | | | X[C] | | |
| Thoracoabdominal computed tomography | | X | | | X |
| Diffusion-weighted magnetic resonance imaging | | X | | | X |
| Cytology (ascites or peritoneal washing) | | | X | | |
| Histopathology (peritoneal biopsies) | | | X | | |
| Questionnaires: quality of life | | X | | X | X |
| Questionnaires: costs[D] | | X | | | X |
| ASSESSMENTS | | | | | |
| Baseline characteristics | X | X | X | | |
| Toxicity | | | X | X | X |
| Environmental safety of ePIPAC-OX[E] | | | X | | |
| Procedure-related characteristics | | | X | | |
| Number of procedures in each patient, reasons for discontinuation | | | X | X | X |
| Postoperative complications | | | X | X | X |
| Hospital stay | | | X | | |
| Readmissions | | | | X | X |
| Clinical evaluation | | | X | X | X |
| Radiological tumour response | | X | | | X |
| Histopathological tumour response | | | X | | |
| Cytological tumour response | | | X | | |
| Macroscopic tumour response | | | X | | |
| Biochemical tumour response | | | X | | X |
| Quality of life | | X | | X | X |
| Costs | | X | | | X |
| Progression-free survival | | | X | X | X |
| Overall survival | | | X | X | X |

ePIPAC-OX electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin; PM peritoneal metastases; [A]drawn on each postoperative day; [B]blood is drawn before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after oxaliplatin injection during/after the first three procedures, urine is collected before ePIPAC-OX and on postoperative days 1, 3, 5, and 7, ascites/PM/normal peritoneum are collected directly after oxaliplatin injection; [C]blood is drawn before ePIPAC-OX; [D]MCQ 4 weeks after each procedure, PCQ 4 weeks after each second procedure; [E]only during the first three procedures in the study.

ePIPAC-OX

The procedure-related principles of (e)PIPAC have been extensively described by Willaert *et al* and Giger-Pabst *et al*.[24,48] In this study, ePIPAC-OX is performed at six-weekly intervals by at least one PIPAC-qualified surgeon in a standard operating room with laminar airflow. In both study centres, the operating personnel attended procedures in experienced PIPAC centres before performing their first procedure. All procedures are performed under general anaesthesia. Antibiotic prophylaxis and venous thromboembolism prophylaxis are not regularly administered. Before each procedure, a checklist is used to ensure all materials are available. The operating personnel wears appropriate chemotherapy-protective clothes according to existing HIPEC protocols.

The Hasson technique is used to insert a 10 mm blunt tip balloon trocar through the abdominal wall. After obtaining a normothermic 12 mmHg capnoperitoneum, a second 10 mm blunt tip balloon trocar is inserted under direct vision and explorative laparoscopy is performed. Only if needed, careful adhesiolysis may be performed to create sufficient working space. In case of an iatrogenic bowel lesion, the procedure is ended after closure of the lesion, and ePIPAC-OX may be postponed by two to four weeks. If the procedure is considered feasible, leucovorin (20 mg/m$^2$ BSA in 10 minutes) and bolus 5-fluorouracil (400 mg/m$^2$ BSA in 15 minutes) are administered intravenously. In the meantime, ascites (or injected saline if ascites is not present) is completely evacuated, sent for cytology and translational research, and the ascites volume is documented. Adhesions are scored with the Zühlke score, the peritoneal cancer index (PCI) is registered, and photographs are taken throughout the peritoneal cavity.[49,50] A piece of normal peritoneum and three peritoneal metastases, preferably from different areas, are biopsied, sent for histopathology and translational research, and their locations are documented and marked with clips to enable biopsies of the same locations during subsequent procedures.

Then, the ePIPAC setup is installed. A stainless steel brush electrode (Ionwand®, Alesi Surgical, Cardiff, United Kingdom) is inserted through a mini-trocar under direct vision, secured with its tip at least 2 cm away from other structures, and connected to its generator (Ultravision®, Alesi Surgical, Cardiff, United Kingdom). A nebuliser (CapnoPen®, Capnomed GmbH, Villingendorf, Germany) is inserted through one of the trocars and secured with its nozzle just inside the peritoneal cavity at a safe distance from visceral organs. The camera, inserted through the other trocar, is secured by a laparoscope holder in a way it permanently visualises the electrode and the nebuliser. The valve of the trocar connected to the $CO_2$ insufflation remains opened, whereas the other trocar is connected to a closed aerosol waste system (CAWS) with its valve closed. The CAWS consecutively consists of a smoke evacuation filter, a water seal drainage system, an infant-paediatric electrostatic microparticle filter, and the air waste system of the hospital. The preoperatively prepared syringe with oxaliplatin (92 mg/m$^2$ BSA diluted in a total volume of 150 ml 5% dextrose) is vented, placed in a standard

angiographic injector, and connected to the nebuliser with a saline-flushed high-pressure line protected by a plastic camera cover. A leak-free capnoperitoneum is ensured by zero-flow of $CO_2$. If necessary, the external fascia may be additionally sutured and Luer lock caps may be placed on balloon valves of trocars. The angiographic injector is installed at a flow rate of 30 ml/min and a maximum pressure of 200 pounds per square inch. Protective films are placed on the floor below the angiographic injector and around the patient. The angiographic injector is positioned above a chemotherapy waste bin. The peripheral venous line of the patient is connected to a 60 ml saline-containing syringe outside the operating room. Vital parameters of the patient, real-time videolaparoscopy, and a patient-aimed camera are displayed on three screens outside the operating room. The screen of the angiographic injector is positioned in front of the window of the operating room. General anaesthesia is ensured for at least another 40 minutes. A checklist is used to confirm that all aforementioned steps have been adequately taken. After completion of the checklist, the entire operating personnel leaves the operating room.

Oxaliplatin is injected through the nebuliser by remote controlled activation of the angiographic injector from outside the operating room. After complete formation of the oxaliplatin-containing aerosol in 5 minutes, the surgeon enters the operating room and turns on the Ultravision® generator, which results in electrostatic precipitation of the aerosol. The electrostatic field and the capnoperitoneum are maintained for another 25 minutes. During this phase, the patient and the procedure are monitored through the three screens and the window of the operating room. Drugs may be administered to the patient through the intravenous access outside the operating room if necessary.

After 25 minutes, the surgeon enters the operating room, turns off the Ultravision® generator, closes the trocar valve connected to the $CO_2$ insufflation, and opens the trocar valve connected to the CAWS. After complete evacuation of the aerosol, the electrode and the nebuliser are removed, the entire operating personnel enters the operating room, and a new capnoperitoneum is obtained. Ascites and peritoneal biopsies are collected for pharmacokinetic purposes. In case no bleeding or perforations are observed, instruments are removed and incisions are closed with absorbable sutures. All instruments and materials are directly disposed in chemotherapy waste bins and the operating room is cleaned according to existing HIPEC protocols. Any procedure-related mistake or difficulty during ePIPAC-OX is recorded directly after occurrence.

After ePIPAC-OX, patients are admitted to the general surgical ward. To relieve postoperative pain, patients receive paracetamol (1 g, four times daily), on-demand morphine, and 1 g of metamizole directly after the procedure. To minimise postoperative nausea and vomiting, patients receive perioperative dexamethasone and on-demand granisetron (1 mg, three times daily). Standard post-surgical clinical evaluations are performed a few hours after the procedure and on every postoperative

day. Blood is drawn for bone marrow, liver, and kidney functions, albumin, and C-reactive protein on every postoperative day. If the postoperative period is uneventful, patients are discharged on the first postoperative day. All body excretes are considered oxaliplatin-contaminated for up to five days after the procedure.

Dose reduction, prohibited and permitted concomitant care, and strategies to improve adherence are not specified *a priori*, but left to the discretion of the treating physician. ePIPAC-OX is repeated until clinical progression, radiological progression (Response Evaluation Criteria In Solid Tumours or at physician's discretion in case of non-measurable disease), macroscopic progression (i.e. ascites volume, PCI), unacceptable toxicity, physician's decision to discontinue, or at patient's request to discontinue. In patients who develop systemic metastases, continuation of ePIPAC-OX can only be considered if the patient has no systemic palliative treatment options and stable peritoneal disease.

Outpatient evaluations

One week after each ePIPAC-OX, patients undergo clinical evaluation by phone. Four weeks after each ePIPAC-OX, patients undergo radiological evaluation (i.e. thoracoabdominal CT, diffusion-weighted magnetic resonance imaging [DW-MRI]), biochemical evaluation (i.e. bone marrow, liver, and kidney functions, albumin, C-reactive protein, tumour markers), and clinical evaluation.

Questionnaires

Patients are asked to complete EQ-5D-5L, QLQ-C30, and QLQ-CR29 at baseline and one and four weeks after each ePIPAC-OX.[51-53] iMTA Productivity Cost Questionnaire (PCQ) and iMTA Medical Consumption Questionnaire (MCQ) are sent to the patients at baseline and four weeks after each ePIPAC-OX (PCQ) and each second ePIPAC-OX (MCQ).[54,55]

Pharmacokinetics

Blood is collected during and after the first three procedures in each patient. Four ml of whole blood is drawn and collected in heparin tubes before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after injection of oxaliplatin. After immediate centrifuging, an aliquot of plasma is stored at -80°C until analysis. Another aliquot of 1 ml of plasma is centrifuged through an ultrafiltration membrane and stored at -80°C until analysis. Urine, ascites, peritoneal metastases, and normal peritoneum are collected during and after all procedures. Four ml of urine is collected in urinalysis tubes before ePIPAC-OX and on the first postoperative day. These are stored at -20°C until analysis. After discharge, patients are asked to collect four ml of urine in urinalysis tubes on the third, fifth, and seventh postoperative day, and to store these specimens at their home address at -20°C until analysis. After electrostatic precipitation of the aerosol, the surgeon aspirates a few ml of ascites and biopsies

two peritoneal metastases and two pieces of normal peritoneum, preferably from different locations. These are collected in aliquots and directly stored at -80°C until analysis. Concentrations of oxaliplatin are measured by using atomic absorption spectrophotometry.

Translational research

Before each ePIPAC-OX, 20 ml of blood is drawn and collected in 10 ml Cell-free DNA BCT tubes (Streck, La Vista, NE, USA). According to the manufacturer's instructions, these tubes are sent to a central lab for isolation and storage (-80°C) of plasma and cell pellet. Collected ascites or saline is centrifuged twice (5 minutes, 420 g, zero break) under sterile conditions. The supernatant is snap frozen and stored at -80°C for further analysis on soluble components. The cell pellet is suspended in organoid culture medium at 4°C for transport and further work up. Of each collected PM, three parts are snap frozen and stored at -80°C for sequencing analysis.

**Outcomes**

An assessment schedule is presented in *Table 1*. The primary outcome is the number of patients with major toxicity, defined as grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0,[56] up to four weeks after the last ePIPAC-OX. Secondary outcomes are:

- the environmental safety of ePIPAC-OX, based on air and surface concentrations of oxaliplatin during the first three procedures, measured by atomic absorption spectrophotometry;
- procedure-related characteristics of ePIPAC-OX (e.g. intraoperative complications, amount of adhesions, procedure-related mistakes and difficulties, operating time);
- the number of procedures in each patient and reasons for discontinuation;
- minor toxicity, defined as grade ≤2 according to CTCAE v4.0,[56] up to four weeks after the last ePIPAC-OX;
- major and minor postoperative complications, defined as grade ≥3 and grade ≤2 according to Clavien-Dindo,[57] respectively, up to four weeks after the last ePIPAC-OX;
- hospital stay, defined as the number of days between ePIPAC-OX and initial discharge;
- readmissions, defined as any hospital admission after initial discharge, up to four weeks after the last ePIPAC-OX;
- radiological tumour response, based on central review of thoracoabdominal CT and DW-MRI at baseline and four weeks after each ePIPAC-OX, performed by two independent radiologists (JN, MLH) blinded to clinical outcomes (classification is not defined *a priori*);

- histopathological tumour response, based on central review of collected peritoneal biopsies during each ePIPAC-OX, performed by two independent pathologists (e.g. CJRH) blinded to clinical outcomes by using the Peritoneal Regression Grading Score;[58]
- macroscopic tumour response, based on PCI and ascites volume during each ePIPAC-OX;
- biochemical tumour response, based on tumour markers measured at different time points (Table 1);
- cytological tumour response, based on collected ascites or peritoneal washing cytology during each ePIPAC-OX;
- quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different time points (Table 1);
- costs, derived from the Dutch costing guidelines for health care research at the time of analysis, based on case report forms, hospital information systems, and questionnaires (iMTA PCQ, iMTA MCQ) at different time points (Table 1);
- progression-free survival, defined as the time between enrolment and clinical, radiological, or macroscopic progression, or death;
- overall survival, defined as the time between enrolment and death;
- the pharmacokinetics of oxaliplatin during and after ePIPAC-OX.

**Sample size**

Given the absence of evident clinical endpoint in this patient category, the investigators pragmatically determined the sample size of this exploratory study. The investigators agreed that 60 procedures are required to explore the feasibility, safety, tolerability, and preliminary efficacy of repetitive ePIPAC-OX in this setting. Since the expected mean number of procedures is three per patient,[36] the initial sample size is determined at 20 patients. This pragmatically determined sample size is approved by the central ethics committee. Enrolled patients who do not undergo a first ePIPAC-OX (e.g. systemic metastases on baseline radiology, non-access, resectable disease) are replaced to enrol 20 patients who receive at least one ePIPAC-OX.

**Recruitment**

The study started in October 2017 and is currently enrolling patients. The investigators anticipate that 20 patients will be enrolled within a maximum of three years. Strategies for achieving adequate participant enrolment are not defined *a priori.*

**Data collection and data management**

Outcomes are collected in all patients who receive at least one ePIPAC-OX. All baseline characteristics and clinical outcomes are prospectively collected and entered in an ISO 27001 certified central study database (De Research Manager, Deventer, Netherlands) with study-specific electronic case report forms by a local investigator in each study centre (RJL, ECEW). This ISO 27001 certified system ensures adequate data integrity, including data coding, security, and storage. Questionnaires (quality of life, costs), peritoneal biopsies (histopathological response), and radiological examinations (radiological response) are collected by the coordinating investigator (KPR) throughout the study and centrally analysed after study completion. Plans to promote data quality, participant retention, and complete follow-up are not specified *a priori.*

**Statistical methods**

Repetitive continuous outcomes (e.g. quality of life, operating time) are analysed by using the Wilcoxon signed-rank test, the paired samples t-test, the Friedman test, or repeated measurements analysis of variance where appropriate. Repetitive categorical outcomes (e.g. intraoperative complications, postoperative complications) are analysed by using the McNemar test, the Wilcoxon signed-rank test, the Cochran's Q test, or generalised estimating equations where appropriate. Time-to-event variables (i.e. overall and progression-free survival) are analysed and displayed by using the Kaplan-Meier method. Other outcomes are analysed by using descriptive statistics. All statistical tests are two-sided and $p<0.05$ is considered statistically significant.

**Data monitoring**

Interim analyses are performed after 8 and 20 procedures. The study is terminated after these interim analyses if CTCAE grade ≥3 toxicity, directly related to ePIPAC-OX, is observed after ≥4 and ≥10 procedures. Furthermore, the study is directly terminated if more than one CTCAE grade 5 toxicity, directly related to ePIPAC-OX, occurs during the study. The coordinating investigator and the principal investigator (IHJTH) have access to these interim results. The principal investigator makes the decision to terminate or continue the study. The investigators decided that a data monitoring committee is not needed given the clear stopping rules and the low expected toxicity of repetitive ePIPAC-OX.

**Harms**

Local investigators report all serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) to the coordinating investigator within 24 hours. The coordinating investigator reports SAEs/SUSARs to the ethics committee within seven days of first knowledge for lethal or life threatening SAEs/SUSARs, and within fifteen days for other SAEs/SUSARs. The time window for reporting SAEs/SUSARs is from enrolment up to four weeks after the last ePIPAC-OX.

**Auditing**

The study is audited by independent qualified monitors of Clinical Trial Centre Maastricht (Maastricht, Netherlands) as a high-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centres. This means that study centres are audited at least three times per year, depending on enrolment, with 100% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification, and SAEs/SUSARs.

**Patient and public involvement**

Patients were not involved in the study design before the start of the study. Shortly after the start of the study, the investigators presented the study design to a patient advisory group. Majors topics of discussion were the rationale for the study, outcome parameters, recruitment strategies, the patient information sheet, dissemination strategies, and the potential risks, benefits, and burden of participation from the patient's perspective. The patient advisory group supported the presented study design. Although the patient advisory group is not involved in the recruitment and the conduct of the study, they will be involved in plans to disseminate the study results to relevant patient groups.

## ETHICS AND DISSEMINATION

**Research ethics approval**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, R17.038), the Dutch competent authority (Centrale Commissie Mensgebonden Onderzoek, NL60405.100.17), and the institutional review boards of Catharina Hospital (Lokale Uitvoerbaarheidscommissie, CZE-2017.50) and St. Antonius Hospital (R&D, L18.021).

**Protocol amendments**

Important protocol modifications are communicated to the ethics committee, the Dutch competent authority, the institutional review boards of both study centres, all investigators, and trial registries.

**Consent or assent**

Written informed consent is obtained by local investigators at the outpatient clinic of the study centres. Patients are given the possibility to give separate permission for undergoing DW-MRI and for storage of specimens for translational research.

**Confidentiality**

Personal information about potential and enrolled patients is collected, shared, and maintained according to the Dutch law (Wet Bescherming Persoonsgegevens).

**Declaration of interests**

The investigators declare no competing interests. The funders have no role in the study design, in writing the report, or in the decision to submit the report for publication.

**Access to data**

All investigators have access to the final datasets, without contractual agreements that limit such access.

**Ancillary and post-study care**

The sponsor (Catharina Hospital, Eindhoven, Netherlands) is insured to provide cover for patients who suffer harm from study participation. After discontinuation of ePIPAC-OX, patients receive standard palliative treatment for unresectable metastatic colorectal cancer according to Dutch guidelines.[4]

**Dissemination policy**

Results of the study are personally communicated to participants and intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders. Authorship eligibility guidelines for the main manuscript and manuscript of side studies are not defined *a priori*. The full protocol and Dutch informed consent forms are, or will become, available upon reasonable request.

## DISCUSSION

To the knowledge of the investigators, this is the first study that prospectively explores the feasibility, safety, tolerability, costs, preliminary efficacy, and pharmacokinetics of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.

This study protocol has potential limitations. The broad eligibility criteria could lead to a heterogeneous cohort with various primary tumours (i.e. colon, appendix) and histologies (e.g. signet ring cell carcinoma, high-grade appendiceal mucinous neoplasm) in different lines of treatment. This clinical heterogeneity could impede the interpretation of survival outcomes. However, survival outcomes are not the major focus of this study. Enrolment is also allowed for patients with an unresected primary tumour and patients who did not receive prior palliative systemic therapy. In these patients, administration of repetitive ePIPAC-OX as a monotherapy could theoretically lead to undertreatment and subsequent systemic progression or progression of the primary tumour.

However, it is thought that the frequent clinical and radiological evaluations detect such progression in a sufficiently early stage. Moreover, patients need to be informed by a medical oncologist about the potential consequences of postponing or discontinuing their standard palliative treatment prior to enrolment. Conclusively, the investigators feel that these controlled circumstances justify enrolment of these patients.

This study protocol has potential strengths. All endpoints are predefined and prospectively assessed. Independent 100% auditing ensures an appropriately conducted study and high-quality data. Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy in all patients. Thereby, outcomes are not influenced by concurrent palliative systemic therapy. Extensive assessment of quality of life provides insights in the tolerability of ePIPAC-OX from a patient perspective, whereas pharmacokinetic analyses provide the first insights in the systemic absorption repetitive ePIPAC-OX. Insights in the costs of ePIPAC-OX could be valuable for policy makers and other teams that aim to implement this procedure or apply for scientific grants, while translational side studies may open new avenues for research.

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**ACKNOWLEDGEMENTS**

None.

**AUTHORS' CONTRIBUTIONS**

KPR is the coordinating investigator. RJL, AMJT, GMC, JWAB, SWN are the local investigators of the first study centre. ECEW, and TJMK, ML, MJW, and DB are the local investigators of the second study centre. RT performs the pharmacokinetic analyses. MJD is the study pharmacologist supervising the pharmacokinetic analyses. JN and MJL are the study radiologists performing the central radiological review. CJRH is the study pathologist performing the central histopathological review. HJS is the study anaesthesiologist who developed the protocols for perioperative care. IE and RJAF are responsible for translational research on blood. AC and OK are responsible for translational research on ascites and PM. IHJTH is the principal investigator. KPR, RJL, and IHJTH made substantial contributions to

conception and design of the study, drafted the protocol, and drafted the manuscript. All other authors made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

**FUNDING**

This study is supported by Catharina Research Foundation (grant number: 2017-5) and St. Antonius Research Foundation (grant number: 17.4).

**COMPETING INTERESTS**

None declared.

**ETHICAL APPROVAL**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, number R17.038), the Dutch competent authority (CCMO, The Hague, Netherlands), and the institutional review boards of both study centres.

**DATA SHARING**

Not applicable.

**PATIENT CONSENT**

Not applicable.

**PROTOCOL VERSION**

Version 6, 10 January 2019

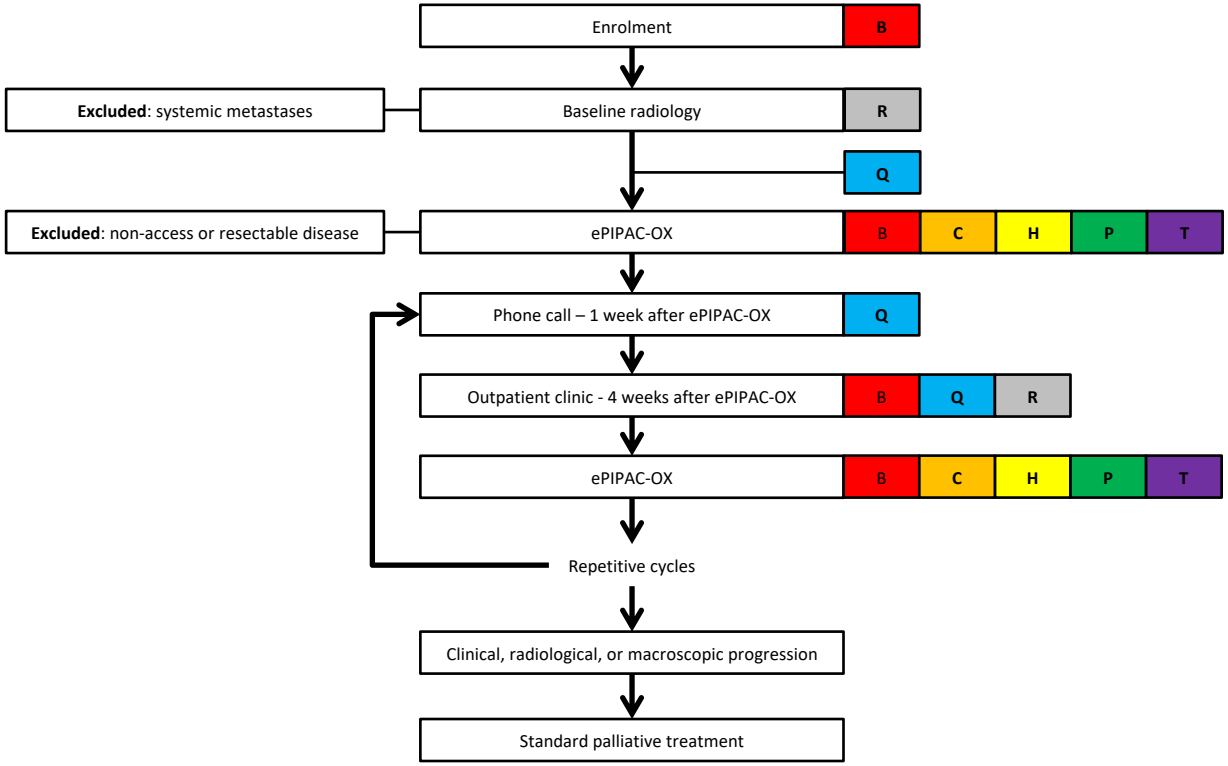
**FIGURE TITLES**

**Figure 1**. Flow chart of the CRC-PIPAC study

**FIGURE LEGENDS**

Figure 1. *ePIPAC-OX* electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin;

- B: Bloods (organ functions, tumour markers)
- C: Cytology (ascites or peritoneal washing with saline)
- H: Histopathology (peritoneal biopsies)
- P: Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)
- Q: Questionnaires (quality of life, costs)
- R: Radiology (thoracoabdominal CT, diffusion-weighted MRI)
- T: Translational research (blood, ascites, PM)


Enrolment
B
Excluded: systemic metastases
Baseline radiology
R
Q
Excluded: non-access or resectable disease
ePIPAC-OX
B
C
H
P
T
Phone call – 1 week after ePIPAC-OX
Q
Outpatient clinic - 4 weeks after ePIPAC-OX
B
Q
R
ePIPAC-OX
B
C
H
P
T
Repetitive cycles
Clinical, radiological, or macroscopic progression
Standard palliative treatment

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | **1** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | **2** |
| | 2b | All items from the World Health Organization Trial Registration Data Set | **Entire manuscript** |
| Protocol version | 3 | Date and version identifier | **20** |
| Funding | 4 | Sources and types of financial, material, and other support | **20** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | **1-2, 19-20** |
| | 5b | Name and contact information for the trial sponsor | **1** |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | **14** |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | **Entire manuscript** |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | **3-5** |
| | 6b | Explanation for choice of comparators | **Not applicable** |
| Objectives | 7 | Specific objectives or hypotheses | **5** |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | **6** |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | **6** |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | **6** |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | **6-11** |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | **9** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | **9** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | **9** |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | **11-12** |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | **Table 1, Figure 1** |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | **12** |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | **12** |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | **Not applicable** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | **Not applicable** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | **Not applicable** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | **Not applicable** |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | **Not applicable** |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | **12** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | **12** |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | **12** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | **13** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | **Not applicable** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | **12** |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | **13** |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | **13** |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | **13** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | **13** |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | **14** |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | **14** |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | **14** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | **14** |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | **14** |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | **14** |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | **14** |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | **15** |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | **15** |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | **15** |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | **15** |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | **Available upon request** |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | **10** |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC).

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**Title**

Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC).

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**Abstract**

*Introduction:* Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX) is offered as a palliative treatment option for patients with isolated unresectable colorectal peritoneal metastases (PM) in several centres worldwide. However, little is known about its feasibility, safety, tolerability, efficacy, costs, and pharmacokinetics in this setting. This study aims to explore these parameters in patients with isolated unresectable colorectal PM who receive repetitive ePIPAC-OX as a palliative monotherapy.

*Methods and analysis:* This multicentre, open-label, single-arm, phase II study is performed in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM. Eligible patients are adults who have histologically or cytologically proven isolated unresectable PM of a colorectal or appendiceal carcinoma, a good performance status, adequate organ functions, and no symptoms of gastrointestinal obstruction. Instead of standard palliative treatment, enrolled patients receive laparoscopy-controlled ePIPAC-OX (92 mg/m$^2$ body-surface area [BSA]) with intravenous leucovorin (20 mg/m$^2$ BSA) and bolus 5-fluorouracil (400 mg/m$^2$ BSA) every six weeks. Four weeks after each procedure, patients undergo clinical, radiological, and biochemical evaluation. ePIPAC-OX is repeated until disease progression, after which standard palliative treatment is (re)considered. The primary outcome is the number of patients with major toxicity (grade ≥3 according to the Common Terminology Criteria for Adverse Events v4.0) up to four weeks after the last ePIPAC-OX. Secondary outcomes are the environmental safety of ePIPAC-OX, procedure-related characteristics, minor toxicity, postoperative complications, hospital stay, readmissions, quality of life, costs, pharmacokinetics of oxaliplatin, progression-free survival, overall survival, and the radiological, histopathological, cytological, biochemical, and macroscopic tumour response.

*Ethics and dissemination:* This study is approved by an ethics committee, the Dutch competent authority, and the institutional review boards of both study centres. Results are intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders.

*Registration:* ClinicalTrials.gov/NCT03246321, ISRCTN/ISRCTN89947480, NTR/NTR6603, EudraCT/2017-000927-29.

**Keywords**

Colorectal surgery (from list); gastrointestinal tumours (from list); colorectal cancer (not from list); peritoneal metastases (not from list); PIPAC (not from list); intraperitoneal chemotherapy (not from list).

**Strengths and limitations of this study**

- This is the first study that prospectively explores predefined endpoints regarding the feasibility, safety, and efficacy of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.
- Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy, thereby minimising the influence of concurrent palliative systemic therapy on study outcomes.
- Apart from exploring clinical outcomes such as feasibility, safety, and efficacy, this study includes assessment of quality of life and costs as well as pharmacokinetic and translational side studies.
- The broad eligibility criteria could lead to enrolment of prognostically heterogeneous patients in different lines of palliative treatment, which could impede the interpretation of efficacy outcomes.

## INTRODUCTION

After the liver, the peritoneum is the second most common isolated metastatic site of colorectal cancer.[1,2] The majority of patients with isolated colorectal peritoneal metastases (PM) does not qualify for curative intent surgical treatment,[3] mostly due to insufficient condition or unresectable disease. Palliative systemic therapy is the standard treatment for patients with isolated unresectable colorectal PM.[4] Although its increasing use has improved the outcomes of these patients,[3] palliative systemic therapy appears less effective for isolated colorectal PM than for isolated non-peritoneal colorectal metastases.[5] This phenomenon may be explained by a relatively low intraperitoneal concentration of systemically administered chemotherapy.[6] Moreover, a relatively high systemic concentration could cause systemic toxicity. Intraperitoneal administration of chemotherapy is thought to increase locoregional efficacy and decrease systemic toxicity through a favourable peritoneum-plasma concentration ratio.[6-8] However, intraperitoneal chemotherapy seems to have three major limitations: a poor direct tissue penetration, an inhomogeneous intraperitoneal drug distribution, and dose-limiting local toxicity.[9,10] This has encouraged development of new intraperitoneal drug delivery systems that aim to overcome these limitations.

Currently, pressurised intraperitoneal aerosol chemotherapy (PIPAC) is one of these systems that internationally gains the most attention.

**Pressurised intraperitoneal aerosol chemotherapy (PIPAC)**

PIPAC is a laparoscopy-controlled repetitive intraperitoneal administration of low-dose chemotherapy as a pressurised aerosol.[11,12] It combines the theoretical pharmacokinetic advantages of low-dose intraperitoneal chemotherapy (i.e. low toxicity, high intraperitoneal concentration, low systemic concentration) with the principles of an aerosol (homogeneous intraperitoneal distribution) and intra-abdominal pressure (deep tissue penetration).[13-20] Two groups systematically reviewed results of non-comparative clinical studies that assessed the feasibility, safety, tolerability, and preliminary efficacy of PIPAC with various drugs for PM of various origins.[21,22] They concluded that PIPAC is a safe, feasible, and well tolerated treatment with good preliminary response rates.[21,22] These preliminary conclusions have led to an increasing acceptance of PIPAC as a palliative treatment option for PM in several centres worldwide.[23] In these centres, patients with isolated unresectable colorectal PM usually receive PIPAC with oxaliplatin (PIPAC-OX) in an empirically chosen dosage of 92 mg/m$^2$ body-surface area (BSA) every four to six weeks.[23] Some centres use electrostatic precipitation of the aerosol during PIPAC-OX (ePIPAC-OX),[24,25] since this could increase tissue penetration of oxaliplatin.[26]

**PIPAC for colorectal PM**

Several clinical studies included patients who received repetitive PIPAC-OX for colorectal PM.[27-36] However, the vast majority of these studies reported outcomes of entire cohorts that received repetitive PIPAC with various drugs for PM of various origins without presenting subgroup analyses of patients who received PIPAC-OX for colorectal PM.[27-34] Only two studies reported separate outcomes of repetitive PIPAC-OX for colorectal PM.[35,36] By using a prospectively maintained database, Teixeira-Farinha *et al* retrospectively included 20 patients with isolated colorectal PM who received 37 procedures.[35] They concluded that repetitive PIPAC-OX causes a modest and transitory inflammatory response without haematological, renal, or hepatic toxicity.[35] Demtröder *et al.* retrospectively included 17 patients with isolated colorectal PM who received 48 procedures within an off-label program.[36] They concluded that repetitive PIPAC-OX induces regression of pretreated colorectal PM and that the toxicity seems to be low.[36] Both studies have a retrospective design without predefined eligibility criteria and endpoints. Moreover, both studies included patients who received repetitive PIPAC-OX as a monotherapy as well as patients who received PIPAC-OX in combination with palliative systemic therapy. These shortcomings strongly impede the interpretation

of these studies. Besides, recently published case reports suggested that PIPAC-OX could lead to severe hypersensitivity reactions and peritoneal sclerosis.[37,38]

**Rationale for this study**

In conclusion, little is known about the safety, tolerability, and efficacy of repetitive PIPAC-OX in patients with isolated unresectable colorectal PM, whereas nothing is known about its costs and pharmacokinetics. Specifically for repetitive ePIPAC-OX, all these outcomes have never been reported. This questions the current use of repetitive ePIPAC-OX as a palliative treatment option for isolated unresectable colorectal PM outside the framework of clinical study protocols. Ideally, these patients are included in prospective studies with predefined eligibility criteria, interventions, and endpoints. However, by the knowledge of the investigators, such studies are currently lacking and not ongoing.[39] Therefore, this study aims to prospectively explore the safety, tolerability, preliminary efficacy, costs, and pharmacokinetics of repetitive ePIPAC-OX as a palliative treatment for isolated unresectable colorectal PM. Although implementation of PIPAC appears feasible and occupationally safe,[21,22,24,40-43] there is no experience with PIPAC in the Netherlands. Hence, this study also aims to assess the feasibility of implementation of ePIPAC-OX in two Dutch tertiary referral hospitals for the surgical treatment of colorectal PM.

**Rationale for intervention**

Repetitive ePIPAC-OX may be administered as part of a bidirectional therapy with palliative systemic therapy or as a monotherapy. The bidirectional therapy hypothetically maximises tumour response, probably at the cost of an increased treatment burden that could interfere with quality of life. Repetitive ePIPAC-OX as a monotherapy hypothetically temporarily stabilises the intraperitoneal disease burden with minimal toxicity and preservation of quality of life. For this study, the investigators decided to administer repetitive ePIPAC-OX as a palliative monotherapy with (re)consideration of standard palliative treatment upon progression. According to internationally used protocols, ePIPAC-OX is administered in a dosage of 92 mg/m$^2$ at six-weekly intervals.[23] The investigators actively followed two ongoing phase I studies in which repetitive PIPAC-OX is administered in various pre-planned dosage levels to evaluate whether the dosage of oxaliplatin in this study needs to be modified.[44,45] Before administration of ePIPAC-OX, patients receive intravenous low-dose leucovorin with bolus 5-fluorouracil, since this is thought to potentiate the effect of intraperitoneal oxaliplatin.[46,47]

## METHODS AND ANALYSIS

**Design and setting**

This prospective, open-label, single-arm, phase II study is performed in two Dutch teaching hospitals qualified as tertiary referral hospitals for the surgical treatment of colorectal PM.

**Eligibility criteria**

Eligible patients are adults who have:

- a World Health Organisation (WHO) performance status of ≤1;
- histological or cytological proof of PM of a colorectal or appendiceal carcinoma;
- unresectable disease determined by the treating physician, based on abdominal computed tomography (CT) and a diagnostic laparotomy or laparoscopy, the latter being a standard tool in the diagnostic work-up of patients with isolated colorectal PM in the Netherlands;
- adequate organ functions (haemoglobin ≥5.0 mmol/L, neutrophils ≥1.5 x $10^9$/L, platelets ≥100 x $10^9$/L, serum creatinine <1.5 x upper limit of normal [ULN], creatinine clearance ≥30 ml/min, and liver transaminsases <5 x ULN);
- no symptoms of gastrointestinal obstruction;
- no radiological evidence of systemic metastases;
- no contraindications for oxaliplatin or 5-fluorouracil/leucovorin;
- no contraindications for a laparoscopy;
- no previous PIPAC-procedures.

Thereby, enrolment is allowed for patients with a signet ring cell carcinoma, patients with a history of prior cytoreductive surgery or HIPEC, and patients with unresected ovarian metastases or an unresected primary tumour (if not causing symptoms of gastrointestinal obstruction). Importantly, enrolment is allowed for patients in various lines of palliative treatment, including patients who refuse, have not had, or do not qualify for first-line palliative systemic therapy. All potentially eligible patients are discussed by a multidisciplinary team. Enrolled patients are informed about the potential consequences of postponing or discontinuing standard palliative treatment by a medical oncologist prior to enrolment.

**Interventions and procedures**

*Figure 1* shows a flow chart of the study. *Table 1* presents a schedule of enrolment, interventions, and assessments.

**Table 1.** Schedule of enrolment, interventions, and assessments.

| | Study period | | | | |
|---|---|---|---|---|---|
| | Enrolment/allocation | Post-enrolment | | | |
| | Outpatient clinics | Baseline radiology | Each ePIPAC-OX | 1 week after each ePIPAC-OX | 4 weeks after each ePIPAC-OX |
| ENROLMENT/ALLOCATION | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| INTERVENTIONS | | | | | |
| ePIPAC-OX | | | X | | |
| Blood (organ functions, tumour markers) | X | | X[A] | | X |
| Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)[B] | | | X | | |
| Translational research (blood, ascites, PM) | | | X[C] | | |
| Thoracoabdominal computed tomography | | X | | | X |
| Diffusion-weighted magnetic resonance imaging | | X | | | X |
| Cytology (ascites or peritoneal washing) | | | X | | |
| Histopathology (peritoneal biopsies) | | | X | | |
| Questionnaires: quality of life | | X | | X | X |
| Questionnaires: costs[D] | | X | | | X |
| ASSESSMENTS | | | | | |
| Baseline characteristics | X | X | X | | |
| Toxicity | | | X | X | X |
| Environmental safety of ePIPAC-OX[E] | | | X | | |
| Procedure-related characteristics | | | X | | |
| Number of procedures in each patient, reasons for discontinuation | | | X | X | X |
| Postoperative complications | | | X | X | X |
| Hospital stay | | | X | | |
| Readmissions | | | | X | X |
| Clinical evaluation | | | X | X | X |
| Radiological tumour response | | X | | | X |
| Histopathological tumour response | | | X | | |
| Cytological tumour response | | | X | | |
| Macroscopic tumour response | | | X | | |
| Biochemical tumour response | | | X | | X |
| Quality of life | | X | | X | X |
| Costs | | X | | | X |
| Progression-free survival | | | X | X | X |
| Overall survival | | | X | X | X |

ePIPAC-OX electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin; PM peritoneal metastases; [A]drawn on each postoperative day; [B]blood is drawn before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after oxaliplatin injection during/after the first three procedures, urine is collected before ePIPAC-OX and on postoperative days 1, 3, 5, and 7, ascites/PM/normal peritoneum are collected directly after oxaliplatin injection; [C]blood is drawn before ePIPAC-OX; [D]MCQ 4 weeks after each procedure, PCQ 4 weeks after each second procedure; [E]only during the first three procedures in the study.

ePIPAC-OX

The procedure-related principles of (e)PIPAC have been extensively described by Willaert *et al* and Giger-Pabst *et al*.[24,48] In this study, ePIPAC-OX is performed at six-weekly intervals by at least one PIPAC-qualified surgeon in a standard operating room with laminar airflow. In both study centres, the operating personnel attended procedures in experienced PIPAC centres before performing their first procedure. All procedures are performed under general anaesthesia. Antibiotic prophylaxis and venous thromboembolism prophylaxis are not regularly administered. Before each procedure, a checklist is used to ensure all materials are available. The operating personnel wears appropriate chemotherapy-protective clothes according to existing HIPEC protocols.

The Hasson technique is used to insert a 10 mm blunt tip balloon trocar through the abdominal wall. After obtaining a normothermic 12 mmHg capnoperitoneum, a second 10 mm blunt tip balloon trocar is inserted under direct vision and explorative laparoscopy is performed. Only if needed, careful adhesiolysis may be performed to create sufficient working space. In case of an iatrogenic bowel lesion, the procedure is ended after closure of the lesion, and ePIPAC-OX may be postponed by two to four weeks. If the procedure is considered feasible, leucovorin (20 mg/m$^2$ BSA in 10 minutes) and bolus 5-fluorouracil (400 mg/m$^2$ BSA in 15 minutes) are administered intravenously. In the meantime, ascites (or injected saline if ascites is not present) is completely evacuated, sent for cytology and translational research, and the ascites volume is documented. Adhesions are scored with the Zühlke score, the peritoneal cancer index (PCI) is registered, and photographs are taken throughout the peritoneal cavity.[49,50] A piece of normal peritoneum and three peritoneal metastases, preferably from different areas, are biopsied, sent for histopathology and translational research, and their locations are documented and marked with clips to enable biopsies of the same locations during subsequent procedures.

Then, the ePIPAC setup is installed. A stainless steel brush electrode (Ionwand®, Alesi Surgical, Cardiff, United Kingdom) is inserted through a mini-trocar under direct vision, secured with its tip at least 2 cm away from other structures, and connected to its generator (Ultravision®, Alesi Surgical, Cardiff, United Kingdom). A nebuliser (CapnoPen®, Capnomed GmbH, Villingendorf, Germany) is inserted through one of the trocars and secured with its nozzle just inside the peritoneal cavity at a safe distance from visceral organs. The camera, inserted through the other trocar, is secured by a laparoscope holder in a way it permanently visualises the electrode and the nebuliser. The valve of the trocar connected to the $CO_2$ insufflation remains opened, whereas the other trocar is connected to a closed aerosol waste system (CAWS) with its valve closed. The CAWS consecutively consists of a smoke evacuation filter, a water seal drainage system, an infant-paediatric electrostatic microparticle filter, and the air waste system of the hospital. The preoperatively prepared syringe with oxaliplatin (92 mg/m$^2$ BSA diluted in a total volume of 150 ml 5% dextrose) is vented, placed in a standard

angiographic injector, and connected to the nebuliser with a saline-flushed high-pressure line protected by a plastic camera cover. A leak-free capnoperitoneum is ensured by zero-flow of $CO_2$. If necessary, the external fascia may be additionally sutured and Luer lock caps may be placed on balloon valves of trocars. The angiographic injector is installed at a flow rate of 30 ml/min and a maximum pressure of 200 pounds per square inch. Protective films are placed on the floor below the angiographic injector and around the patient. The angiographic injector is positioned above a chemotherapy waste bin. The peripheral venous line of the patient is connected to a 60 ml saline-containing syringe outside the operating room. Vital parameters of the patient, real-time videolaparoscopy, and a patient-aimed camera are displayed on three screens outside the operating room. The screen of the angiographic injector is positioned in front of the window of the operating room. General anaesthesia is ensured for at least another 40 minutes. A checklist is used to confirm that all aforementioned steps have been adequately taken. After completion of the checklist, the entire operating personnel leaves the operating room.

Oxaliplatin is injected through the nebuliser by remote controlled activation of the angiographic injector from outside the operating room. After complete formation of the oxaliplatin-containing aerosol in 5 minutes, the surgeon enters the operating room and turns on the Ultravision® generator, which results in electrostatic precipitation of the aerosol. The electrostatic field and the capnoperitoneum are maintained for another 25 minutes. During this phase, the patient and the procedure are monitored through the three screens and the window of the operating room. Drugs may be administered to the patient through the intravenous access outside the operating room if necessary.

After 25 minutes, the surgeon enters the operating room, turns off the Ultravision® generator, closes the trocar valve connected to the $CO_2$ insufflation, and opens the trocar valve connected to the CAWS. After complete evacuation of the aerosol, the electrode and the nebuliser are removed, the entire operating personnel enters the operating room, and a new capnoperitoneum is obtained. Ascites and peritoneal biopsies are collected for pharmacokinetic purposes. In case no bleeding or perforations are observed, instruments are removed and incisions are closed with absorbable sutures. All instruments and materials are directly disposed in chemotherapy waste bins and the operating room is cleaned according to existing HIPEC protocols. Any procedure-related mistake or difficulty during ePIPAC-OX is recorded directly after occurrence.

After ePIPAC-OX, patients are admitted to the general surgical ward. To relieve postoperative pain, patients receive paracetamol (1 g, four times daily), on-demand morphine, and 1 g of metamizole directly after the procedure. To minimise postoperative nausea and vomiting, patients receive perioperative dexamethasone and on-demand granisetron (1 mg, three times daily). Standard post-surgical clinical evaluations are performed a few hours after the procedure and on every postoperative

day. Blood is drawn for bone marrow, liver, and kidney functions, albumin, and C-reactive protein on every postoperative day. If the postoperative period is uneventful, patients are discharged on the first postoperative day. All body excretes are considered oxaliplatin-contaminated for up to five days after the procedure.

Dose reduction, prohibited and permitted concomitant care, and strategies to improve adherence are not specified *a priori*, but left to the discretion of the treating physician. ePIPAC-OX is repeated until clinical progression, radiological progression (Response Evaluation Criteria In Solid Tumours or at physician's discretion in case of non-measurable disease), macroscopic progression (i.e. ascites volume, PCI), unacceptable toxicity, physician's decision to discontinue, or at patient's request to discontinue. In patients who develop systemic metastases, continuation of ePIPAC-OX can only be considered if the patient has no systemic palliative treatment options and stable peritoneal disease.

Outpatient evaluations

One week after each ePIPAC-OX, patients undergo clinical evaluation by phone. Four weeks after each ePIPAC-OX, patients undergo radiological evaluation (i.e. thoracoabdominal CT, diffusion-weighted magnetic resonance imaging [DW-MRI]), biochemical evaluation (i.e. bone marrow, liver, and kidney functions, albumin, C-reactive protein, tumour markers), and clinical evaluation.

Questionnaires

Patients are asked to complete EQ-5D-5L, QLQ-C30, and QLQ-CR29 at baseline and one and four weeks after each ePIPAC-OX.[51-53] iMTA Productivity Cost Questionnaire (PCQ) and iMTA Medical Consumption Questionnaire (MCQ) are sent to the patients at baseline and four weeks after each ePIPAC-OX (PCQ) and each second ePIPAC-OX (MCQ).[54,55]

Pharmacokinetics

Blood is collected during and after the first three procedures in each patient. Four ml of whole blood is drawn and collected in heparin tubes before ePIPAC-OX and at 5, 10, 20, 30, 60, 120, 240, 360, and 1080 minutes after injection of oxaliplatin. After immediate centrifuging, an aliquot of plasma is stored at -80°C until analysis. Another aliquot of 1 ml of plasma is centrifuged through an ultrafiltration membrane and stored at -80°C until analysis. Urine, ascites, peritoneal metastases, and normal peritoneum are collected during and after all procedures. Four ml of urine is collected in urinalysis tubes before ePIPAC-OX and on the first postoperative day. These are stored at -20°C until analysis. After discharge, patients are asked to collect four ml of urine in urinalysis tubes on the third, fifth, and seventh postoperative day, and to store these specimens at their home address at -20°C until analysis. After electrostatic precipitation of the aerosol, the surgeon aspirates a few ml of ascites and biopsies

two peritoneal metastases and two pieces of normal peritoneum, preferably from different locations. These are collected in aliquots and directly stored at -80°C until analysis. Concentrations of oxaliplatin are measured by using atomic absorption spectrophotometry.

Translational research

Before each ePIPAC-OX, 20 ml of blood is drawn and collected in 10 ml Cell-free DNA BCT tubes (Streck, La Vista, NE, USA). According to the manufacturer's instructions, these tubes are sent to a central lab for isolation and storage (-80°C) of plasma and cell pellet. Collected ascites or saline is centrifuged twice (5 minutes, 420 g, zero break) under sterile conditions. The supernatant is snap frozen and stored at -80°C for further analysis on soluble components. The cell pellet is suspended in organoid culture medium at 4°C for transport and further work up. Of each collected PM, three parts are snap frozen and stored at -80°C for sequencing analysis.

**Outcomes**

An assessment schedule is presented in *Table 1*. The primary outcome is the number of patients with major toxicity, defined as grade ≥3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0,[56] up to four weeks after the last ePIPAC-OX. Secondary outcomes are:

- the environmental safety of ePIPAC-OX, based on air and surface concentrations of oxaliplatin during the first three procedures, measured by atomic absorption spectrophotometry;
- procedure-related characteristics of ePIPAC-OX (e.g. intraoperative complications, amount of adhesions, procedure-related mistakes and difficulties, operating time);
- the number of procedures in each patient and reasons for discontinuation;
- minor toxicity, defined as grade ≤2 according to CTCAE v4.0,[56] up to four weeks after the last ePIPAC-OX;
- major and minor postoperative complications, defined as grade ≥3 and grade ≤2 according to Clavien-Dindo,[57] respectively, up to four weeks after the last ePIPAC-OX;
- hospital stay, defined as the number of days between ePIPAC-OX and initial discharge;
- readmissions, defined as any hospital admission after initial discharge, up to four weeks after the last ePIPAC-OX;
- radiological tumour response, based on central review of thoracoabdominal CT and DW-MRI at baseline and four weeks after each ePIPAC-OX, performed by two independent radiologists (JN, MLH) blinded to clinical outcomes (classification is not defined *a priori*);

- histopathological tumour response, based on central review of collected peritoneal biopsies during each ePIPAC-OX, performed by two independent pathologists (e.g. CJRH) blinded to clinical outcomes by using the Peritoneal Regression Grading Score;[58]
- macroscopic tumour response, based on PCI and ascites volume during each ePIPAC-OX;
- biochemical tumour response, based on tumour markers measured at different time points (Table 1);
- cytological tumour response, based on collected ascites or peritoneal washing cytology during each ePIPAC-OX;
- quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) at different time points (Table 1);
- costs, derived from the Dutch costing guidelines for health care research at the time of analysis, based on case report forms, hospital information systems, and questionnaires (iMTA PCQ, iMTA MCQ) at different time points (Table 1);
- progression-free survival, defined as the time between enrolment and clinical, radiological, or macroscopic progression, or death;
- overall survival, defined as the time between enrolment and death;
- the pharmacokinetics of oxaliplatin during and after ePIPAC-OX.

**Sample size**

Given the absence of evident clinical endpoint in this patient category, the investigators pragmatically determined the sample size of this exploratory study. The investigators agreed that 60 procedures are required to explore the feasibility, safety, tolerability, and preliminary efficacy of repetitive ePIPAC-OX in this setting. Since the expected mean number of procedures is three per patient,[36] the initial sample size is determined at 20 patients. This pragmatically determined sample size is approved by the central ethics committee. Enrolled patients who do not undergo a first ePIPAC-OX (e.g. systemic metastases on baseline radiology, non-access, resectable disease) are replaced to enrol 20 patients who receive at least one ePIPAC-OX.

**Recruitment**

The study started in October 2017 and is currently enrolling patients. The investigators anticipate that 20 patients will be enrolled within a maximum of three years. Strategies for achieving adequate participant enrolment are not defined *a priori.*

**Data collection and data management**

Outcomes are collected in all patients who receive at least one ePIPAC-OX. All baseline characteristics and clinical outcomes are prospectively collected and entered in an ISO 27001 certified central study database (De Research Manager, Deventer, Netherlands) with study-specific electronic case report forms by a local investigator in each study centre (RJL, ECEW). This ISO 27001 certified system ensures adequate data integrity, including data coding, security, and storage. Questionnaires (quality of life, costs), peritoneal biopsies (histopathological response), and radiological examinations (radiological response) are collected by the coordinating investigator (KPR) throughout the study and centrally analysed after study completion. Plans to promote data quality, participant retention, and complete follow-up are not specified *a priori.*

**Statistical methods**

Repetitive continuous outcomes (e.g. quality of life, operating time) are analysed by using the Wilcoxon signed-rank test, the paired samples t-test, the Friedman test, or repeated measurements analysis of variance where appropriate. Repetitive categorical outcomes (e.g. intraoperative complications, postoperative complications) are analysed by using the McNemar test, the Wilcoxon signed-rank test, the Cochran's Q test, or generalised estimating equations where appropriate. Time-to-event variables (i.e. overall and progression-free survival) are analysed and displayed by using the Kaplan-Meier method. Other outcomes are analysed by using descriptive statistics. All statistical tests are two-sided and $p<0.05$ is considered statistically significant.

**Data monitoring**

Interim analyses are performed after 8 and 20 procedures. The study is terminated after these interim analyses if CTCAE grade ≥3 toxicity, directly related to ePIPAC-OX, is observed after ≥4 and ≥10 procedures. Furthermore, the study is directly terminated if more than one CTCAE grade 5 toxicity, directly related to ePIPAC-OX, occurs during the study. The coordinating investigator and the principal investigator (IHJTH) have access to these interim results. The principal investigator makes the decision to terminate or continue the study. The investigators decided that a data monitoring committee is not needed given the clear stopping rules and the low expected toxicity of repetitive ePIPAC-OX.

**Harms**

Local investigators report all serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) to the coordinating investigator within 24 hours. The coordinating investigator reports SAEs/SUSARs to the ethics committee within seven days of first knowledge for lethal or life threatening SAEs/SUSARs, and within fifteen days for other SAEs/SUSARs. The time window for reporting SAEs/SUSARs is from enrolment up to four weeks after the last ePIPAC-OX.

**Auditing**

The study is audited by independent qualified monitors of Clinical Trial Centre Maastricht (Maastricht, Netherlands) as a high-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centres. This means that study centres are audited at least three times per year, depending on enrolment, with 100% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification, and SAEs/SUSARs.

**Patient and public involvement**

Patients were not involved in the study design before the start of the study. Shortly after the start of the study, the investigators presented the study design to a patient advisory group. Majors topics of discussion were the rationale for the study, outcome parameters, recruitment strategies, the patient information sheet, dissemination strategies, and the potential risks, benefits, and burden of participation from the patient's perspective. The patient advisory group supported the presented study design. Although the patient advisory group is not involved in the recruitment and the conduct of the study, they will be involved in plans to disseminate the study results to relevant patient groups.

## ETHICS AND DISSEMINATION

**Research ethics approval**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, R17.038), the Dutch competent authority (Centrale Commissie Mensgebonden Onderzoek, NL60405.100.17), and the institutional review boards of Catharina Hospital (Lokale Uitvoerbaarheidscommissie, CZE-2017.50) and St. Antonius Hospital (R&D, L18.021).

**Protocol amendments**

Important protocol modifications are communicated to the ethics committee, the Dutch competent authority, the institutional review boards of both study centres, all investigators, and trial registries.

**Consent or assent**

Written informed consent is obtained by local investigators at the outpatient clinic of the study centres. Patients are given the possibility to give separate permission for undergoing DW-MRI and for storage of specimens for translational research.

**Confidentiality**

Personal information about potential and enrolled patients is collected, shared, and maintained according to the Dutch law (Wet Bescherming Persoonsgegevens).

**Declaration of interests**

The investigators declare no competing interests. The funders have no role in the study design, in writing the report, or in the decision to submit the report for publication.

**Access to data**

All investigators have access to the final datasets, without contractual agreements that limit such access.

**Ancillary and post-study care**

The sponsor (Catharina Hospital, Eindhoven, Netherlands) is insured to provide cover for patients who suffer harm from study participation. After discontinuation of ePIPAC-OX, patients receive standard palliative treatment for unresectable metastatic colorectal cancer according to Dutch guidelines.[4]

**Dissemination policy**

Results of the study are personally communicated to participants and intended for publication in peer-reviewed medical journals and for presentation to patients, healthcare professionals, and other stakeholders. Authorship eligibility guidelines for the main manuscript and manuscript of side studies are not defined *a priori*. The full protocol and Dutch informed consent forms are, or will become, available upon reasonable request.

## DISCUSSION

To the knowledge of the investigators, this is the first study that prospectively explores the feasibility, safety, tolerability, costs, preliminary efficacy, and pharmacokinetics of repetitive ePIPAC-OX as a palliative monotherapy in patients with isolated unresectable colorectal PM.

This study protocol has potential limitations. The broad eligibility criteria could lead to a heterogeneous cohort with various primary tumours (i.e. colon, appendix) and histologies (e.g. signet ring cell carcinoma, high-grade appendiceal mucinous neoplasm) in different lines of treatment. This clinical heterogeneity could impede the interpretation of survival outcomes. However, survival outcomes are not the major focus of this study. Enrolment is also allowed for patients with an unresected primary tumour and patients who did not receive prior palliative systemic therapy. In these patients, administration of repetitive ePIPAC-OX as a monotherapy could theoretically lead to undertreatment and subsequent systemic progression or progression of the primary tumour.

However, it is thought that the frequent clinical and radiological evaluations detect such progression in a sufficiently early stage. Moreover, patients need to be informed by a medical oncologist about the potential consequences of postponing or discontinuing their standard palliative treatment prior to enrolment. Conclusively, the investigators feel that these controlled circumstances justify enrolment of these patients.

This study protocol has potential strengths. All endpoints are predefined and prospectively assessed. Independent 100% auditing ensures an appropriately conducted study and high-quality data. Unlike other studies, repetitive ePIPAC-OX is administered as a palliative monotherapy in all patients. Thereby, outcomes are not influenced by concurrent palliative systemic therapy. Extensive assessment of quality of life provides insights in the tolerability of ePIPAC-OX from a patient perspective, whereas pharmacokinetic analyses provide the first insights in the systemic absorption repetitive ePIPAC-OX. Insights in the costs of ePIPAC-OX could be valuable for policy makers and other teams that aim to implement this procedure or apply for scientific grants, while translational side studies may open new avenues for research.

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None.

**AUTHORS' CONTRIBUTIONS**

KPR is the coordinating investigator. RJL, AMJT, GMC, JWAB, and SWN are the local investigators of the first study centre. ECEW, TJMK, ML, MJW, and DB are the local investigators of the second study centre. RT performs the pharmacokinetic analyses. MJD is the study pharmacologist supervising the pharmacokinetic analyses. JN and MJL are the study radiologists performing the central radiological review. CJRH is the study pathologist performing the central histopathological review. HJS is the study anaesthesiologist who developed the protocols for perioperative care. IE and RJAF are responsible for translational research on blood. AC and OK are responsible for translational research on ascites and PM. IHJTH is the principal investigator. KPR, RJL, and IHJTH made substantial contributions to

conception and design of the study, drafted the protocol, and drafted the manuscript. ECEW, TJMK, HJS, RT, MJD, JN, MJL, CJRH, IE, RJAF, AC, OK, ML, AMJT, GMC, JWAB, MJW, DB, and SWN made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. KPR, RJL, ECEW, TJMK, HJS, RT, MJD, JN, MJL, CJRH, IE, RJAF, AC, OK, ML, AMJT, GMC, JWAB, MJW, DB, SWN, and IHJTH gave final approval of the version to be published and agree to be accountable for all aspects of the work.

**DATA SHARING**

All data relevant to the study will be included in the article or uploaded as supplementary information. This will not include patient identifiable data.

**FUNDING**

This study is supported by Catharina Research Foundation (grant number: 2017-5) and St. Antonius Research Foundation (grant number: 17.4).

**COMPETING INTERESTS**

None declared.

**ETHICAL APPROVAL**

This study is approved by an ethics committee (MEC-U, Nieuwegein, Netherlands, number R17.038), the Dutch competent authority (CCMO, The Hague, Netherlands), and the institutional review boards of both study centres.

**DATA SHARING**

Not applicable.

**PATIENT CONSENT**

Not applicable.

**PROTOCOL VERSION**

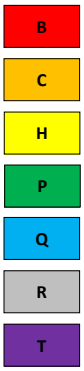
Version 6, 10 January 2019

**FIGURE TITLES**

**Figure 1**. Flow chart of the CRC-PIPAC study

**FIGURE LEGENDS**

Figure 1. *ePIPAC-OX* electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin;




Bloods (organ functions, tumour markers)

Cytology (ascites or peritoneal washing with saline)

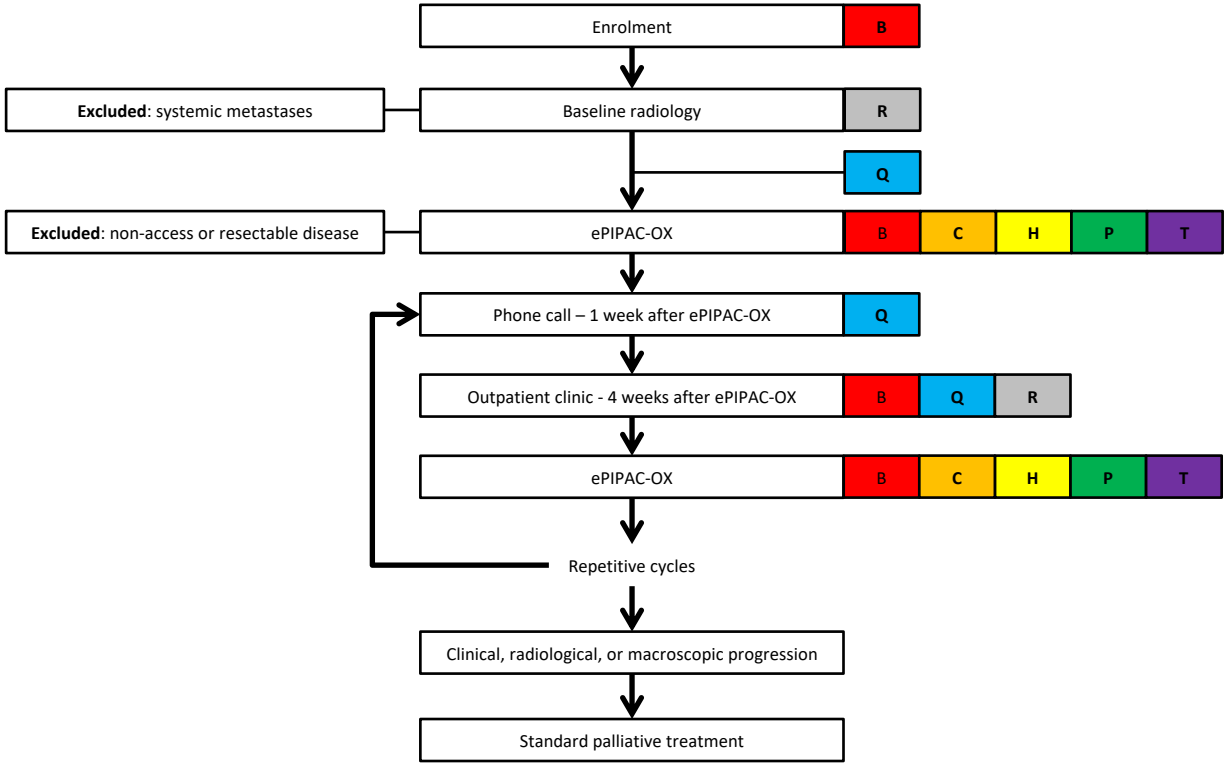
Histopathology (peritoneal biopsies)

Pharmacokinetics (blood, urine, ascites, PM, normal peritoneum)

Questionnaires (quality of life, costs)

Radiology (thoracoabdominal CT, diffusion-weighted MRI)

Translational research (blood, ascites, PM)


Enrolment
B
Excluded: systemic metastases
Baseline radiology
R
Q
Excluded: non-access or resectable disease
ePIPAC-OX
B
C
H
P
T
Phone call – 1 week after ePIPAC-OX
Q
Outpatient clinic - 4 weeks after ePIPAC-OX
B
Q
R
ePIPAC-OX
B
C
H
P
T
Repetitive cycles
Clinical, radiological, or macroscopic progression
Standard palliative treatment

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | **1** |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | **2** |
| | 2b | All items from the World Health Organization Trial Registration Data Set | **Entire manuscript** |
| Protocol version | 3 | Date and version identifier | **20** |
| Funding | 4 | Sources and types of financial, material, and other support | **20** |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | **1-2, 19-20** |
| | 5b | Name and contact information for the trial sponsor | **1** |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | **14** |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | **Entire manuscript** |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | **3-5** |
| | 6b | Explanation for choice of comparators | **Not applicable** |
| Objectives | 7 | Specific objectives or hypotheses | **5** |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | **6** |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | **6** |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | **6** |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | **6-11** |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | **9** |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | **9** |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | **9** |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | **11-12** |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | **Table 1, Figure 1** |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | **12** |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | **12** |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | **Not applicable** |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | **Not applicable** |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | **Not applicable** |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | **Not applicable** |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | **Not applicable** |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | **12** |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | **12** |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | **12** |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | **13** |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | **Not applicable** |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | **12** |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | **13** |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | **13** |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | **13** |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | **13** |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | **14** |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | **14** |

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|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | **14** |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | **14** |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | **14** |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | **14** |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | **14** |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | **15** |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | **15** |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | **15** |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | **15** |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | **Available upon request** |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | **10** |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.