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First-line palliative systemic therapy alternated with electrostatic pressurized intraperitoneal aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases: protocol of a multicenter, single-arm, phase II study (CRC-PIPAC-II).

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1 Title Page

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| 2 | THUE |

- 3 First-line palliative systemic therapy alternated with electrostatic pressurized intraperitoneal
- 4 aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases:
- 5 protocol of a multicenter, single-arm, phase II study (CRC-PIPAC-II).
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| 50 51 52 53 54 55 56 57 58 59 60 | 20 | |
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1 Abstract

Introduction: Despite its increasing use, first-line palliative systemic therapy alternated with
electrostatic pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX), also
known as first-line bidirectional therapy, has never been prospectively investigated in patients with
colorectal peritoneal metastases (CPM). As a first step to address the present evidence gap, this
study aims to assess the safety, feasibility, anti-tumor activity, patient-reported outcomes, costs, and
systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated unresectable
CPM.

Methods and analysis: In this single-arm, phase II study in two Dutch tertiary referral centers, 20 patients are enrolled. Key eligibility criteria are a good performance status, pathologically proven isolated unresectable CPM, no previous palliative systemic therapy for colorectal cancer, no (neo)adjuvant systemic therapy <6 months prior to enrolment, and no previous PIPAC. Patients receive three cycles of bidirectional therapy. Each cycle consists of six weeks of first-line palliative systemic therapy at the medical oncologists' decision (CAPOX-bevacizumab, FOLFOX-bevacizumab, FOLFIRI-bevacizumab, or FOLFOXIRI-bevacizumab) followed by ePIPAC-OX (92 mg/m²) with an intraoperative bolus of intravenous leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²). Study treatment ends after the third ePIPAC-OX. The primary outcome is the number of patients with – and procedures leading to – grade \geq 3 adverse events (Common Terminology Criteria for Adverse Events v5.0) up to four weeks after the last procedure. Key secondary outcomes include the number of bidirectional cycles in each patient, treatment-related characteristics, grade ≤ 2 adverse events, tumor response (histopathological, cytological, radiological, biochemical, macroscopic, ascites), patient-reported outcomes, systemic pharmacokinetics of oxaliplatin, costs, progression-free survival, and overall survival.

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Ethics and dissemination: This study is approved by the Dutch competent authority, a medical ethics 1

2 committee, and the institutional review boards of both study centers. Results will be submitted for

3 publication in peer-reviewed medical journals and presented to patients and healthcare

4 professionals.

5 Trial registration number: Netherlands Trial Register: NL8303.

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| 3 | 1 | Strengths and limitations of this study |
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| 12 | 4 | with pressurized intrapentoneal aerosol chemotherapy (oxaliplatin) for colorectal pentoneal |
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| 14 | 5 | metastases; |
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| 16 | 6 | - The present study includes a homogenous population of patients receiving first-line palliative |
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| 18 | 7 | treatment, which contrasts the heterogeneous populations in various lines of palliative |
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| 20 | 8 | treatment included in available studies on PIPAC-OX for colorectal peritoneal metastases; |
| 21 | | |
| 22 | 9 | - Besides clinical outcomes, the present study also analyzes important other outcomes such as |
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| 24 25 | 10 | patient-reported outcomes, costs, and the systemic pharmacokinetics of oxaliplatin; |
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| 20 | 11 | - Translational side studies of the present study may open new opportunities for research in |
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1 Introduction

The peritoneum is a common metastatic site in colorectal cancer and the presence of colorectal
peritoneal metastases (CPM) is characterized by a poor prognosis (1, 2). Most patients with CPM are
treated with palliative intent (3). When treated with systemic therapy, patients with CPM have a
shorter survival than patients with systemic metastases of colorectal cancer (4).

6 Theoretically, intraperitoneal chemotherapy could be an interesting palliative treatment option due 7 to a favorable peritoneum-plasma concentration ratio (5). However, the use of intraperitoneal 8 chemotherapy is limited by poor direct tumor penetration, inhomogeneous intraperitoneal drug 9 distribution, and dose-limiting local toxicity (6, 7). Pressurized intraperitoneal aerosol chemotherapy 10 (PIPAC) has been developed to overcome these limitations (8-11). PIPAC is a laparoscopic method for 11 the repetitive intraperitoneal administration of low-dose chemotherapy as a pressurized aerosol, 12 claiming enhanced tumor penetration, homogeneous intraperitoneal drug distribution, and low 13 toxicity in preliminary studies (8-11). The first clinical reports have suggested that PIPAC is feasible, 14 safe, and well tolerated in patients with peritoneal metastases of various primary tumors (12, 13). 15 Given these results, PIPAC is currently implemented in a rapidly increasing number of centers 16 worldwide (12, 14). In these centers, patients with CPM are generally treated with PIPAC with 17 oxaliplatin (92 mg/m2) every six to eight weeks, with or without concomitant systemic therapy (14). 18 Electrostatic precipitation of the aerosol is thought to enhance tissue penetration and is practiced in 19 several centers (15-17).

Previously, a multicenter, single-arm, phase II study (CRC-PIPAC) investigated the safety, feasibility,
anti-tumor activity, patient-reported outcomes (PROs), costs, and pharmacokinetics of repetitive
electrostatic PIPAC with oxaliplatin (ePIPAC-OX) as a palliative monotherapy in 20 patients with
isolated unresectable CPM in any line of palliative treatment (18).

24 Repetitive ePIPAC-OX could also be added to first-line systemic therapy in order to maximize

⁰ 25 intraperitoneal tumor response and eliminate systemic micrometastases. The combination of first-

line systemic therapy (including bevacizumab) and repetitive ePIPAC-OX, hereinafter referred to as first-line bidirectional therapy, is already offered to patients with isolated unresectable CPM in several PIPAC centers worldwide (14).

Despite its increasing use, the feasibility, safety, and anti-tumor activity of first-line bidirectional therapy have never been prospectively investigated in patients with isolated unresectable CPM in clinical trials with predefined eligibility criteria, interventions, and outcomes. Moreover, nothing is known about PROs and costs of – and the systemic pharmacokinetics of oxaliplatin during – first-line bidirectional therapy in this setting. As a first step to address this evidence gap, the present multicenter, single-arm, phase 2 study (CRC-PIPAC-II) aims to assess the safety, feasibility, anti-tumor activity, PROs, costs, and systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated unresectable CPM.

| 1 2 3 | | |
|----------------------|----|--|
| 4 5 | 1 | Methods and analysis |
| 6 7 8 | 2 | Setting |
| 9 10 11 | 3 | This study is performed in two Dutch tertiary referral centers for the surgical treatment of CPM. |
| 12 13 14 | 4 | Eligibility criteria |
| 15 16 17 | 5 | Eligibility criteria are: |
| 17 18 19 | 6 | ≥18 years of age; |
| 20 21 | 7 | World Health Organization performance status of 0-1; |
| 22 23 24 | 8 | - Histologically or cytologically proven peritoneal metastases of a colorectal or appendiceal |
| 25 26 | 9 | carcinoma; |
| 20 27 28 | 10 | - Unresectable disease, based on abdominal CT, laparoscopy, or laparotomy; |
| 29 30 | 11 | Adequate organ functions (hemoglobin ≥5.0 mmol/L, neutrophils ≥1.5×10⁹/L, platelets |
| 31 32 33 | 12 | ≥100×10 ⁹ /L, serum creatinine <1.5 × upper limit of normal [ULN], creatinine clearance |
| 34 35 | 13 | ≥30 mL/min, and liver transaminases <5 × ULN); |
| 36 37 | 14 | No symptoms of gastrointestinal obstruction; |
| 38 39 | 15 | - No systemic metastases; |
| 40 41 42 | 16 | - No contraindications for the planned systemic therapy or laparoscopy; |
| 43 44 | 17 | - No previous PIPAC; |
| 45 46 | 18 | No previous palliative systemic therapy for colorectal cancer; |
| 47 48 49 | 19 | - No (neo)adjuvant systemic therapy for colorectal cancer ≤6 months prior to enrolment; |
| 50 51 | 20 | Interventions and procedures |
| 53 54 | 21 | The study flowchart is shown in Figure 1. The schedule of enrolment, interventions, and assessments |
| 55 56 | 22 | is shown in <i>Table 1</i> . |
| 57 58 59 60 | 23 | |

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| 1 | All patients receive three cycles of first-line bidirectional therapy. Each cycle consists of six weeks of |
|----|--|
| 2 | first-line systemic therapy followed by one ePIPAC-OX. Study treatment ends after the third ePIPAC- |
| 3 | OX in all patients. |
| 4 | First-line palliative systemic therapy |
| 5 | The treating medical oncologist determines which of the following first-line regimens will be used: |
| 6 | - Two three-weekly cycles of CAPOX-bevacizumab (intravenous [IV] oxaliplatin [130 mg/m ² |
| 7 | body-surface area (BSA)] on day 1, oral capecitabine [1000 mg/m ² BSA] twice daily on days |
| 8 | 1-14, IV bevacizumab [7.5 mg/kg body weight] on day 1), or; |
| 9 | - Three two-weekly cycles of FOLFOX-bevacizumab (IV oxaliplatin [85 mg/m ² BSA] on day 1, |
| 10 | IV leucovorin [400 mg/m ² BSA] on day 1, IV bolus/continuous 5-fluorouracil [400/2400 |
| 11 | mg/m ² BSA] on days 1-2, IV bevacizumab [5 mg/kg body weight] on day 1), or; |
| 12 | - Three two-weekly cycles of FOLFIRI-bevacizumab (IV irinotecan [180 mg/m ² BSA] on day 1, |
| 13 | IV leucovorin [400 mg/m² BSA] on day 1, IV bolus/continuous 5-fluorouracil [400/2400 |
| 14 | mg/m ² BSA] on days 1-2, IV bevacizumab [5 mg/kg body weight] on day 1), or; |
| 15 | - Three two-weekly cycles of FOLFOXIRI-bevacizumab (IV oxaliplatin [85 mg/m ² BSA] on day 1, |
| 16 | IV irinotecan [165 mg/m ² BSA] on day 1, IV leucovorin [400 mg/m ² BSA] on day 1, IV |
| 17 | continuous 5-fluorouracil [2400 mg/m ² BSA] on days 1-2, IV bevacizumab [5 mg/kg body |
| 18 | weight] on day 1). |
| 19 | These regimens are based on the ESMO guideline for the treatment of metastatic colorectal cancer |
| 20 | (19). Dose reductions, switches between allowed regimens, and management of toxicity are left to |
| 21 | the discretion of the treating medical oncologist. Dihydropyrimidine dehydrogenase status is |
| 22 | assessed by genotyping before the first administration of systemic therapy, and dosages of |
| 23 | capecitabine or 5-fluorouracil are modified accordingly (20). |
| | |

ePIPAC-OX

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| 1 | The procedure has been extensively described in the protocol of the CRC-PIPAC study (18). In |
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| 2 | summary, after creating a 12 mmHg pneumoperitoneum with two balloon trocars using an open |
| 3 | introduction, an explorative laparoscopy is performed with adhesiolysis if needed to create enough |
| 4 | working space. If ePIPAC-OX seems feasible, leucovorin (20 mg/m ² BSA in 10 minutes) and 5- |
| 5 | fluorouracil (400 mg/m ² BSA in 15 minutes) are administered intravenously, since these drugs are |
| 6 | thought to increase the efficacy of oxaliplatin (21, 22). Meanwhile, ascites (or peritoneal lavage using |
| 7 | saline if ascites is absent) is evacuated and sent for cytology, the peritoneal cancer index (PCI) and |
| 8 | ascites volume are registered (23), and three peritoneal metastases from different intraabdominal |
| 9 | areas (if possible) are biopsied and sent for histopathology. Biopsy locations are marked with clips to |
| 10 | enable similar biopsies during subsequent procedures. |
| | |
| 11 | Then, after building the PIPAC setup and ensuring a leak-free pheumoperitoneum, oxaliplatin (92 |
| 12 | mg/m ² BSA [maximum 184 mg] diluted to a total volume of 150 mL in a 5% dextrose solution) is |
| 13 | aerosolized into the peritoneal cavity through a nebulizer (CapnoPen, Capnomed GmbH, |
| 14 | Villingendorf, Germany) using an angiographic injector at a maximum pressure of 200 psi and a flow |
| 15 | of 30 mL/min, all according to internationally used protocols (14). After formation of the aerosol in 5 |
| 16 | minutes, it is electrostatically precipitated for another 25 minutes using Ultravision technology (Alesi |
| 17 | Surgical, Cardiff, United Kingdom) as described by others (16), as this could enhance tumor |
| 18 | penetration of oxaliplatin (15). |
| 19 | Then, the peritoneal cavity is exsufflated through a closed aerosol waste system, a new |
| 20 | pneumoperitoneum is obtained to explore if complications have occurred, instruments are removed, |
| 21 | and incisions are closed. |
| 22 | Postoperatively, patients receive analgesics and anti-emetics according to local protocol. Standard |
| | |
| 23 | postoperative clinical evaluations are performed a few hours after ePIPAC-OX and on every |
| 24 | postoperative day until discharge. Postoperative laboratory tests are only performed if indicated. |
| 25 | Patients are intentionally discharged on the day of ePIPAC-OX or on the first postoperative day. |

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Evaluations 1

| 2 | Before each cycle of systemic therapy, patients undergo clinical and biochemical (i.e. tumor markers, |
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| 3 | organ functions) evaluation by the treating medical oncologist. Before each ePIPAC-OX, patients |
| 4 | undergo clinical evaluation by the treating surgeon. During and shortly after ePIPAC-OX, patients |
| 5 | undergo macroscopic (i.e. peritoneal cancer index [PCI] (23)), ascites volume), histopathological (i.e. |
| 6 | peritoneal regression grading score [PRGS] of peritoneal biopsies (24,25)) and cytological evaluation. |
| 7 | Radiological evaluation is performed one week before the second ePIPAC-OX and four weeks after |
| 8 | the third ePIPAC-OX (26). Patients are discussed by a multidisciplinary tumor board after the second |
| 9 | and third ePIPAC-OX. |
| 10 | After completing six weeks of systemic therapy, the subsequent ePIPAC-OX is planned within one to |
| 11 | four weeks thereafter. After ePIPAC-OX, systemic therapy is restarted one to four weeks |
| 12 | postoperatively. Study treatment is discontinued in case of physician-determined disease |
| 13 | progression, unacceptable toxicity, or physician's or patient's decision to discontinue participation. |
| | |
| 14 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according |
| 14 15 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). |
| 14 15 16 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling |
| 14 15 16 17 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and |
| 14 15 16 17 18 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: |
| 14 15 16 17 18 19 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal |
| 14 15 16 17 18 19 20 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal oxaliplatin injection; |
| 14 15 16 17 18 19 20 21 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal oxaliplatin injection; - CAPOX-bevacizumab: at t=0, t=0.5, t=1, and t=2 hours and t=3 weeks after intravenous |
| 14 15 16 17 18 19 20 21 21 22 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal oxaliplatin injection; - CAPOX-bevacizumab: at t=0, t=0.5, t=1, and t=2 hours and t=3 weeks after intravenous administration of oxaliplatin; |
| 14 15 16 17 18 19 20 21 22 23 | Study treatment ends after the third ePIPAC-OX, after which patients receive standard care according to the Dutch national guideline (27). Pharmacokinetic sampling Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal oxaliplatin injection; - CAPOX-bevacizumab: at t=0, t=0.5, t=1, and t=2 hours and t=3 weeks after intravenous administration of oxaliplatin; - FOLFOX-bevacizumab or FOLFOXIRI-bevacizumab: at t=0, t=0.5, t=1, t=2, t=48 hours and t=2 |

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1 After direct centrifuging, a plasma aliquot is stored at -80°C until analysis. To obtain the free fraction 2 of oxaliplatin, a second 1 mL plasma aliquot is centrifuged through an ultrafiltration membrane and 3 stored at -80°C until analysis. Oxaliplatin concentrations are measured using atomic absorption 4 spectrometry performed on a Thermo Fisher Solaar ICE 3500 graphite-furnace spectrophotometer 5 with Zeeman correction (Thermo Fisher Scientific, Bremen, Germany). 6 Translational research 7 Two 10 mL cell-free DNA BCT tubes (Streck, La Vista, Nebraska, USA) are used to collect 20 mL of 8 whole blood at baseline and before each ePIPAC-OX. Tubes are sent to a central laboratory for 9 isolation and storage (-80°C) of plasma and cell pellet according to the manufacturer's instructions. 10 Collected ascites or peritoneal lavage is centrifuged twice (5 minutes, 420 g, zero break) under sterile 11 conditions. The supernatant is snap frozen and stored (-80°C) until further analysis. The cell pellet is 12 suspended into an organoid culture medium at 4°C for transport and further preparation. 13 Outcomes The primary outcome is the number of patients with – and procedures leading to – grade \geq 3 adverse 14 15 events according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (primary 16 classification) and Clavien-Dindo (secondary classification) up to four weeks after the last ePIPAC-OX 17 (28, 29). 18 Secondary outcomes are: 19 The number of completed cycles of bidirectional therapy in each patient and reasons for discontinuation; 20 21 Characteristics of systemic therapy (e.g. administered regimens, number of completed 22 cycles, dose reductions); Characteristics of ePIPAC-OX (e.g. intraoperative complications, operating time); 23

| 3 1 | 1 | - | The number of patients with – and procedures leading to – grade ≤2 adverse events |
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| 5 | 2 | | according to the CTCAE v5.0 (primary classification) and Clavien-Dindo (secondary |
| 0 7 8 | 3 | | classification) up to four weeks after the last ePIPAC-OX (28, 29); |
| 9 10 | 4 | _ | Hospital stay, defined as the number of days between ePIPAC-OX and initial discharge: |
| 11 | · | | |
| 12 13 | 5 | - | Readmissions, defined as any unplanned hospital admission after initial discharge up to four |
| 14 15 | 6 | | weeks after the last ePIPAC-OX; |
| 16 17 | 7 | - | Radiological tumor response, centrally evaluated by two assessors blinded to clinical |
| 18 19 | 8 | | outcomes, using the Response Evaluation Criteria In Solid Tumors v1.1 and the radiological |
| 20 21 22 | 9 | | PCI (26) ; |
| 22 23 24 | 10 | - | Histopathological tumor response, centrally evaluated by two assessors blinded to clinical |
| 25 26 | 11 | | outcomes, using the four tier PRGS of collected peritoneal biopsies during each ePIPAC-OX |
| 27 28 | 12 | | (24, 25); |
| 29 30 | 13 | - | Macroscopic tumor response, based on the PCI during each ePIPAC-OX; |
| 32 33 | 14 | - | Ascites response, based on ascites volume during each ePIPAC-OX; |
| 34 35 | 15 | - | Biochemical tumor response, based on carcinoembryonic antigen levels at baseline and |
| 36 37 | 16 | | before each ePIPAC-OX; |
| 38 39 | 17 | - | Cytological tumor response, based on the presence or absence of malignant cells in ascites |
| 40 41 42 | 18 | | or peritoneal lavage collected during each ePIPAC-OX; |
| 43 44 | 19 | - | PROs, based on the EQ-5D-5L (30), EORTC QLQ-C30 (31), and EORTC QLQ-CR29 (32) |
| 45 46 | 20 | | questionnaires at baseline, one week before the first ePIPAC-OX, and one and four weeks |
| 47 48 | 21 | | after each ePIPAC-OX; |
| 49 50 | 22 | - | The bioavailability of oxaliplatin, based on the systemic pharmacokinetics of oxaliplatin |
| 52 53 | 23 | | during and after one intravenous administration, as well as during and after one ePIPAC-OX; |
| 54 55 | 24 | - | Costs, derived from the Dutch cost guideline for healthcare research at the time of analysis, |
| 56 57 | 25 | | based on hospital information systems, case report forms, and the iMTA Productivity cost |
| 58 59 60 | | | |

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| 60 | 24 | explorative nature of the analyzed outcomes, basic statistical methods are not defined a priori. These |
| 58 59 | 23 | presented as number (percentage). Due to the single-arm design of the present study and the |
| 55 56 57 | 22 | Continuous data are presented as a median with (interquartile) range and categorical data are |
| 52 53 54 | 21 | Statistical methods |
| 50 51 52 | 20 | optimizes data quanty by standardized data entry, counig, security, and storage. |
| 48 49 | 20 TA | ontimizes data quality by standardized data ontry coding socurity and storage |
| 46 47 | 10 | study database (De Research Manager, Deventer, the Netherlands). This ISO 27001 certified system |
| 44 45 | 10 | study center using standardized electronic case report forms linked to an ISO 27001 certified central |
| 41 42 43 | 17 | baseline characteristics and outcomes are prospectively collected by a local investigator in each |
| 39 40 41 | 16 | Outcomes are collected in all patients who complete at least one cycle of bidirectional therapy. All |
| 36 37 38 | 15 | Data collection and data management |
| 34 35 | 14 | maximum of three years. Strategies for achieving adequate patient accrual are not defined a priori. |
| 31 32 33 | 13 | The first patient was enrolled in February 2020. The investigators expect to complete accrual within a |
| 29 30 | 12 | Recruitment |
| 26 27 28 | 11 | of 20 patients who receive at least one cycle of bidirectional therapy. |
| 24 25 | 10 | Enrolled patients who are unable to receive the first ePIPAC-OX are replaced to enrol a total number |
| 22 23 | 9 | feasibility, and anti-tumor activity of the study treatment, similar to the CRC-PIPAC study (18). |
| 20 21 | 8 | a pragmatically determined sample size of 20 patients as a sufficient number to explore the safety, |
| 10 17 18 19 | 7 | Given the absence of data to guide a sample size calculation, the central ethics committee approved |
| 14 15 16 | 6 | Sample size |
| 11 12 13 | 5 | - Overall survival, defined as the time between enrolment and death. |
| 9 10 | 4 | disease progression or death; |
| 7 8 | 3 | - Progression-free survival, defined as the time between enrolment and physician-determined |
| 5 6 | 2 | four weeks after each ePIPAC-OX; |
| 3 4 | 1 | questionnaire (33) and the iMTA Medical consumption questionnaire (34) at baseline and |

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methods will be defined before data analysis. Time-to-event variables, such as progression-free and
 overall survival, are analyzed and presented using the Kaplan-Meier method.

3 Data monitoring

Interim analyses are performed four weeks after the fifth, fifteenth, thirtieth and forty-fifth 4 5 procedure. The study is terminated, or temporarily halted for evaluation and potential adaption of 6 the study protocol, if more than three CTCAE grade 3 or 4 adverse events occur or more than one 7 CTCAE grade 5 adverse event occur that are considered directly related to ePIPAC-OX. Adverse 8 events related to systemic therapy are not included in the stopping rules. If the study is terminated, 9 enrolled patients do not receive any further ePIPAC-OX. The principal investigators (IHJTH and DB) 10 have access to the interim results and make the final decision to terminate or continue the study. 11 Given the long term experience with the study drugs and low expected toxicity from PIPAC (given the 12 experience from the CRC-PIPAC study), the investigators have agreed that a data monitoring 13 committee is not indicated for this study.

14 <u>Harms</u>

All serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) that
occur from enrolment up to four weeks after the last ePIPAC-OX are reported by local investigators
to the coordinating investigator within 24 hours. The coordinating investigator reports these
SAEs/SUSARs to the central ethics committee within 7 days of first knowledge for lethal or lifethreatening SAEs/SUSARs, and within 15 days for other SAEs/SUSARs.

20 <u>Auditing</u>

- 21 Auditing is performed by independent qualified monitors of the study centers. The study is
- 22 considered a medium risk study according to the brochure 'Kwaliteitsborging mensgebonden
- 23 onderzoek 2.0' by the Dutch Federation of University Medical Centers, meaning that study centers
- 24 are audited two to three times per year, depending on enrolment, with 25% auditing of the study

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1 master file, investigator site files, informed consent forms, eligibility criteria, source data verification,

2 and SAEs/SUSARs.

3 Patient and public involvement

4 Patients are not involved in the design, recruitment, and conduct of the study, but will be involved in

5 the dissemination of study results.

6 Ethics and dissemination

7 Research ethics approval

- 8 The present study is approved by a central ethics committee (MEC-U, Nieuwegein, Netherlands,
- 9 number R19.087) and the institutional review boards of both study centers.

10 Protocol amendments

- 11 Important modifications to the study protocol need to be authorized by the central ethics
- 12 committee. After authorization, these modifications are communicated to the Dutch competent
- 13 authority, the institutional review boards of both study centers, all investigators, study registries, and
- 14 patients (if required by the central ethics committee).

15 Informed consent

- 16 Patients are enrolled by their treating physician and provide written informed consent. Patients are
- 17 able to give separate consent for participation in translational side studies.

18 <u>Confidentiality</u>

19 Personal data of patients is collected, shared and maintained according to the Dutch law.

20 Access to data

21 All authors have access to the final dataset, without any contractual agreements that limit such access.

22 Ancillary and post-study care

One of the study centers (Catharina Hospital, Eindhoven, the Netherlands) is insured to cover harms
caused by study participation in either participating hospital. After stopping study treatment,
patients receive further supportive, palliative, or curative intent treatment according to Dutch

4 guideline (27).

5 Dissemination policy

Study results will be personally communicated to participants, submitted for publication in peerreviewed medical journals, and presented to patients, healthcare professionals, and the public on
(inter)national meetings. Authorship eligibility guidelines are not defined a priori. The full study
protocol and the Dutch informed consent form are available from the corresponding author. After
study completion, the participant-level dataset and statistical code will be available on reasonable
request.

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To the knowledge of the authors, CRC-PIPAC-II is the first study that prospectively investigates the
safety, feasibility, anti-tumor activity, PROs, costs and systemic pharmacokinetics of first-line
bidirectional therapy (i.e. first-line systemic therapy alternated with ePIPAC-OX) in patients with
isolated unresectable CPM.

The present study has several strengths. All patients in the present study receive bidirectional therapy as first-line palliative treatment with standard first-line systemic regimens based on the ESMO guideline for the treatment of metastatic colorectal cancer (19), which contrasts the heterogeneous populations included in available studies on (e)PIPAC-OX for CPM. The homogeneity of the study population may facilitate a comparison between the present study and other first-line studies in metastatic colorectal cancer. Furthermore, assessment of outcomes such as PROs, costs, and systemic pharmacokinetics will provide further insight in the tolerability, costs, and pharmacokinetic profile of first-line bidirectional therapy in this setting. Translational side studies may open new opportunities for research in understanding and treating CPM. A potential limitation of the present study could be the histopathological heterogeneity within our clinically homogeneous study population, since the inclusion criteria allow the enrolment of patients with both colorectal and appendiceal carcinomas, as well as including distinct pathological features such as signet ring cell carcinomas. Although this could impede the interpretation of survival outcomes, this is not the major focus of this study. There are two ongoing dose escalation studies investigating the maximum tolerated dose of

21 repetitive PIPAC-OX (35, 36). These studies will be actively followed by the investigators to evaluate

22 whether dose adaption of ePIPAC-OX is required in the present study.

23 Results of several other ongoing single-arm, phase II studies are closely monitored. The first study

24 primarily assesses the histopathological response of PIPAC with various drugs for peritoneal

25 metastases of various origins (including PIPAC-OX for CPM), with or without concomitant systemic

therapy, in 137 patients in any line of palliative treatment (37). The second study assesses the safety of PIPAC with various drugs for peritoneal metastases of various origins (including PIPAC-OX for CPM), with or without concomitant systemic therapy, in 16 patients in a later line of palliative treatment (Clinicaltrials.gov, NCT04329494). The third study assesses progression-free survival of 30 patients with CPM receiving PIPAC-OX, with or without concomitant systemic therapy, in any line of <text> palliative treatment (Clinicaltrials.gov, NCT03868228). Results of the previous CRC-PIPAC study, the present CRC-PIPAC-II study, and these ongoing studies may help designing future randomized trials to determine the role of (e)PIPAC-OX in the palliative treatment of patients with isolated unresectable CPM.

1 Author Contributions

RL and PR are the coordinating investigators. RL, KR, AT, GC, JB, SN, and IH are the local investigators of the first study center. PR, EW, KH, ML, MW, and DB are the local investigators of the second study center. MD is the study pharmacologist supervising the pharmacokinetic analyses. JN and EH are the study radiologists performing the central radiological review. CH and CS are the study pathologists performing the central histopathological review. IE and RF are responsible for translational research on blood. AC and OK are responsible for translational research on ascites and peritoneal lavage. IH is the principal investigator. RL, PR, DB, and IH made substantial contributions to the conception and design of the study, drafted the protocol and drafted the manuscript. KR, AT, GC, JB, SN, EW, KH, ML, MW, MD, JN, EH, CH, CS, IE, RF, AC, and OK made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. RL, PR, KR, EW, MD, JN, CH, IE, RF, EH, CS, AC, OK, ML, KH, AT, GC, JB, MW, SN, DB and IH gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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| 3 ⊿ | 1 | Figures |
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| 7 | 2 | Figure titles: |
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| 9 10 | 3 | Figure 1. Study flowchart. |
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| 15 | 5 | Figure 1. B bloods (organ functions and tumor markers); C cytology (ascites or peritoneal lavage); CRS |
| 17 | | |
| 18 | 6 | cytoreductive surgery; ePIPAC-OX electrostatic pressurized intraperitoneal aerosol chemotherapy |
| 19 | | |
| 20 | 7 | with oxaliplatin; <i>H</i> histopathology (peritoneal biopsies); <i>MDT</i> multidisciplinary tumor board; <i>HIPEC</i> |
| 21 | - | |
| 22 | 8 | hyperthermic intraperitoneal chemotherapy; <i>P</i> pharmacokinetic sampling; <i>Q</i> questionnaires (costs |
| 23 24 | | |
| 25 | 9 | and patient-reported outcomes); Q^* questionnaires (patient-reported outcomes); R radiology |
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| 27 | 10 | (thoracoabdominal C1, diffusion-weighted Wiki peritoneum); R* thoracoabdominal C1; 7 translational |
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Table 1. Schedule of enrolment, interventions and assessments.

| evaluation | ePIPAC-OX eval | weeks first- ePIPA line systemic therapy | ePIPAC-OX | weeks first- line systemic therapy | ePIPAC-OX | weeks first- line systemic therapy | Baseline | enroiment | |
|------------|-----------------------|--|------------------------------|---|---|---|---|--|---|
| | | | | | | | | | Enrolment |
| | | | | | | | | Х | Eligibility Screen |
| | | | | | | | | X | Informed consent |
| | | | | | | | | | Interventions |
| Х | Х | X X | Х | Х | Х | Х | Х | | Blood samples (organ functions, tumor markers) |
| Х | | | | X (c) | | | Х | | Thoracoabdominal CT |
| Х | | | | | | | Х | | Diffusion-weighted MRI peritoneum |
| | Х | Х | Х | | Х | | | | Collection of ascites or peritoneal lavage |
| | Х | Х | Х | | Х | | | | Peritoneal biopsies |
| X (d) | | X (d) | | X (d) | | X (a) | X | | Questionnaires: Patient reported outcomes |
| X (e) | | X (e) | | X (e) | | | Х | | Questionnaires: Costs |
| | | | | | Х | X | | | Blood samples for pharmacokinetics |
| | X (b) | Х | X (b) | | X (b) | | Х | | Translational research (blood) |
| | X | Х | X | | X | | | | Translational research (ascites or peritoneal lavage) |
| | | | | | | | | | Assessments |
| | | | | | | | Х | | Baseline characteristics |
| | | Х | | Х | | х | | | Treatment-related characteristics (systemic therapy) |
| | Х | Х | Х | | Х | | | | Treatment-related characteristics (ePIPAC-OX) |
| Х | Х | х х | Х | X | х | х | | | Adverse events |
| | Х | Х | Х | | Х | | | | Hospital stay |
| Х | | Х | | х | | | | | Readmissions |
| Х | Х | х х | Х | Х | Х | Х | Х | | Clinical evaluation |
| Х | Х | X X | X | Х | х | х | | | Biochemical response |
| Х | | | | X (c) | | | | | Radiological response |
| | Х | Х | х | | х | | | | Histopathological response |
| | Х | Х | Х | | Х | | | | Cytological response |
| | Х | Х | х | | х | | | | Macroscopic response |
| | Х | Х | Х | | Х | | | | Ascites response |
| X (d) | | X (d) | | X (d) | | X (a) | х | | Patient-reported outcomes |
| X (e) | | X (e) | | X (e) | | | Х | | Costs |
| X | Х | X X | Х | X | Х | х | | | Progression-free survival |
| Х | Х | х х | Х | Х | Х | Х | | | Overall survival |
| : t | X X Yeek before | X X (d) X (e) X X X X aging; (a) one week bef | X X X Resonance Im. | X (d) X (e) X X ; MRI, Magnetic ifter ePIPAC-OX. | X X X vith oxaliplatin; e) four weeks a | X (a) X X Chemotherapy w er ePIPAC-OX; (e | X X neal Aerosol (our weeks aft | ssurized Intraperitor AC-OX; (d) one and fo | Ascites response Patient-reported outcomes Costs Progression-free survival Overall survival CT, Computed tomography; ePIPAC-OX, electrostatic Pres before ePIPAC-OX; (c) one week before the second ePIPA |



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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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Section/item ItemNo Description Page and line number(s) Administrative information Title 1 Descriptive title identifying the study design, population, interventions, and, if Page 1, line 3-5 applicable, trial acronym Trial registration Trial identifier and registry name. If not yet registered, name of intended registry Page 4, line 5 2a All items from the World Health Organization Trial Registration Data Set 2hProtocol version 3 Date and version identifier Page 2, line 16 Funding 4 Sources and types of financial, material, and other support Page 2, line 17-19 Roles and Names, affiliations, and roles of protocol contributors Page 1, line 6-21 5a responsibilities Page 2, line 1-4 Page 20, line 1-13 5h Name and contact information for the trial sponsor Page 2, line 5-10 Role of study sponsor and funders, if any, in study design; collection, Page 2, line 17-19 5c 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 5d Composition, roles, and responsibilities of the coordinating centre, steering Page 20, line 1-13 committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Introduction Description of research question and justification for undertaking the trial, Background and Page 6, line 6-25 6a rationale including summary of relevant studies (published and unpublished) examining Page 7, line 1-3 benefits and harms for each intervention 6b Explanation for choice of comparators Not applicable Objectives 7 Specific objectives or hypotheses Page 7, line 4-11 8 Description of trial design including type of trial (eg, parallel group, crossover, Trial design Page 7, line 8-11 factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Methods: Participants, interventions, and outcomes Description of study settings (eg, community clinic, academic hospital) and list Page 8, line 2-3 Study setting 9 of countries where data will be collected. Reference to where list of study sites can be obtained Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria Page 8, line 4-19 for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Interventions 11a Interventions for each group with sufficient detail to allow replication, including Page 8, line 20-22 how and when they will be administered Page 9, line 1-24 Page 10, line 1-25 11b Page 9, line 20-23 Criteria for discontinuing or modifying allocated interventions for a given trial Page 11, line 12-15 participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Not applicable |
|--|--------------|--|--|
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Not applicable |
| 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 | Page 12, line 13-23 Page 13, line 1-25 Page 14, line 1-5 |
| 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) | 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 | Page 14, line 6-11 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 14, line 12-14 |
| Methods: Assignmen | t of interve | entions (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 collec | ction, mana | gement, 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 | Page 14, line 15-20 |
| | 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 | Page 14, line 15-20 |
| 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 | Page 14, line 15-20 |
| 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 | Page 14, line 21-24 Page 15, line 1-2 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 14, line 21-24 Page 15, line 1-2 |
| | 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) | Page 14, line 21-24 Page 15, line 1-2 |
| Methods: Monitoring | g | | |
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| 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 | Page 15, line 3-11 |
|-----------------------------------|------|---|---------------------------------------|
| | 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 | Page 15, line 3-11 |
| 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 | Page 15, line 12-17 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Page 15, line 18-24 |
| Ethics and disseminat | tion | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 16, line 5-7 |
| 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) | Page 16, line 8-12 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 16, line 13-15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Page 16, line 13-15 |
| 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 | Page 16, line 16-17 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 2, line 14-15 |
| 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 | Page 16, line 18-19 |
| 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 | Page 16, line 20 Page 17, line 1-3 |
| 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 | Page 17, line 4-10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Page 17, line 7 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Page 17, line 8-10 |
| Appendices | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not applicable |
| 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 | Not applicable |

*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 "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.

BMJ Open

First-line palliative systemic therapy alternated with electrostatic pressurized intraperitoneal aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases: protocol of a multicenter, single-arm, phase II study (CRC-PIPAC-II).

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| Secondary Subject Heading: | Surgery, Palliative care, Gastroenterology and hepatology |
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| 2 | 1 | Abstract |
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| 6 7 | 2 | Introduction: Despite its increasing use, first-line palliative systemic therapy alternated with |
| 8 9 | 3 | electrostatic pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX), |
| 10 11 | 4 | hereinafter referred to as first-line bidirectional therapy, has never been prospectively investigated in |
| 12 13 | 5 | patients with colorectal peritoneal metastases (CPM). As a first step to address this evidence gap, the |
| 15 16 | 6 | present study aims to assess the safety, feasibility, anti-tumor activity, patient-reported outcomes, |
| 17 18 | 7 | costs, and systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated |
| 19 20 | 8 | unresectable CPM. |
| 21 | | |
| 22 23 24 | 9 | Methods and analysis: In this single-arm, phase II study in two Dutch tertiary referral centers, 20 |
| 25 26 | 10 | patients are enrolled. Key eligibility criteria are a good performance status, pathologically proven |
| 27 28 | 11 | isolated unresectable CPM, no previous palliative systemic therapy for colorectal cancer, no |
| 29 30 | 12 | (neo)adjuvant systemic therapy ≤6 months prior to enrolment, and no previous PIPAC. Patients receive |
| 31 32 | 13 | three cycles of bidirectional therapy. Each cycle consists of six weeks first-line palliative systemic |
| 33 34 35 | 14 | therapy at the medical oncologists' decision (CAPOX-bevacizumab, FOLFOX-bevacizumab, FOLFIRI- |
| 36 37 | 15 | bevacizumab, or FOLFOXIRI-bevacizumab) followed by ePIPAC-OX (92 mg/m ²) with an intraoperative |
| 38 39 | 16 | bolus of intravenous leucovorin (20 mg/m ²) and 5-fluorouracil (400 mg/m ²). Study treatment ends |
| 40 41 | 17 | after the third ePIPAC-OX. The primary outcome is the number of patients with – and procedures |
| 42 43 | 18 | leading to – grade ≥3 adverse events (Common Terminology Criteria for Adverse Events v5.0) up to four |
| 44 45 46 | 19 | weeks after the last procedure. Key secondary outcomes include the number of bidirectional cycles in |
| 47 48 | 20 | each patient, treatment-related characteristics, grade ≤ 2 adverse events, tumor response |
| 49 50 | 21 | (histopathological, cytological, radiological, biochemical, macroscopic, ascites), patient-reported |
| 51 52 | 22 | outcomes, systemic pharmacokinetics of oxaliplatin, costs, progression-free survival, and overall |
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1 Ethics and dissemination: This study is approved by the Dutch competent authority, a medical ethics

2 committee, and the institutional review boards of both study centers. Results will be submitted for

3 publication in peer-reviewed medical journals and presented to patients and healthcare professionals.

4 **Trial registration number:** Netherlands Trial Register: NL8303.

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| 2 3 4 | 1 | Strengths and limitations of this study |
|--|----|---|
| 5 6 7 | 2 | - First prospective phase-II study assessing the safety, feasibility, and anti-tumor activity of first- |
| 8 9 | 3 | line palliative systemic therapy with bevazicumab alternated with PIPAC (oxaliplatin) for |
| 10 11 | 4 | colorectal peritoneal metastases (CPM); |
| 12 13 14 | 5 | - Inclusion of a clinically homogenous population of CPM patients receiving first-line palliative |
| 15 16 | 6 | treatment; |
| 17 18 | 7 | - Assessment of multiple secondary outcomes, e.g. patient-reported outcomes, costs, and the |
| 19 20 21 | 8 | systemic pharmacokinetics of oxaliplatin; |
| 22 23 | 9 | - Translational side studies of the present study may open new opportunities for research in |
| 24 25 | 10 | understanding and treating colorectal peritoneal metastases; |
| 26 27 28 | 11 | - Potential limitation: histopathological heterogeneity (i.e. enrolment allowed for both |
| 28 29 30 | 12 | appendiceal and colorectal primary tumors; and signet ring cell carcinoma). |
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1 Introduction

The peritoneum is a common metastatic site in colorectal cancer and the presence of colorectal
peritoneal metastases (CPM) is characterized by a poor prognosis (1, 2). Most patients with CPM are
treated with palliative intent (3). When treated with systemic therapy, patients with CPM have a
shorter survival than patients with systemic metastases of colorectal cancer (4).

Theoretically, intraperitoneal chemotherapy could be an interesting palliative treatment option due to a favorable peritoneum-plasma concentration ratio (5). However, the use of intraperitoneal chemotherapy is limited by poor direct tumor penetration, inhomogeneous intraperitoneal drug distribution, and dose-limiting local toxicity (6, 7). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been developed to overcome these limitations (8-11). PIPAC is a laparoscopic method for the repetitive intraperitoneal administration of low-dose chemotherapy as a pressurized aerosol, claiming enhanced tumor penetration, homogeneous intraperitoneal drug distribution, and low toxicity in preliminary studies (8-11). The first clinical reports have suggested that PIPAC is feasible, safe, and well tolerated in patients with peritoneal metastases of various primary tumors (12, 13). Given these results, PIPAC is currently implemented in a rapidly increasing number of centers worldwide (12, 14). In these centers, patients with CPM are generally treated with PIPAC with oxaliplatin (92 mg/m2) every six to eight weeks, with or without concomitant systemic therapy (14). Electrostatic precipitation of the aerosol is thought to enhance tissue penetration and is practiced in several centers (15-18).

Previously, a multicenter, single-arm, phase II study (CRC-PIPAC) investigated the safety, feasibility,
 anti-tumor activity, patient-reported outcomes (PROs), costs, and pharmacokinetics of repetitive
 electrostatic PIPAC with oxaliplatin (ePIPAC-OX) as a palliative monotherapy in 20 patients with isolated
 unresectable CPM in any line of palliative treatment (19, 20).

23 Repetitive ePIPAC-OX could also be added to first-line systemic therapy with the aim to maximize
 24 intraperitoneal tumor response and eliminate systemic micrometastases. The combination of first-line

25 systemic therapy (including bevacizumab) and repetitive ePIPAC-OX, hereinafter referred to as first-line

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1 bidirectional therapy, is already offered to patients with isolated unresectable CPM in several PIPAC

2 centers worldwide (14).

Despite its increasing use, the feasibility, safety, and anti-tumor activity of first-line bidirectional
therapy have never been prospectively investigated in patients with isolated unresectable CPM in clinical
trials with predefined eligibility criteria, interventions, and outcomes. Moreover, nothing is known about
PROs and costs of – and the systemic pharmacokinetics of oxaliplatin during – first-line bidirectional
therapy in this setting. As a first step to address this evidence gap, the present multicenter, single-arm,
phase 2 study (CRC-PIPAC-II) aims to assess the safety, feasibility, anti-tumor activity, PROs, costs, and
systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated unresectable CPM.

| 2 3 4 | 1 | Methods and analysis |
|----------------|----|--|
| 5 6 7 | 2 | Setting |
| 8 9 10 | 3 | This study is performed in two Dutch tertiary referral centers for the surgical treatment of CPM. |
| 11 12 13 | 4 | Eligibility criteria |
| 14 15 16 | 5 | Eligibility criteria are: |
| 17 18 19 | 6 | ≥18 years of age; |
| 20 21 | 7 | - World Health Organization performance status of 0-1; |
| 22 23 | 8 | - Histologically or cytologically proven peritoneal metastases of a colorectal or appendiceal |
| 24 25 | 9 | carcinoma; |
| 26 27 28 | 10 | - Unresectable disease, defined as a Peritoneal Cancer Index (PCI) >20 or if complete resection |
| 20 29 30 | 11 | of peritoneal metastases is surgically not feasible, based on abdominal CT, laparoscopy, or |
| 31 32 | 12 | laparotomy; |
| 33 34 | 13 | - Adequate organ functions (hemoglobin \geq 5.0 mmol/L, neutrophils \geq 1.5×10 ⁹ /L, platelets |
| 35 36 27 | 14 | ≥100×10 ⁹ /L, serum creatinine <1.5 × upper limit of normal [ULN], creatinine clearance |
| 37 38 39 | 15 | ≥30 mL/min, and liver transaminases <5 × ULN); |
| 40 41 | 16 | - No symptoms of gastrointestinal obstruction; |
| 42 43 | 17 | - No systemic metastases; |
| 44 45 | 18 | - No contraindications for the planned systemic therapy or laparoscopy; |
| 46 47 48 | 19 | - No previous PIPAC; |
| 49 50 | 20 | - No previous palliative systemic therapy for colorectal cancer; |
| 51 52 | 21 | No (neo)adjuvant systemic therapy for colorectal cancer ≤6 months prior to enrolment; |
| 55 54 55 | 22 | Interventions and procedures |
| 57 58 | 23 | The study flowchart is shown in <i>Figure 1</i> . The schedule of enrolment, interventions, and assessments is |
| 59 60 | 24 | shown in <i>Table 1</i> . |

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| 4 | | |
| 5 6 7 | 2 | All patients receive three cycles of first-line bidirectional therapy. Each cycle consists of six weeks of |
| / 8 0 | 3 | first-line systemic therapy followed by one ePIPAC-OX. Study treatment ends after the third ePIPAC-OX |
| 9 10 11 | 4 | in all patients. |
| 12 13 14 | 5 | First-line palliative systemic therapy |
| 15 16 17 | 6 | The treating medical oncologist determines which of the following first-line regimens will be used: |
| 18 19 | 7 | - Two three-weekly cycles of CAPOX-bevacizumab (intravenous [IV] oxaliplatin [130 mg/m ² |
| 20 21 22 | 8 | body-surface area (BSA)] on day 1, oral capecitabine [1000 mg/m ² BSA] twice daily on days 1- |
| 22 23 24 | 9 | 14, IV bevacizumab [7.5 mg/kg body weight] on day 1), or; |
| 25 26 | 10 | - Three two-weekly cycles of FOLFOX-bevacizumab (IV oxaliplatin [85 mg/m ² BSA] on day 1, IV |
| 27 28 | 11 | leucovorin [400 mg/m ² BSA] on day 1, IV bolus/continuous 5-fluorouracil [400/2400 mg/m ² |
| 29 30 31 | 12 | BSA] on days 1-2, IV bevacizumab [5 mg/kg body weight] on day 1), or; |
| 32 33 | 13 | - Three two-weekly cycles of FOLFIRI-bevacizumab (IV irinotecan [180 mg/m ² BSA] on day 1, IV |
| 34 35 | 14 | leucovorin [400 mg/m ² BSA] on day 1, IV bolus/continuous 5-fluorouracil [400/2400 mg/m ² |
| 36 37 20 | 15 | BSA] on days 1-2, IV bevacizumab [5 mg/kg body weight] on day 1), or; |
| 30 39 40 | 16 | - Three two-weekly cycles of FOLFOXIRI-bevacizumab (IV oxaliplatin [85 mg/m ² BSA] on day 1, IV |
| 41 42 | 17 | irinotecan [165 mg/m ² BSA] on day 1, IV leucovorin [400 mg/m ² BSA] on day 1, IV continuous |
| 43 44 45 | 18 | 5-fluorouracil [2400 mg/m ² BSA] on days 1-2, IV bevacizumab [5 mg/kg body weight] on day 1). |
| 45 46 47 | 19 | These regimens are based on the ESMO and the Dutch guideline for the treatment of metastatic |
| 48 49 | 20 | colorectal cancer (21, 22). According to the ESMO guideline, both bevacizumab and anti-EGFR therapy |
| 50 51 52 | 21 | can be added to first-line systemic chemotherapy when disease control is the main goal of treatment. |
| 52 53 54 | 22 | According to the Dutch guideline, bevacizumab is the first-choice biological agent for the treatment of |
| 55 56 | 23 | metastatic colorectal cancer, as it can be administered to patients with wildtype KRAS and patients with |
| 57 58 | 24 | mutated KRAS, in contrast to anti-EGFR therapy. |
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Dose reductions, switches between allowed regimens, and management of toxicity are left to the
 discretion of the treating medical oncologist. Dihydropyrimidine dehydrogenase status is assessed by
 genotyping before the first administration of systemic therapy, and dosages of capecitabine or 5-

4 fluorouracil are modified accordingly (23).

5 <u>ePIPAC-OX</u>

6 The procedure has been extensively described in the protocol of the CRC-PIPAC study (19,20). In 7 summary, after creating a 12 mmHg pneumoperitoneum with two balloon trocars using an open 8 introduction, an explorative laparoscopy is performed with adhesiolysis if needed to create enough 9 working space. If ePIPAC-OX seems feasible, leucovorin (20 mg/m² BSA in 10 minutes) and 5-0 fluorouracil (400 mg/m² BSA in 15 minutes) are administered intravenously, since these drugs are thought to increase the efficacy of oxaliplatin (24, 25). Meanwhile, ascites (or peritoneal lavage using 1 2 saline if ascites is absent) is evacuated and sent for cytology, the PCI and ascites volume are registered 3 (26), and three peritoneal metastases from different intraabdominal areas (if possible) are biopsied and sent for histopathology. Biopsy locations are marked with clips to enable similar biopsies during 4 5 subsequent procedures. 6 Then, after building the PIPAC setup and ensuring a leak-free pneumoperitoneum, oxaliplatin (92 7 mg/m² BSA [maximum 184 mg] diluted to a total volume of 150 mL in a 5% dextrose solution) is

aerosolized into the peritoneal cavity through a nebulizer (CapnoPen, Capnomed GmbH, Villingendorf,
 Germany) using an angiographic injector at a maximum pressure of 200 psi and a flow of 30 mL/min, all

20 according to internationally used protocols (14). After formation of the aerosol in 5 minutes, it is

21 electrostatically precipitated for another 25 minutes using Ultravision technology (Alesi Surgical,

Cardiff, United Kingdom) as described by others (16), as this could enhance tumor penetration of
oxaliplatin (15).

Then, the peritoneal cavity is exsufflated through a closed aerosol waste system, instruments are
 removed, and incisions are closed.

| 1 | | |
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| 2 3 4 | 1 | Postoperatively, patients receive analgesics and anti-emetics according to local protocol. Standard |
| 5 6 | 2 | postoperative clinical evaluations are performed a few hours after ePIPAC-OX and on every |
| 7 8 | 3 | postoperative day until discharge. Postoperative laboratory tests are only performed if indicated. |
| 9 10 11 | 4 | Patients are intentionally discharged on the day of ePIPAC-OX or on the first postoperative day. |
| 12 13 | 5 | Evaluations |
| 14 15 16 | 6 | Before each cycle of systemic therapy, patients undergo clinical and biochemical (i.e. tumor markers, |
| 17 18 | 7 | organ functions) evaluation by the treating medical oncologist. Before each ePIPAC-OX, patients |
| 19 20 | 8 | undergo clinical evaluation by the treating surgeon. During and shortly after ePIPAC-OX, patients |
| 21 22 23 | 9 | undergo macroscopic (i.e. peritoneal cancer index [PCI] (26)), ascites volume), histopathological (i.e. |
| 23 24 25 | 10 | peritoneal regression grading score [PRGS] of peritoneal biopsies (27,28)) and cytological evaluation. |
| 26 27 | 11 | Radiological evaluation is performed one week before the second ePIPAC-OX and four weeks after the |
| 28 29 | 12 | third ePIPAC-OX (29). Patients are discussed by a multidisciplinary tumor board after the second and |
| 30 31 32 | 13 | third ePIPAC-OX. |
| 33 34 | 14 | After completing six weeks of systemic therapy, the subsequent ePIPAC-OX is planned within one to |
| 35 36 37 | 15 | four weeks thereafter. After ePIPAC-OX, systemic therapy is restarted one to four weeks |
| 38 39 | 16 | postoperatively. Study treatment is discontinued in case of physician-determined disease progression, |
| 40 41 | 17 | unacceptable toxicity, or physician's or patient's decision to discontinue participation. Study treatment |
| 42 43 | 18 | ends after the third ePIPAC-OX, regardless of response to therapy, after which patients receive |
| 44 45 46 | 19 | standard supportive, palliative, or curative care according to the Dutch national guideline without |
| 40 47 48 | 20 | further ePIPAC-OX (22). |
| 50 51 | 21 | Pharmacokinetic sampling |
| 52 53 54 | 22 | Four mL of whole blood samples are collected in heparin tubes at multiple time points during and after |
| 55 56 57 | 23 | the first ePIPAC-OX as well as during and after the first cycle of systemic therapy: |
| 57 58 59 | 24 | - ePIPAC-OX: at t=0, t=0.5, t=1, t=2, and t=16 hours and t=1 week after intraperitoneal |
| 60 | 25 | oxaliplatin injection; |

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| 2 3 | 1 | - CAPOX-bevacizumab: at t=0, t=0.5, t=1, and t=2 hours and t=3 weeks after intravenous |
|----------------------|----|---|
| 4 5 6 | 2 | administration of oxaliplatin; |
| 0 7 8 | 3 | - FOLFOX-bevacizumab or FOLFOXIRI-bevacizumab: at t=0, t=0.5, t=1, t=2, t=48 hours and t=2 |
| 9 10 11 | 4 | weeks after intravenous administration of oxaliplatin. |
| 12 13 | 5 | After direct centrifuging, a plasma aliquot is stored at -80°C until analysis. To obtain the free fraction of |
| 14 15 | 6 | oxaliplatin, a second 1 mL plasma aliquot is centrifuged through an ultrafiltration membrane and stored |
| 16 17 | 7 | at -80°C until analysis. Oxaliplatin concentrations are measured using atomic absorption spectrometry |
| 18 19 20 | 8 | performed on a Thermo Fisher Solaar ICE 3500 graphite-furnace spectrophotometer with Zeeman |
| 20 21 22 | 9 | correction (Thermo Fisher Scientific, Bremen, Germany). |
| 23 24 25 | 10 | Translational research |
| 26 27 28 | 11 | Two 10 mL cell-free DNA BCT tubes (Streck, La Vista, Nebraska, USA) are used to collect 20 mL of whole |
| 29 30 | 12 | blood at baseline and before each ePIPAC-OX. Tubes are sent to a central laboratory for isolation and |
| 31 32 | 13 | storage (-80°C) of plasma and cell pellet according to the manufacturer's instructions. Collected ascites |
| 33 34 | 14 | or peritoneal lavage is centrifuged twice (5 minutes, 420 g, zero break) under sterile conditions. The |
| 35 36 37 | 15 | supernatant is snap frozen and stored (-80°C) until further analysis. The cell pellet is suspended into an |
| 38 39 | 16 | organoid culture medium at 4°C for transport and further preparation. |
| 40 41 42 43 | 17 | Outcomes |
| 44 45 | 18 | The primary outcome is the number of patients with – and procedures leading to – grade \geq 3 adverse |
| 46 47 | 19 | events according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (primary |
| 48 49 | 20 | classification) and Clavien-Dindo (secondary classification) up to four weeks after the last ePIPAC-OX |
| 50 51 52 | 21 | (30, 31). |
| 53 54 55 | 22 | Secondary outcomes are: |
| 56 57 58 | 23 | - The number of completed cycles of bidirectional therapy in each patient and reasons for |
| 59 60 | 24 | discontinuation; |

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| 2 3 | 1 | - | Characteristics of systemic therapy (e.g. administered regimens, number of completed cycles, |
|----------------|----|---|---|
| 4 5 | 2 | | dose reductions); |
| 6 7 8 | 3 | - | Characteristics of ePIPAC-OX (e.g. intraoperative complications, operating time); |
| 9 10 | 4 | - | The number of patients with – and procedures leading to – grade ≤ 2 adverse events according |
| 11 12 | 5 | | to the CTCAE v5.0 (primary classification) and Clavien-Dindo (secondary classification) up to |
| 13 14 | 6 | | four weeks after the last ePIPAC-OX (30, 31); |
| 15 16 17 | 7 | - | Hospital stay, defined as the number of days between ePIPAC-OX and initial discharge; |
| 17 18 19 | 8 | - | Readmissions, defined as any unplanned hospital admission after initial discharge up to four |
| 20 21 | 9 | | weeks after the last ePIPAC-OX; |
| 22 23 | 10 | - | Radiological tumor response, centrally evaluated by two assessors blinded to clinical |
| 24 25 26 | 11 | | outcomes, using the Response Evaluation Criteria In Solid Tumors v1.1 and the radiological PCI |
| 20 27 28 | 12 | | (29); |
| 29 30 | 13 | - | Histopathological tumor response, centrally evaluated by two assessors blinded to clinical |
| 31 32 | 14 | | outcomes, using the four tier PRGS of collected peritoneal biopsies during each ePIPAC-OX (27, |
| 33 34 | 15 | | 28); |
| 35 36 37 | 16 | - | Macroscopic tumor response, based on the PCI during each ePIPAC-OX; |
| 38 39 | 17 | - | Ascites response, based on ascites volume during each ePIPAC-OX; |
| 40 41 | 18 | - | Biochemical tumor response, based on carcinoembryonic antigen (CEA) levels at baseline and |
| 42 43 | 19 | | before each ePIPAC-OX; |
| 44 45 46 | 20 | - | Cytological tumor response, based on the presence or absence of malignant cells in ascites or |
| 40 47 48 | 21 | | peritoneal lavage collected during each ePIPAC-OX; |
| 49 50 | 22 | - | PROs, based on the EQ-5D-5L (32), EORTC QLQ-C30 (33), and EORTC QLQ-CR29 (34) |
| 51 52 | 23 | | questionnaires at baseline, one week before the first ePIPAC-OX, and one and four weeks after |
| 53 54 55 | 24 | | each ePIPAC-OX; |
| 56 57 | 25 | - | The bioavailability of oxaliplatin, based on the systemic pharmacokinetics of oxaliplatin during |
| 58 59 60 | 26 | | and after one intravenous administration, as well as during and after one ePIPAC-OX; |

| 2 3 | 1 | - Costs, derived from the Dutch cost guideline for healthcare research at the time of analysis, |
|----------------------------|----|---|
| 4 5 6 | 2 | based on hospital information systems, case report forms, and the iMTA Productivity cost |
| 7 8 | 3 | questionnaire (35) and the iMTA Medical consumption questionnaire (36) at baseline and four |
| 9 10 | 4 | weeks after each ePIPAC-OX; |
| 11 12 | 5 | - Progression-free survival, defined as the time between enrolment and physician-determined |
| 13 14 15 | 6 | disease progression or death; |
| 16 17 | 7 | - Overall survival, defined as the time between enrolment and death. |
| 18 19 20 | 8 | Sample size |
| 21 22 23 | 9 | Given the absence of data to guide a sample size calculation, the central ethics committee approved a |
| 24 25 | 10 | pragmatically determined sample size of 20 patients as a sufficient number to explore the safety, |
| 26 27 28 29 30 | 11 | feasibility, and anti-tumor activity of the study treatment, similar to the CRC-PIPAC study (19, 20). |
| | 12 | Enrolled patients who are unable to receive the first ePIPAC-OX are replaced to enrol a total number of |
| 31 32 | 13 | 20 patients who receive at least one cycle of bidirectional therapy. |
| 33 34 35 | 14 | Recruitment |
| 36 37 | 15 | The study commenced on 30 January 2020 and the first patient was enrolled on 5 February 2020. The |
| 38 39 40 | 16 | investigators expect to complete accrual within a maximum of three years. Strategies for achieving |
| 41 42 | 17 | adequate patient accrual are not defined a priori. |
| 43 44 45 | 18 | Data collection and data management |
| 46 47 48 | 19 | Outcomes are collected in all patients who complete at least one cycle of bidirectional therapy. All |
| 49 50 | 20 | baseline characteristics and outcomes are prospectively collected by a local investigator in each study |
| 51 52 | 21 | center using standardized electronic case report forms linked to an ISO 27001 certified central study |
| 53 54 55 | 22 | database (De Research Manager, Deventer, the Netherlands). This ISO 27001 certified system optimizes |
| 56 57 | 23 | data quality by standardized data entry, coding, security, and storage. |
| 58 59 60 | 24 | Statistical methods |

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Continuous data are presented as a median with (interquartile) range and categorical data are
 presented as number (percentage). Due to the single-arm design of the present study and the
 explorative nature of the analyzed outcomes, basic statistical methods are not defined a priori. These
 methods will be defined before data analysis. Time-to-event variables, such as progression-free and
 overall survival, are analyzed and presented using the Kaplan-Meier method.

6 Data monitoring

7 Interim analyses are performed four weeks after the fifth, fifteenth, thirtieth and forty-fifth procedure. 8 The study is terminated, or temporarily halted for evaluation and potential adaption of the study 9 protocol, if more than three CTCAE grade 3 or 4 adverse events occur or more than one CTCAE grade 5 10 adverse event occur that are considered directly related to ePIPAC-OX. Adverse events related to systemic therapy are not included in the stopping rules. If the study is terminated, enrolled patients do 11 12 not receive any further ePIPAC-OX. The principal investigators (IHJTH and DB) have access to the interim results and make the final decision to terminate or continue the study. No data monitoring 13 committee was formed for this study. 14

15 <u>Harms</u>

All serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) that
 occur from enrolment up to four weeks after the last ePIPAC-OX are reported by local investigators to
 the coordinating investigator within 24 hours. The coordinating investigator reports these SAEs/SUSARs
 to the central ethics committee within 7 days of first knowledge for lethal or life-threatening
 SAEs/SUSARs, and within 15 days for other SAEs/SUSARs.

21 Auditing

Auditing is performed by independent qualified monitors of the study centers. The study is considered a
 medium risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the
 Dutch Federation of University Medical Centers, meaning that study centers are audited two to three

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1 times per year, depending on enrolment, with 25% auditing of the study master file, investigator site

2 files, informed consent forms, eligibility criteria, source data verification, and SAEs/SUSARs.

3 Patient and public involvement

4 Patients are not involved in the design, recruitment, and conduct of the study, but will be involved in

5 the dissemination of study results.

6 **Ethics and dissemination**

7 <u>Research ethics approval</u>

8 The present study is approved by a central ethics committee (MEC-U, Nieuwegein, Netherlands,

9 number R19.087) and the institutional review boards of both study centers.

10 Protocol amendments

- 11 Important modifications to the study protocol need to be authorized by the central ethics committee.
- 12 After authorization, these modifications are communicated to the Dutch competent authority, the
- 13 institutional review boards of both study centers, all investigators, study registries, and patients (if
- 14 required by the central ethics committee).

15 Informed consent

- 16 Patients are enrolled by their treating physician and provide written informed consent. Patients are
- b 17 able to give separate consent for participation in translational side studies.

8 18 **Confidentiality**

19 Personal data of patients is collected, shared and maintained according to the Dutch law.

20 Access to data

All authors have access to the final dataset, without any contractual agreements that limit such access.

60 22 Ancillary and post-study care

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1 One of the study centers (Catharina Hospital, Eindhoven, the Netherlands) is insured to cover harms

2 caused by study participation in either participating hospital. After stopping study treatment, patients

3 receive further supportive, palliative, or curative intent treatment according to Dutch guideline (22).

4 **Dissemination policy**

Study results will be personally communicated to participants, submitted for publication in peerreviewed medical journals, and presented to patients, healthcare professionals, and the public during
(inter)national meetings. Authorship eligibility guidelines are not defined a priori. The full study
protocol and the Dutch informed consent form are available from the corresponding author. After
study completion, the participant-level dataset and statistical code will be available on reasonable
request.

12 Discussion

To the knowledge of the authors, CRC-PIPAC-II is the first study that prospectively investigates the
safety, feasibility, anti-tumor activity, PROs, costs and systemic pharmacokinetics of first-line systemic
chemotherapy and bevacizumab alternated with repetitive ePIPAC-OX (i.e. first-line bidirectional
therapy) in patients with isolated unresectable CPM.

17 The present study has several strengths. All patients in the present study receive standard first-line 18 systemic regimens based on the ESMO guideline for the treatment of metastatic colorectal cancer (21), 19 which contrasts the heterogeneity in treatment lines in available studies on (e)PIPAC-OX for CPM. The 20 homogeneity in first-line treatment may facilitate a comparison between the present study and other 21 first-line studies in metastatic colorectal cancer. Furthermore, assessment of outcomes such as PROs, 22 costs, and systemic pharmacokinetics will provide further insight in the tolerability, costs, and 23 pharmacokinetic profile of first-line bidirectional therapy in this setting. Translational side studies may 24 open new opportunities for research in understanding and treating CPM.

A potential limitation of the present study is the histopathological heterogeneity of the study
population, since the eligibility criteria allow the enrolment of patients with both colorectal and
appendiceal carcinomas, as well as including distinct pathological features such as signet ring cell
histology. Furthermore, different first-line palliative systemic regimens are allowed, including
FOLFOXIRI-bevacizumab, which might result in clinical heterogeneity. Although the potential clinical
and histopathological heterogeneity could impede the interpretation of preliminary efficacy outcomes,
this is not the major focus of this study.

8 With regards to the chemotherapy regimen used in this study, the results of the recently published 9 PRODIGE-7 trial may question the intraperitoneal use of oxaliplatin (combined with 5-fluorouracil and 10 leucovorin) in patients with CPM (37). However, in contrast with PRODIGE-7, patients in the present 11 study are either systemic therapy-naïve or had undergone a mandatory six-month wash-out period of 12 systemic therapy. As a result, the previously untreated patients in this study may be more sensitive to 13 intraperitoneal oxaliplatin than patients in the PRODIGE-7 trial.

Most importantly, patients in the present study undergo palliative instead of curative intent treatment and receive repetitive instead of a single administration of intraperitoneal oxaliplatin. Repetitive PIPAC-OX (with or without intraoperative intravenous bolus 5-fluorouracil/leucovorin) is increasingly offered and frequently combined with first-line systemic chemotherapy and bevacizumab in many centers worldwide (12, 14, 38, 39). Despite the increasing use, the safety and feasibility of this combination has never been prospectively investigated in clinical trials. Altogether, it remains important to assess the feasibility and safety of the combination of first-line palliative systemic therapy and repetitive PIPAC-OX, hence the major focus of this study.

With regards to the oxaliplatin dose during PIPAC, two phase 1 dose-escalation trials recently assessed the maximum tolerated dose of repetitive PIPAC-OX for unresectable peritoneal metastases of various origins (40, 41). The French PIPOX trial observed two dose-limiting toxicities of systemic therapy with repetitive PIPAC-OX at 140 mg/m² and the investigators defined a maximum tolerated dose of repetitive PIPAC-OX of 90 mg/m². The PIPAC-OX trial from Singapore reported no dose-limiting

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| 2 3 4 | 1 | toxicities with repetitive PIPAC-OX 120 mg/m ² monotherapy, however, this trial was prematurely |
| - 5 6 | 2 | terminated due to the dose-limiting toxicities of the PIPOX trial. As a result, both trials are currently |
| 7 8 | 3 | recruiting phase 2 expansion cohorts to investigate various systemic regimens combined with repetitive |
| 9 10 11 | 4 | PIPAC-OX at 90 mg/m ² : a dose similar to the oxaliplatin dose in the current trial. |
| 12 13 | 5 | Results of several other ongoing single-arm, phase II studies are closely monitored. The first study |
| 14 15 | 6 | primarily assesses the histopathological response of PIPAC with various drugs for peritoneal metastases |
| 16 17 | 7 | of various origins (including PIPAC-OX for CPM), with or without concomitant systemic therapy, in 137 |
| 18 19 20 | 8 | patients in any line of palliative treatment (42). The second study assesses the safety of PIPAC with |
| 21 22 | 9 | various drugs for peritoneal metastases of various origins (including PIPAC-OX for CPM), with or without |
| 23 24 | 10 | concomitant systemic therapy, in 16 patients in a later line of palliative treatment (Clinicaltrials.gov, |
| 25 26 | 11 | NCT04329494). The third study assesses progression-free survival of 30 patients with CPM receiving |
| 27 28 20 | 12 | PIPAC-OX, with or without concomitant systemic therapy, in any line of palliative treatment |
| 30 31 | 13 | (Clinicaltrials.gov, NCT03868228). Results of the previous CRC-PIPAC study, the present CRC-PIPAC-II |
| 32 33 | 14 | study, and these ongoing studies may help designing future randomized trials to determine the role of |
| 34 35 | 15 | (e)PIPAC-OX in the palliative treatment of patients with isolated unresectable CPM. |
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1 Author Contributions

RL and PR are the coordinating investigators. RL, KR, AT, GC, JB, SN, and IH are the local investigators of the first study center. PR, EW, KH, ML, MW, and DB are the local investigators of the second study center. MD is the study pharmacologist supervising the pharmacokinetic analyses. JN and EH are the study radiologists performing the central radiological review. CH and CS are the study pathologists performing the central histopathological review. IE and RF are responsible for translational research on blood. AC and OK are responsible for translational research on ascites and peritoneal lavage. IH is the principal investigator. RL, PR, DB, and IH made substantial contributions to the conception and design of the study, drafted the protocol and drafted the manuscript. KR, AT, GC, JB, SN, EW, KH, ML, MW, MD, JN, EH, CH, CS, IE, RF, AC, and OK made substantial contributions to conception and design of the study and critically revised the protocol and the manuscript for important intellectual content. RL, PR, KR, EW, MD, JN, CH, IE, RF, EH, CS, AC, OK, ML, KH, AT, GC, JB, MW, SN, DB and IH gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Tables

Table 1. Schedule of enrolment, interventions and assessments.

| | Enrolment | Baseline | First six weeks first- line systemic therapy | First ePIPAC-OX | Second six weeks first- line systemic therapy | Second ePIPAC-OX | Third six weeks first- line systemic therapy | Third ePIPAC-OX | Final evaluation | Foll |
|---|-----------|----------|--|--------------------|---|---------------------|--|--------------------|---------------------|------|
| Enrolment | | | | | | | | | | |
| Eligibility Screen | Х | | | | | | | | | |
| Informed consent | Х | | | | | | | | | |
| Interventions | | | | | | | | | | |
| Blood samples (organ functions, tumor markers) | | Х | Х | Х | Х | Х | Х | Х | Х | |
| Thoracoabdominal CT | | x | | | X (c) | | | | х | |
| Diffusion-weighted MRI peritoneum | | Х | | | | | | | Х | |
| Collection of ascites or peritoneal lavage | | | | Х | | х | | х | | |
| Peritoneal biopsies | | | | х | | Х | | Х | | |
| Questionnaires: Patient reported outcomes | | х | X (a) | | X (d) | | X (d) | | X (d) | |
| Questionnaires: Costs | | Х | | | X (e) | | X (e) | | X (e) | |
| Blood samples for pharmacokinetics | | | х | х | | | | | | |
| Translational research (blood) | | Х | | X (b) | | X (b) | | X (b) | | |
| Translational research (ascites or peritoneal lavage) | | | | Х | | х | | х | | |
| Assessments | | | | | | | | | | |
| Baseline characteristics | | X | | | | | | | | |
| Treatment-related characteristics (systemic therapy) | | | х | | х | | х | | | |
| Treatment-related characteristics (ePIPAC-OX) | | | | х | | х | | Х | | |
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| Adverse events | | Х | Х | Х | Х | Х | Х | Х | |
|----------------------------|---|-------|---|-------|---|-------|---|-------|---|
| Hospital stay | | | Х | | Х | | Х | | |
| Readmissions | | | | Х | | Х | | Х | |
| Clinical evaluation | Х | Х | Х | Х | Х | Х | Х | Х | |
| Biochemical response | | Х | Х | Х | Х | Х | Х | Х | |
| Radiological response | | | | X (c) | | | | Х | |
| Histopathological response | | | Х | | х | | Х | | |
| Cytological response | | | Х | | Х | | Х | | |
| Macroscopic response | | | х | | х | | х | | |
| Ascites response | | | Х | | Х | | Х | | |
| Patient-reported outcomes | X | X (a) | | X (d) | | X (d) | | X (d) | |
| Costs | Х | | | X (e) | | X (e) | | X (e) | |
| Progression-free survival | | X | X | Х | х | Х | Х | х | Х |
| Overall survival | | х | Х | Х | Х | Х | Х | Х | Х |
| | | | | | | | | | |

CT, Computed tomography; ePIPAC-OX, electrostatic Pressurized Intraperitoneal Aerosol Chemotherapy with oxaliplatin; MRI, Magnetic Resonance Imaging; (a) one week before the first ePIPAC-OX; (b) just before ePIPAC-OX; (c) one week before the second ePIPAC-OX; (d) one and four weeks after ePIPAC-OX; (e) four weeks after ePIPAC-OX.

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| 3 | 1 | Figures |
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| 9 | 3 | Figure 1. Study flowchart. |
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| 12 | 4 | Figure legends: |
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| 15 | 5 | Figure 1 . <i>B</i> bloods (organ functions and tumor markers): <i>C</i> cytology (ascites or peritoneal layage): <i>CRS</i> |
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| 21 | 8 | hyperthermic intraperitoneal chemotherapy: <i>P</i> pharmacokinetic sampling: <i>Q</i> questionnaires (costs and |
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| 24 | 9 | patient-reported outcomes); Q* questionnaires (patient-reported outcomes); R radiology |
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| 26 | 10 | (thoracoabdominal CT, diffusion-weighted MRI peritoneum); <i>R*</i> thoracoabdominal CT; <i>T</i> translational |
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| 28 | 11 | research (blood and ascites or peritoneal lavage); <i>T*</i> translational research (blood). |
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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Section/item ItemNo Description Page and line number(s) Administrative information Title 1 Descriptive title identifying the study design, population, interventions, and, if Page 1, line 3-5 applicable, trial acronym Trial registration Trial identifier and registry name. If not yet registered, name of intended registry Page 4, line 5 2a All items from the World Health Organization Trial Registration Data Set 2hProtocol version 3 Date and version identifier Page 2, line 16 Funding 4 Sources and types of financial, material, and other support Page 2, line 17-19 Roles and Names, affiliations, and roles of protocol contributors Page 1, line 6-21 5a responsibilities Page 2, line 1-4 Page 20, line 1-13 5h Name and contact information for the trial sponsor Page 2, line 5-10 Role of study sponsor and funders, if any, in study design; collection, Page 2, line 17-19 5c 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 5d Composition, roles, and responsibilities of the coordinating centre, steering Page 20, line 1-13 committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Introduction Description of research question and justification for undertaking the trial, Background and Page 6, line 6-25 6a rationale including summary of relevant studies (published and unpublished) examining Page 7, line 1-3 benefits and harms for each intervention 6b Explanation for choice of comparators Not applicable Objectives 7 Specific objectives or hypotheses Page 7, line 4-11 8 Description of trial design including type of trial (eg, parallel group, crossover, Trial design Page 7, line 8-11 factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Methods: Participants, interventions, and outcomes Description of study settings (eg, community clinic, academic hospital) and list Page 8, line 2-3 Study setting 9 of countries where data will be collected. Reference to where list of study sites can be obtained Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria Page 8, line 4-19 for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Interventions 11a Interventions for each group with sufficient detail to allow replication, including Page 8, line 20-22 how and when they will be administered Page 9, line 1-24 Page 10, line 1-25 11b Page 9, line 20-23 Criteria for discontinuing or modifying allocated interventions for a given trial Page 11, line 12-15 participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

| 1 2 | | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Not applicable |
|----------------------------|--|--------------|--|--|
| 3 4 5 | | 11 d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Not applicable |
| 6 7 8 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 | Page 12, line 13-23 Page 13, line 1-25 Page 14, line 1-5 |
| 10 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) | Figure 1 |
| 13 14 15 | 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 | Page 14, line 6-11 |
| 16 17 18 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Page 14, line 12-14 |
| 10 | Methods: Assignmen | t of interve | entions (for controlled trials) | |
| 20 21 | Allocation: | | | |
| 22 23 24 25 26 | 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 |
| 20 27 28 29 | 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 |
| 30 31 | Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Not applicable |
| 32 33 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Not applicable |
| 34 35 | | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | Not applicable |
| 36 37 | Methods: Data collec | tion, mana | agement, and analysis | |
| 38 39 40 41 42 | 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 | Page 14, line 15-20 |
| 43 44 45 46 | | 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 | Page 14, line 15-20 |
| 47 48 49 | 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 | Page 14, line 15-20 |
| 50 51 52 | 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 | Page 14, line 21-24 Page 15, line 1-2 |
| 55 55 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Page 14, line 21-24 Page 15, line 1-2 |
| 56 57 58 | | 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) | Page 14, line 21-24 Page 15, line 1-2 |
| 59 | Methods: Monitoring | ļ, | | |

| 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 | Page 15, line 3-11 |
|-----------------------------------|------|---|---------------------------------------|
| | 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 | Page 15, line 3-11 |
| 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 | Page 15, line 12-17 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Page 15, line 18-24 |
| Ethics and disseminat | tion | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Page 16, line 5-7 |
| 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) | Page 16, line 8-12 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Page 16, line 13-15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Page 16, line 13-15 |
| 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 | Page 16, line 16-17 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | Page 2, line 14-15 |
| 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 | Page 16, line 18-19 |
| 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 | Page 16, line 20 Page 17, line 1-3 |
| 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 | Page 17, line 4-10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | Page 17, line 7 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Page 17, line 8-10 |
| Appendices | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not applicable |
| 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 | Not applicable |

*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 "<u>Attribution-NonCommercial-NoDerivs 3.0 Unported</u>" license.