



Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) in the management of cancers of the colon, ovary and stomach: a randomised controlled phase II trial of efficacy in peritoneal metastases.

Protocol

Vn1.0, 26th April 2023

Sponsor:	Cardiff and Vale University Health Board Joint Research Office, Lakeside Building 2 nd Floor, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW
Sponsor ref:	21/SEP/8237E
Funder:	NIHR
Funder ref:	NIHR151274
REC ref:	TBC
IRAS number:	1006905
EudraCT ref:	2022-003680-26
ISRCTN ref:	
Q-Pulse Document Template Number:	TPL/003/1 v4.0

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR SOPs.

We agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

We also confirm that we will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:			
Name	Position	Signature	Date
Maureen Edgar	Research Governance Manager	Please see email dated 26 th April 2023 for approval signature	26 th April 2023
CTR Director:			
Name	Signature	Date	
Richard Adams	Please see email dated 26 th April 2023 for approval signature	26 th April 2023	
Chief Investigators:			
Names	Signatures	Date	
Sadie Jones	Please see email dated 26 th April 2023 for approval signature	26 th April 2023	
Jared Torkington	Please see email dated 26 th April 2023 for approval signature	26 th April 2023	

General Information This protocol describes the PICCOS clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

CONTACT DETAILS

CHIEF INVESTIGATORS (CI)	
Professor Jared Torkington Consultant Colorectal Surgeon Cardiff and Vale UHB Tel: 02920745148 Email: jared.torkington@wales.nhs.uk	Mrs Sadie Jones Consultant Gynaecology Oncology Surgeon Cardiff and Vale UHB Tel: 029220741249 Email: sadie.jones2@wales.nhs.uk
CO-INVESTIGATORS	
Colorectal Oncology Lead	Colorectal Surgical Lead
Professor Richard Adams Consultant Clinical Oncologist/ CTR Director Cardiff University / Velindre NHS Trust E-mail: richard.adams@wales.nhs.uk	Professor Jamie Murphy Consultant Surgeon Imperial College London E-mail: jamie.murphy@imperial.ac.uk
Ovarian Oncology Lead	Ovarian Surgical Lead
Dr Emma Hudson Consultant Clinical Oncologist Velindre NHS Trust E-mail: emma.hudson@wales.nhs.uk	Mr Jonathan Frost Consultant Gynaecology Oncology Surgeon Royal United Hospital Bath NHS Foundation Trust E-mail: j.frost@nhs.net
Stomach Oncology Lead	Stomach Surgical Lead
Dr Sarah Gwynne Consultant Clinical Oncologist Swansea Bay University Health Board E-mail: sarah.gwynne@wales.nhs.uk	Mr Christopher Peters Consultant Surgeon Imperial College London E-mail: christopher.peters@imperial.ac.uk
Radiology Lead	Health Related Quality of Life Lead
Professor Gina Brown Consultant Radiologist / Chair of Gastrointestinal Radiology Imperial College London E-mail: gina.brown@imperial.ac.uk	Professor Deborah Fitzsimmons Chair of Health Economics and Outcomes Research, Swansea University E-mail: d.fitzsimmons@swansea.ac.uk
Qualitative sub study Lead	Lead Statistician
Professor Jane Blazeby Professor of Surgery University of Bristol E-mail: j.m.blazeby@bristol.ac.uk	Angela Casbard Senior Research Fellow (Statistics) / Deputy Direction of the Cancer Division Centre for Trials Research, Cardiff University E-mail: CasbardAC@cardiff.ac.uk
CTR Study Lead	
Dr Lisette Nixon Senior Research Fellow; Deputy Head of Trial Management (Cancer) Centre for Trials Research, Cardiff University E-mail: NixonLS@cardiff.ac.uk	

SPONSOR REPRESENTATIVE

Mrs Maureen Edgar
Research Governance Manager
Joint Research Office (R&D)
Cardiff and Vale University Health Board
E-mail: maureen.edgar@wales.nhs.uk

RESEARCH PARTNERS

David Chuter, Joy Garfitt and Harry Hall
c/o PICCOS@cardiff.ac.uk

TRIAL CO-ORDINATION

The PICCOS trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the PICCOS Trial Management Group (TMG).

For **all queries** please contact the PICCOS team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email: **PICCOS@cardiff.ac.uk**

Trial Administrator: Zoe Smith

Senior Trial Manager: Elena Brogden

Trial Manager: Rebecca Hamilton

Data Manager: Huda Mohamed/ Philip Markham

Trial Statistician: Tairirai (Lincoln) Mahachi

Study Lead: Lisette Nixon

Director: Richard Adams

Pharmacovigilance and Safety Specialist Team

Email: ctr-safety@cardiff.ac.uk

Randomisation:

Randomisation

The randomisation system can be accessed via: <https://trials.cardiff.ac.uk/portal/>

See section 9.4 for more details.

Clinical queries:

Clinical queries

Please send any clinical queries to PICCOS@cardiff.ac.uk. All queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the CTR Safety Team (ctr-safety@cardiff.ac.uk) within 24 hours of becoming aware of the event (See section 14 for more details).

Table of Contents

1	Amendment History	12
2	Synopsis	13
3	Trial summary & schema	18
3.1	Trial schema/ Participant flow diagram	18
3.2	Trial lay summary	19
4	Background	20
4.1	Laboratory studies	21
4.2	Experimental medicine studies	22
4.3	Pilot data	22
4.4	Epidemiological or case series data	22
4.5	Initial cases series	23
	Colorectal	23
	Ovarian	23
	Stomach	23
5	Trial objectives/endpoints and outcome measures.....	24
5.1	Primary objectives	24
5.2	Secondary objectives	24
5.3	Tertiary/Exploratory objectives	24
5.4	Primary outcome measure	25
5.5	Secondary outcomes measures	25
5.6	Tertiary/Exploratory outcomes	25
6	Trial design and setting	26
6.1	Risk assessment	26
7	Site and Investigator selection	27
8	Participant selection	28
8.1	Inclusion criteria	28
	All disease groups:	28
	Colorectal group only:	29
	Ovarian group only:	29
	Stomach group only:	29
8.2	Exclusion criteria	29
	All disease groups:	29
	Colorectal group only:	29
	Ovarian group only:	30
	Stomach group only:	30
9	Recruitment, screening and registration	30
9.1	Participant identification	30
9.2	Screening logs	31
9.3	Informed consent	31
	Consent for the qualitative sub-study.....	32
9.4	Randomisation	32
10	Withdrawal & lost to follow-up	33
10.1	Withdrawal	33
10.2	Lost to follow up	34
11	Trial Intervention	34
11.1	Treatments.....	34
	Colorectal group treatment	35
	Ovarian group treatment	40
	Stomach group treatment.....	42
11.2	Treatment supply and storage (all disease groups)	48
11.3	Treatment prescribing and dispensing (all disease groups)	48
11.4	Drug administration	49

SACT	49
PIPAC chemotherapy	49
PIPAC procedure – all groups	49
11.5 Delays	50
PIPAC	50
SACT	50
11.6 Dose modification for toxicity	50
11.7 Management of toxicity and hypersensitivity reactions	51
11.8 Management of overdose/ underdose	51
11.9 Pre-medication	51
11.10 Prohibited medications and interaction with other drugs	51
Prohibited medications	51
Medications permitted with caution / procedures	52
11.11 Permitted concomitant medications	52
11.12 Supportive care	52
11.13 Accountability procedures	52
11.14 Drug labelling	52
11.15 Drug disposal	52
SACT	52
PIPAC chemotherapy	53
12 Sample management	53
13 Trial procedures	53
13.1 Assessments	53
Baseline assessments- all participants	53
Assessments prior to each cycle of SACT	54
Assessment prior to each PIPAC	56
Assessments 30 days after each PIPAC	57
CT scans	57
QoL questionnaires (EORTC QLQ-C30)	57
PIPAC procedure	58
Monitoring during surgery	60
Post-surgery procedure	61
13.2 Follow-up	61
13.3 Payment	62
13.4 Disease response assessment	62
14 Pharmacovigilance	62
14.1 Definitions	63
14.2 Trial specific SAE reporting requirements	64
Events requiring reporting	64
Events that do not require reporting	64
14.3 Causality	64
14.4 Expectedness	65
14.5 Reporting procedures	67
Participating site responsibilities	67
The CTR responsibilities	68
14.6 SUSAR reporting	69
14.7 Safety reports	69
14.8 Contraception and pregnancy	70
Contraception	70
Pregnancy reporting whilst participating in the trial	70
14.9 Urgent Safety Measures (USMs)	71
15. Statistical considerations	71
15.1 Randomisation	71

15.2	Sample Size	71
	Colorectal	72
	Ovarian.....	72
	Stomach	72
15.3	Missing, unused & spurious data.....	72
15.4	Procedures for reporting deviation(s) from the original SAP	73
15.5	Termination of the trial.....	73
15.6	Inclusion of analysis	73
16	Analysis	74
16.1	Main analysis	74
16.2	Sub-group & interim analysis.....	75
17	Data Management	75
17.1	Data collection	75
17.2	Completion of CRFs.....	75
17.3	Quality of Life questionnaires.....	76
18	Translational research.....	76
19	Qualitative sub-study.....	76
20	Protocol/GCP non-compliance.....	79
21	End of trial definition	79
22	Archiving	79
23	Regulatory considerations	80
23.1	CE Mark.....	80
23.2	CTA.....	80
23.3	Ethical and governance approval.....	80
23.4	Amendments	80
23.5	Data protection.....	80
23.6	Indemnity.....	81
23.7	Trial sponsorship.....	81
23.8	Funding	82
23.9	Participant payments.....	82
24	Trial management.....	82
24.1	TMG	82
24.2	Trial Steering Committee (TSC).....	83
24.3	IDMC	83
25	Quality Control and Assurance	83
25.1	Monitoring	83
25.2	Central review of radiology.....	83
25.3	Audits & inspections	83
26	Publication policy.....	84
27	Milestones.....	84
28	References	85
29	Appendices.....	93
29.1	PCI	93
29.2	ECOG	95
29.3	RECIST V1.1	96
29.4	Schedule of assessments	97
29.5	PIPAC and SACT schedule vs CT scans and QoL questionnaires	109
29.6	Clavien Dindo classification of surgical complications.....	112

Table of tables

Table 1: Screening requirements.....	30
Table 2 Colorectal group dosing schedule	36

Table 3 Ovarian group dosing schedule.....	40
Table 4 Stomach group dosing schedule	43
Table 5: PIPAC preparation details	49
Table 6: Baseline Assessments	54
Table 7: Assessments required prior to each SACT cycle	56
Table 8 Assessments required prior to PIPAC	56
Table 9: Requirements to be met prior to PIPAC	60
Table 10: Follow-up Assessments.....	61
Table 11: SAE definitions	63
Table 12: Colorectal Causality	64
Table 13: Ovarian Causality	64
Table 14: Stomach Causality.....	65
Table 15: SAE relationship	65
Table 16: Colorectal RSI	66
Table 17: Ovarian RSI.....	66
Table 18: Stomach RSI	67
Table 19: Laparoscopic surgery RSI	67
Table 20: Anatomic structures involved in the 13 abdominopelvic regions of the PCI	94
Table 21: ECOG Criteria	95
Table 22: Colorectal group control arm schedule.....	97
Table 23 Colorectal group intervention arm schedule	99
Table 24 Ovarian group control arm schedule	101
Table 25 Ovarian group intervention arm schedule	103
Table 26 Stomach group control arm schedule.....	105
Table 27 Stomach group intervention arm schedule	107
Table 28: Clavien Dindo classification of surgical complications	112

Table of Figures

Figure 1: Trial Schema	18
Figure 2 Colorectal group treatment schema.....	35
Figure 3 Ovarian group treatment schema	40
Figure 4 Stomach group treatment schema	42
Figure 5: PCI.....	94
Figure 6: Colorectal group	109
Figure 7: Ovarian group	110
Figure 8: Stomach group.....	111

Glossary of abbreviations

5FU	Fluorouracil	IUS	Intrauterine hormone-releasing system
AE	Adverse Event	ISSPP	International Society for Study of Pleura and Peritoneum
ALT	Alanine transaminase	IV	Intravenous
AR	Adverse Reaction	kg	Kilograms
AST	Aspartate transaminase	LFT	Liver Function Test
bPFS	Biochemical Progression free survival	LS	Lesion Size
C&C	Capability and Capacity	MDT	Multi-Disciplinary Team
C&V	Cardiff and Vale University Health Board	mg	Milligrams
CA125	Cancer Antigen 125	MHRA	Medicine and Healthcare products Regulatory Agency
CAWS	Closed Aerosol Waste System	mOS	Median Overall Survival
CEA	Carcinoembryonic Antigen	MSI	Micro-Satellite Instability
CF	Consent Form	NCA	National Competent Authority
CI	Chief Investigator	NHS	National Health Service
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments	NICE	National Institute for Health and Care Excellence
CPS	Combined Positive Score	NIHR	National Institute for Health and Care Research
CrCl	Creatinine Clearance	NIMP	Non-Investigational Medicinal Product
CRF	Case Report Form	ORR	Overall Response Rate
CRS	Cytoreductive surgery	OS	Overall Survival
CT	Computerized Tomography	PAG	Patient Advisory Group
CTA	Clinical Trials Authorisation	PCI	Peritoneal Cancer Index
CTCAE	NCI Common Terminology Criteria for Adverse Events	PFS	Progression free survival
CTR	Centre for Trials Research	PI	Principal Investigator
DCR	Disease Control Rate	PICCOS	PIPAC In Cancers of the Colon, Ovaries and Stomach
DSUR	Development Safety Update Report	PIPAC	Pressurised IntraPeritoneal Aerosolised Chemotherapy
DPYD	Dihydropyrimidine dehydrogenase deficiency	PIS	Participant Information Sheet
ECG	Electrocardiogram	PM	Peritoneal Metastasis
ECOG	Eastern Cooperative Oncology Group	pPFS	Peritoneal specific Progression Free Survival
EORTC	European Organisation for Research and Treatment of Cancer	PROMS	Patient Reported Outcome Measures
ePFS	Extraperitoneal Progression Free Survival	PV	Pharmacovigilance
ePIPAC	Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy	QoL	Quality of Life
EudraCT	European Clinical Trials Database	R&D	Research and Development
FBC	Full Blood Count	RCT	Randomised Controlled Trial
FFPE	Formalin Fixed Paraffin Embedded	REC	Research Ethics Committee
GCP	Good Clinical Practice	RECIST	Response Evaluation Criteria in Solid Tumours

GDPR	General Data Protection Regulations	RSI	Reference Safety Information
GMP	Good Manufacturing Practice	SACT	Systemic Anti-Cancer Therapy
GP	General Practitioner	SAE	Serious Adverse Event
HCRW	Health Care Research Wales	SAP	Statistical Analysis Plan
HER2	Human epidermal growth factor receptor 2	SAR	Serious Adverse Reaction
HIPEC	Hyperthermic intraperitoneal chemotherapy	SmPC	Summary Product Characteristics
HR	Hazard Ratio	SoC	Standard of Care
HRA	Health Research Authority	SOP	Standard Operating Procedure
ID	Identifier	SUSAR	Suspected Unexpected Serious Adverse Reactions
IDEAL	Idea, Development, Exploration, Assessment, Long Term Study: Framework	TMF	Trial Master File
IDMC	Independent Data Monitoring Committee	TMG	Trial Management Group
IMP	Investigational Medicinal Product	TSC	Trial Steering Committee
IP	Intraperitoneal	TSF	Trial Statistical File
IRAS	Integrated Research Application System	U&E	Urea and Electrolytes
ISF	Investigator Site File	UK	United Kingdom
ISR	Investigator Safety Report	USM	Urgent Safety Measure
ISRCTN	International Standard Randomised Controlled Trial Number	WOCBP	Women of Childbearing Potential

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A	1.0		N/A

2. Synopsis

Short title	Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) in the management of cancers of the colon, ovary and stomach: a randomised controlled phase II trial of efficacy in peritoneal metastases.
Acronym	PICCOS
Sponsor ref. no.	21/SEP/8237E
Clinical phase	Phase II
Funder and ref.	NIHR EME: NIHR151274
Trial design	Multicentre, unblinded, phase II, basket trial, randomised controlled trial
Trial participants	Patients with colorectal, ovarian or stomach cancer with peritoneal metastases (PM)
Planned sample size	Colorectal group: 78 Ovarian group: 66 Stomach group: 72
Planned number of sites	10 PIPAC sites and 30 Recruiting sites
Inclusion criteria	<p>All disease groups:</p> <ol style="list-style-type: none"> 1) 16 Years and older. 2) Visible (measurable or non-measurable) peritoneal lesion(s) on computerised tomography (CT) imaging as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. 3) Eastern Cooperative Oncology Group (ECOG) performance status 0–1 4) Adequate bone marrow, liver and kidney function (within 7 days prior to randomisation): <ol style="list-style-type: none"> a) Neutrophil $\geq 1.5 \times 10^9/L$ b) White blood cells $\geq 3.0 \times 10^9/L$ c) Platelets $\geq 100 \times 10^9/L$ d) Haemoglobin $\geq 90 \text{ g/l}$ e) Serum bilirubin $\leq 3 \times \text{ULN}$ f) ALT/AST $\leq 2.5 \times \text{ULN}$ (if both done, both must meet criteria) g) Creatinine clearance $\geq 60 \text{ mls/min}$ 5) Fit enough to receive full dose of systemic anti-cancer therapy (SACT) in cycle 1 as defined in the protocol. 6) Ability to provide informed consent obtained prior to any trial-specific screening procedures. <p>Colorectal group only:</p> <ol style="list-style-type: none"> 1) PM from histologically proven primary adenocarcinoma of the colorectum. <p>Ovarian group only:</p> <ol style="list-style-type: none"> 1) PM from histologically confirmed primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant carcinoma (including clinical recurrence, refractory disease, or persistent disease within 6 months of last chemotherapy).

	<p>Stomach group only:</p> <ol style="list-style-type: none"> 1) PM from histologically proven primary adenocarcinoma (any subtype) of stomach or Siewert type 3 gastro-oesophageal junction tumour (any Human Epidermal Growth Factor Receptor 2 (HER2) status or Combined Positive Score (CPS)).
Exclusion criteria	<p>All disease groups:</p> <ol style="list-style-type: none"> 1) Any prior malignancy not considered in complete remission for at least 2 years, excluding non-melanoma skin cancer. 2) Pregnant or breastfeeding. 3) Untreated central nervous system disease or symptomatic central nervous system metastasis, history or evidence of thrombotic or haemorrhagic disorders not considered currently in complete remission. 4) Bevacizumab / Aflibercept should not be used in either arm (minimum 4 weeks from any prior bevacizumab / Aflibercept). 5) Contraindication to any drug contained in the chemotherapy regimen. 6) Medical, geographical, sociological, psychological, or legal conditions that would prevent the patient from completing the study or signing the informed consent. 7) Unresolved bowel obstruction or parenteral nutrition or gastric tube. 8) Contraindication to surgery. 9) Participating in other oncological trials that may impact on endpoint. <p>Colorectal group only:</p> <ol style="list-style-type: none"> 1) Extra-peritoneal metastases except for: <ol style="list-style-type: none"> a) retroperitoneal lymph nodes <2cm b) lung metastases; with < 5 lung metastases none >1cm 2) Eligible for and chooses cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) upfront. 3) Prior systemic therapy for colorectal cancer in the last 6 months. 4) Dihydropyrimidine Dehydrogenase Deficiency (DPYD) variant detected. 5) Microsatellite instability (MSI) high. <p>Ovarian group only:</p> <ol style="list-style-type: none"> 1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes). 2) Parenchymal liver or spleen metastases. 3) Malignant pleural effusion. 4) Non-epithelial pathology subtype. 5) Peritoneal disease, amenable to surgical resection. 6) Radiological suspicion of involved lymph nodes (e.g. radiological features suspicious of malignancy). <p>Stomach group only:</p> <ol style="list-style-type: none"> 1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes). 2) Prior SACT, radiotherapy or surgery for stomach cancer. 3) Gastric or duodenal stent in-situ.

	4) Gastro-oesophageal junction Sievert Type 1 or Type 2 tumour. 5) Symptoms and/or radiology suggestive of impending and/or current bowel obstruction. 6) Uncontrolled and persistent ascites. 7) MSI high. 8) DPYD variant detected.		
Treatment duration	Colorectal group	Intervention arm	18 weeks
		Control arm	18 weeks
	Ovarian group	Intervention arm	14-15 weeks
		Control arm	18 or 24 weeks
	Stomach group	Intervention arm	18 or 21 weeks
		Control arm	18 weeks
Follow-up duration	Participants will be followed up for a minimum 6 months from their date of randomisation		
Planned trial period	<ul style="list-style-type: none"> Trial set up: 6 months. Recruitment period: 2.5 years. Follow up period: at least 6 months from randomisation. Analysis and report writing: 6 months. 4 years total. 		
Primary objective	<ul style="list-style-type: none"> To determine if PIPAC given with (colorectal, stomach) or instead of (ovarian) SACT improves Peritoneal Progression Free Survival (pPFS) compared to standard SACT. 		
Secondary objectives	<ul style="list-style-type: none"> To determine how PIPAC impacts quality of life (QoL) compared to standard of care (SOC). To determine the safety of PIPAC in terms of the proportion of patients experiencing toxicity and/or surgical complications, compared with SACT only group. To determine the proportion of patients who complete three PIPAC procedures. To determine if disease can be reduced to the point of resectability. To evaluate Overall Survival (OS) in both groups. To evaluate overall Progression Free Survival (PFS) in both groups. To assess the impact on patient's symptoms (and need for intervention to relieve them – in ovarian cancer). To determine peritoneal specific overall response rate (ORR) and disease control rate (DCR). 		
Tertiary/Exploratory objectives	<ul style="list-style-type: none"> To determine the feasibility of randomisation. Explore stakeholder perspectives and experiences of PIPAC treatment, including its impact on symptoms and QoL. 		

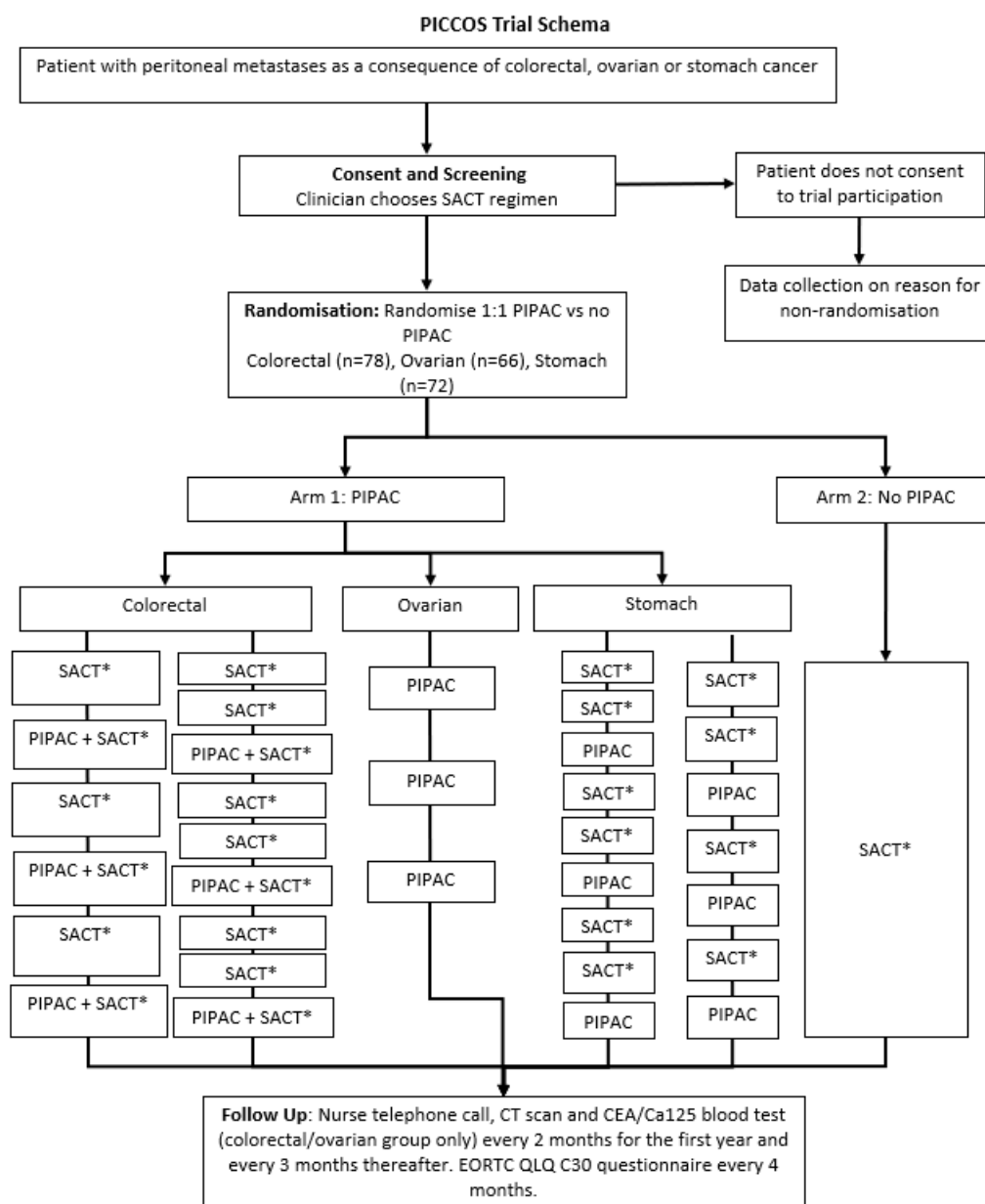
	<ul style="list-style-type: none"> To determine the patient related outcomes of interest for patients with PM undergoing PIPAC and establish if a new measurement scale/item is needed. To identify/develop a patient reported measure for patients with PM undergoing PIPAC and test this in patients recruited in the latter half of the trial. To evaluate and compare between the two arms the response of Carcinoembryonic Antigen (CEA) (in colorectal cancer) and Cancer Antigen 125 (CA125) (in ovarian cancer) with the radiological response of peritoneal disease. To cross correlate the radiological evaluation to assess scan effectiveness and mismatches with PCI scoring at laparoscopy.
Primary outcomes	<ul style="list-style-type: none"> pPFS
Secondary outcomes	<ul style="list-style-type: none"> QoL (EORTC QLQ C30) Safety and surgical complication rates <ul style="list-style-type: none"> Toxicity and grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE) V5.0 <ul style="list-style-type: none"> Episodes of neutropenic sepsis Clavien Dindo classification (within 30 days of each PIPAC) Incidence of radiologically proven bowel obstruction Proportion of patients completing 3 PIPAC procedures, and reasons why not if <3 completed. Number of conversions to operable disease in stomach or colorectal cancer OS, defined as days from randomisation to death for any reason. PFS. This is defined as the time from date of randomisation to the date of progression (anywhere in the patient) or death from any cause. <ul style="list-style-type: none"> Extraperitoneal Progression free survival (ePFS), defined as the time from date of randomisation to the date of progression (outside of the peritoneum) or death from any cause. Episodes of therapeutic ascitic drainages (in ovarian cancer) Peritoneal specific ORR observed at any time during treatment and follow-up. Peritoneal specific DCR defined as the proportion of patients with complete response, partial response or stable disease maintained at end of treatment scan (i.e. 3rd scan).

Tertiary/Exploratory outcomes	<ul style="list-style-type: none"> • The proportion of eligible patients who consent to randomisation out of those invited to take part. • Patient related outcomes of interest in patients with PM undergoing PIPAC as determined by qualitative interviews with healthcare professionals and patients. • Identification/development of a patient-reported measure for patients with PM undergoing PIPAC. • CEA (in colorectal cancer) and CA125 (in ovarian cancer) response from baseline to the end of follow up. • PCI scoring at laparoscopy.
Investigational medicinal products (IMPs)	<p>For Colorectal group:</p> <ul style="list-style-type: none"> • Oxaliplatin 120mg/m² IP as PIPAC (dose reduction to 90mg/m² for patients with frailty or neuropathy as agreed by site oncologist). • Mitomycin 7.5mg/m² IP as PIPAC for patients who are hypersensitive to, or unable to have Oxaliplatin.
	<p>For Ovarian group:</p> <ul style="list-style-type: none"> • Cisplatin 10.5mg/m² IP as PIPAC • Doxorubicin 2.1mg/m² IP as PIPAC • Paclitaxel 80mg/m² IV • Liposomal doxorubicin 50mg/m² IV • Gemcitabine 1000mg/m² IV
	<p>For Stomach group:</p> <ul style="list-style-type: none"> • Cisplatin 10.5mg/m² IP as PIPAC • Doxorubicin 2.1mg/m² IP as PIPAC

3 Trial summary & schema

3.1 Trial schema/ Participant flow diagram

Figure 1: Trial Schema



* SACT = Systemic Anti-Cancer Therapy. Should be as per standard of care options listed within the PICCOS protocol. There are 2 or 3 weekly options for colorectal/ stomach groups, regimen given is chosen by treating clinician, ovarian SACT is 4 weekly.

3.2 Trial lay summary

Aims

Bowel, ovarian and stomach cancer will often spread (metastasise) to the lining (peritoneum) of the abdominal cavity. This trial aims to determine if a new way of delivering chemotherapy as a spray, directly into the peritoneal cavity, would improve survival in patients with peritoneal metastases, compared to conventional intravenous chemotherapy. Critically, we will also assess the impact of treatment on patient QoL.

Background

Up to 13%, 50% and 14% of patients with bowel, ovarian and stomach cancer respectively, present with peritoneal metastases. When this form of spread occurs, patients are normally informed that their disease is incurable. As well as a relatively rapid decline, peritoneal metastases can cause a series of unpleasant symptoms due to new tumour growth. Peritoneal metastases are difficult to treat with conventional anticancer drugs and there is an urgent need to develop new treatment strategies. A new strategy showing potential is Pressurised IntraPeritoneal Aerosol Chemotherapy (PIPAC). PIPAC delivers anti-cancer drugs into the peritoneal cavity as an aerosol during keyhole surgery. PIPAC has been shown to deliver higher doses of chemotherapy directly to tumour sites compared to conventional treatment, with fewer side-effects due to less chemotherapy circulating in the blood. PIPAC has been shown to be both safe and feasible in a series of clinical trials. The question that now remains is whether PIPAC is effective or not. The National Institute for Health and Care Excellence (NICE) has recommended that PIPAC should only be offered to United Kingdom (UK) patients within a research trial setting. There are trials for patients in Europe but not in the UK.

Design and Methods

This randomised controlled trial will be open to patients with bowel, ovarian or stomach cancer. Each cancer type will have individual eligibility criteria and protocols to allow for the necessary variations in treatment. In all cancer types, patients will be randomised to receive either standard chemotherapy delivered via the bloodstream or a combination of standard chemotherapy and/or PIPAC, where three PIPAC procedures are performed. This trial design enables the variation required to include patients with different cancer types and the ability to stop the trial for any one cancer type if it is not working whilst continuing with the others.

Patient and Public involvement

Many patients in the UK are aware of PIPAC treatment with specialists frequently approached by patients and carers requesting it. This has been a driving force in developing this trial. Patients have been involved from an early stage and helped to determine acceptable time points for investigations, design travel policies, select the best QoL assessment tools, define the priority of research questions and write the proposal to this point. They will continue to support trial design, raise trial awareness and ensure patient concerns and well-being are given paramount importance going forwards. PIPAC has excited much interest in patient groups. We will disseminate trial results through social media,

relevant charitable organisations, presentation at academic conferences, peer-reviewed journals, and through the Centre for Trials Research (CTR) trial web page. Information leaflets, public presentations and media coverage are integral elements of our public engagement plans. The results will strongly influence future NICE review of PIPAC use in the UK.

4 Background

Colorectal, ovarian and stomach cancers account for 24,500 deaths a year in the UK. When these tumours spread or recur within the peritoneum, they are generally deemed incurable as no effective treatment strategy exists (1–3). As many as 10% of colorectal, 50% of ovarian and 14% of stomach cancers will have PM at the time of presentation (4). In colorectal cancer, 2% have peritoneal disease as the only site of metastases. A minority of fit patients with low volume disease may be suitable for major surgery in combination with Hyperthermic Intraperitoneal Chemotherapy (HIPEC). However, for many this is not an option as it is not suitable for extensive disease and patients must have a high level of fitness to tolerate such an invasive procedure. Patients unable to undergo or access HIPEC have a median PFS of 6 months and OS of 16.3 months (5). In ovarian cancer 25% of patients will have disease that is resistant to platinum chemotherapy. Platinum resistance is a poor prognostic factor with a median PFS of 3-4 months and OS of 9-13 months (6–8). Patients with stomach cancer and PM have a particularly poor OS of 3-6 months, extended to 9-11 months with standard SACT (9,10). PM can cause ascites and bowel obstruction leading to abdominal pain, nausea, vomiting and significant suffering. Patients are left with an uncertain future, reduced QoL and very few treatment options. It is clear and is acknowledged by the clinical community that standard SACT across all three disease groups is not having the desired impact. Peritoneal metastatic disease represents a significant unmet clinical need and there is an urgent need for improved treatments for these poor prognosis patient groups. A novel anti-cancer technology is PIPAC. PIPAC aims to improve target specificity of anti-cancer therapies such as chemotherapy by delivering the medication directly to the PM (11,12). Chemotherapy is delivered as an aerosol into the closed abdominal cavity at conventional laparoscopy. It is suggested that the small size of the droplets under the raised intraperitoneal pressure utilised during laparoscopy drives the chemotherapy directly into the tumour nodules. There is reduced systemic absorption creating a greater local tumour effect and reducing the common side effects of systemic chemotherapy.

The PICCOS trial (PIPAC In Cancers of the Colon, Ovaries and Stomach) is a multi-arm, prospective, randomised controlled trial (RCT) designed to provide high quality evidence regarding the efficacy of PIPAC in improving PFS. PIPAC has already achieved rapid uptake across Europe, driven often by patient demand and clinician enthusiasm. However, high quality efficacy data is lacking and is required now. In October 2021, NICE Interventional Procedures Guidance (IPG681) for PIPAC was published and stipulated that PIPAC should only be used within the context of research. The NICE stated that this research should be in the form of RCTs to demonstrate efficacy compared to standard treatments (13). PICCOS will provide the opportunity to address this in the UK and provide direction for future phase III trials. PICCOS will provide a unique opportunity to further understand impact of PIPAC on patients with PM on patient QoL. A mechanistic sub-study has been created to understand what is important to patients with PM and how to measure these factors using the COnsensus-based

Standards for the selection of health Measurement INstruments (COSMIN) methodology. This output from PICCOS will be crucial to future trials of therapy in PM.

Our team initially approached NICE and provided evidence highlighting PIPAC as a subject of interest. The NICE statement document (IPG681) was published, concluding that the existing evidence signalled that PIPAC may improve disease response, PFS, OS and QoL, but the research was heterogeneous in quality and described infrequent but serious side effects (13). NICE were clear in recommending that in the UK, PIPAC should only be performed in the context of an RCT. Without establishing such a trial, we will be unable to address the existing knowledge gap. Prior to the NICE statement we had established the UK PIPAC collaborative to investigate PIPAC as a treatment modality. In response to the NICE statement the PICCOS trial developed. We are aware of no additional ongoing or planned RCTs assessing PIPAC in the UK currently.

We initially conducted comprehensive literature reviews to fully understand the existing evidence base and inform the design of the PICCOS trial. In 2020, we published a review of the worldwide introduction of PIPAC in relation to the Idea, Development, Exploration, Assessment, Long-Term (IDEAL) Study framework. This review identified 86 relevant publications but no RCTs and concluded that there was acceptable safety data, but a lack of robust prospective data on the efficacy of the treatment (14) and was updated and republished in 2022 (15). Our updated review has demonstrated that many of the registered studies and published evidence worldwide remain in the early phases of the IDEAL framework underlining the need for high quality clinical trials. We have also undertaken a systematic review of the literature specifically relevant to stomach cancer that was submitted for publication in April 2022 and are currently undertaking the same for ovarian cancer. Both are registered on the PROSPERO database (16,17). A systematic review for colorectal cancers was published in 2021 by another group so this has not been repeated (18). The searches for these studies were conducted on Medline and Ovid databases using search terms to include studies involving PIPAC and peritoneal metastases, irrespective of cancer origin, up to 28th February 2022. ClinicalTrials.gov and the EU Clinical Trials registers were searched for trial registrations (up to 19th January 2022) involving PIPAC. The list illustrates the impact of the NICE statement and the importance of establishing a UK based RCT. The teams from Lyon and Paris have already indicated their interest in future pooling of appropriate RCT data for meta-analysis with us.

This approach of strong scientific exploration through RCT data and international collaboration will lead to the most rapid understanding of the efficacy of PIPAC and its effect on patient QoL. The adoption and optimisation of PIPAC (or indeed its discard) as a treatment modality will lead to a step change in patient care across the world.

4.1 Laboratory studies

The published laboratory studies include the use of simulators, animal models, cell lines, in vitro and ex vivo studies. The first description of a “therapeutic pneumoperitoneum”, was using an in vivo swine model, published in 2000(19). Studies demonstrated superiority of PIPAC over conventional lavage with regards to peritoneal distribution and depth of drug penetration using methylene blue dye, and Dbait (non-coding DNA fragments) with a fluorescent marker(20,21). Further studies, utilising both in

vivo and ex vivo swine models and a laparoscopic box simulator, demonstrated that depth of drug penetration was highest closest to the delivery device, and that distribution of the aerosol around the peritoneum was heterogeneous (22–24). Parameters to optimise drug penetration and distribution were explored; in one study, increasing the intra-abdominal pressure to 15mmHg (from 12mmHg) increased the cytotoxic action of oxaliplatin on an in vitro human colon adenocarcinoma cell line, but a higher temperature did not have a significant effect (25).

4.2 Experimental medicine studies

Attempts have been made to optimise the technique in vitro. These include demonstrating the stability of nano or micro particles (26,27), the successful use of an anti-adhesive polymer as a delivery system (28), and demonstrating that liposomal doxorubicin caused almost complete inhibition of drug action during PIPAC (29). Further experiments aimed to address the issue of non-homogenous drug distribution with the use of a rotational or multi-directional nozzle, to change the direction of spray in the abdomen (30,31). Use of these devices with in vivo swine models demonstrated wider distribution than the conventional microinjection pump. A modification involved the use of electrostatic precipitation and was named ePIPAC (32). Improvement of spatial distribution and tissue penetration was shown with the addition of an electrostatic charge (ePIPAC) to fluorescent albumin bound paclitaxel nanoparticles in a rat model (33).

4.3 Pilot data

The first in-human studies were performed by the Bochum group on patients with PM and no alternative treatment options and published in 2013 and 2014 (34,35). They demonstrated histological tumour regression of peritoneal disease in the three patients treated, with limited renal and liver toxicity despite repeated PIPAC cycles. The surgical set-up described would become the most widely used technique, and consisted of pressurised aerosolization of cisplatin and doxorubicin, with a CO₂ pneumoperitoneum at a pressure of 12 mmHg over 30 mins, at a temperature of 37°C. Dosage of cisplatin (7.5mg/m² body surface) and doxorubicin (1.5mg/m² body surface) were set as 10% of their usual systemic dose.

Occupational health studies demonstrated safety for theatre staff (36), although almost all new groups embarking on PIPAC each performed their own occupational safety tests despite using similar equipment and operating procedures (37–39).

4.4 Epidemiological or case series data

Case reports were used to describe the first use of PIPAC for different indications, including pancreatic cancer, PM in organ donor recipients, ovarian cancer and pseudomyxoma peritonei (40–42). Complications included peritoneal sclerosis and rare instances of severe hypersensitivity reactions to platinum (43,44). The latter was described in a case series involving 132 patients, of whom four (3%) had a severe reaction to platinum, manifesting instantaneously, to 50 minutes after application of PIPAC.

4.5 Initial cases series

One study assessed QoL in 91 patients at admission and after their first and second round of PIPAC treatment. A moderate transient increase in pain score was found, but no therapy related decrease in the QoL score was demonstrated (45). The most commonly used chemotherapy regimen used in PIPAC is either oxaliplatin as a sole agent or cisplatin with doxorubicin. Over the last few years, progress has been made regarding formal dose escalation studies. In a phase I study, the Bochum group found that patients undergoing PIPAC could tolerate an increase in the dose of cisplatin and doxorubicin to 10.5mg/m² and 2.1mg/m² respectively (46). A French group found that the maximum tolerated dose of oxaliplatin was 90 mg/m² (47), due to dose-limiting toxicity at the higher dose of 140mg/m² (grade IV allergic reaction and grade III neutropenia). However, the Turin group found in their phase 1 dose escalation study that patients (n=3) could tolerate a maximum dose of 135 mg/m² (48) with no dose-limiting toxicity observed. They also looked at cisplatin and doxorubicin and found a maximum dose of 30mg/m² and 6mg/m²; significantly higher than used in any previous PIPAC application. Common adverse events across all these studies included nausea, vomiting and abdominal pain.

Colorectal

There are no published RCTs of PIPAC in patients with colorectal cancer. PIPAC has an acceptable safety profile and is feasible in patients with colorectal PM with oxaliplatin being the commonest agent used (18). Median OS with the use of PIPAC in non-randomised studies ranges from 8-27 months but with variability in treatment regimens, especially in the stratification between those receiving prior systemic therapy (49–53).

Ovarian

There are no published RCTs of PIPAC in patients with ovarian cancer, studies are either single-arm prospective or retrospective. There are four retrospective studies and one prospective study reporting median overall survival ranging from 6.8–22 months (52–56). The study populations amongst these trials were heterogeneous varying from primary presentation patients to platinum resistant recurrent cases. In 2015, Tempfer et al performed a prospective cohort study assessing mean PFS in 64 patients with recurrent ovarian cancer (platinum resistant and sensitive) and reported PFS of 144 days and 174 days and overall, 1-year survival of 50% and 63% in the intention to treat and per-protocol subgroups respectively (56). A prospective study of 21 patients with unresectable peritoneal metastasis undergoing PIPAC with systemic chemotherapy compared patients who had received bevacizumab with those who had not (57).

Stomach

There are no published RCTs of PIPAC in stomach cancer to determine efficacy, the studies are either single arm prospective or retrospective. There have been 11 retrospective (52,54,58–66), and four prospective studies (50,51,67,68). Median overall survival (mOS) ranged from 8 – 19.1 months and 1-year OS between 49.8-77.9%. Reporting of histological response was heterogeneous, but complete

response was reported in 0-35%, and partial response in 0-83.3%. Grade 3 and 4 toxicity was 0.7-25% and 0-4.1% respectively. Three studies assessed QoL, reporting no significant difference after PIPAC (50,58,68). A published systematic review with an emphasis on patients with ovarian cancer but including patients with colorectal and stomach cancer too, investigated the safety and efficacy of PIPAC demonstrated proof of concept within 28 clinical trials including 1547 patients (69). No RCTs were identified. It concluded that PIPAC was technically feasible in 89% of cases. Safety analysis of 1197 cases revealed adverse events CTCAE grades 4 and 5 in 10 (0.8%) and 19 (1.6%) of patients respectively. Pooled analysis revealed an overall tumour regression rate of 69% (184/264) and an improvement of peritoneal cancer index (PCI), in 69% (116/168). Further analysis of three studies reported a mean PFS of 5.8 months and in 17 studies an OS of 13.7 months. QoL was maintained in all studies with improvement of global health reported in four studies.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

- To determine if PIPAC given with (colorectal, stomach) or instead of (ovarian) SACT improves pPFS compared to standard SACT.

5.2 Secondary objectives

- To determine how PIPAC impacts QoL compared to SOC.
- To determine the safety of PIPAC in terms of the proportion of patients experiencing toxicity and/or surgical complications, compared to the SACT only group.
- To determine the proportion of patients who complete three PIPAC procedures.
- To determine if disease can be reduced to the point of resectability.
- To evaluate OS in both groups.
- To evaluate overall PFS in both groups.
- To assess the impact on patient's symptoms (and need for intervention to relieve them – in ovarian cancer).
- To determine peritoneal specific ORR and DCR.

5.3 Tertiary/Exploratory objectives

- To determine the feasibility of randomisation
- Explore stakeholder perspectives and experiences of PIPAC treatment, including its impact on symptoms and QoL.
- To determine the patient reported outcomes of interest for patients with PM undergoing PIPAC and establish if a new measurement scale/item is needed.
- To identify/develop a patient reported measure for patients with PM undergoing PIPAC and test this in patients recruited in the latter half of the trial.
- To evaluate and compare between the two arms the response of CEA (in colorectal cancer) and CA125 (in ovarian cancer) with the radiological response of peritoneal disease.

- To cross correlate the radiological evaluation to assess scan effectiveness and mismatches with PCI scoring at laparoscopy

5.4 Primary outcome measure

- pPFS - defined as the interval between the date of randomisation and the first radiologically documented progression of peritoneal disease or the date of death from any cause. The pPFS interval measurement will be regardless of intercurrent events of SACT or PIPAC discontinuation, or any change to treatment. Peritoneal disease progression will be assessed using RECIST V1.1 criteria based on CT scans performed according to disease group schedules.

5.5 Secondary outcomes measures

- QoL (EORTC QLQ C30)
- Safety and surgical complication rates
 - Toxicity and grade according to NCI CTCAE V5.0
 - Episodes of neutropenic sepsis
 - Clavien Dindo classification (within 30 days of each PIPAC)
 - Incidence of radiologically proven bowel obstruction
- Proportion of patients completing three PIPAC procedures, and reasons why not if <3 completed.
- Number of conversions to operable disease in stomach or colorectal cancer.
- OS, defined as days from randomisation to death for any reason.
- PFS. This is defined as the time from date of randomisation to the date of progression (anywhere in the patient) or death from any cause.
 - ePFS, defined as the time from date of randomisation to the date of progression (outside of the peritoneum) or death from any cause.
- Episodes of therapeutic ascitic drainages (in ovarian cancer).
- Peritoneal specific ORR observed at any time during treatment and follow-up.
- Peritoneal specific DCR defined as the proportion of patients with complete response, partial response or stable disease maintained at end of treatment scan (i.e. 3rd scan).

5.6 Tertiary/Exploratory outcomes

- The proportion of eligible patients who consent to randomisation out of those invited to take part.
- Patient related outcomes of interest in patients with PM undergoing PIPAC as determined by qualitative interviews with healthcare professionals and patients.
- Identification/ development of a patient-reported measure for patients with PM undergoing PIPAC.
- CEA (in colorectal cancer) and CA125 (in ovarian cancer) response from baseline to the end of follow up.
- PCI scoring at laparoscopy.

6 Trial design and setting

This is a Phase II, unblinded, multicentre, superiority basket randomised controlled trial. Patients will be identified through clinicians at Multi-Disciplinary Team (MDT) meetings in selected recruiting centres. Recruiting clinicians will log onto a central web-based platform that will randomise patients in a 1:1 ratio to either standard of care SACT or the PIPAC intervention arm. We aim to recruit 78 colorectal, 66 ovarian and 72 stomach cancer patients over 2.5 years, and follow-up will last a minimum of 6 months for all participants.

Allocation will be minimised by PIPAC centre to ensure there is not a disparity in per patient resource costs between PIPAC sites and balanced on prognostic factors for each cancer type to avoid bias. Within each centre and disease site, the first patient will be allocated at random, and then minimisation with a 20% random element will be used to allocate the next patient to the treatment which reduces the overall imbalance across all prognostic factors.

Within this trial, there will be a sub-study to utilise the unique opportunity provided by the PICCOS trial to explore QoL issues that are unique to patients with peritoneal metastases undergoing PIPAC and identify/ develop a patient-reported outcome scale or item which can capture the specific QoL issues faced by patients.

The PICCOS trial will also collaborate as a 'host' trial with the Medical Research Council (MRC) funded PrincipIL study: Developing Core Principles for Sharing Information about Potential Intervention Benefits and Harms in Patient Information Leaflets (Research Ethics Committee (REC) reference 22/PR/0063, IRAS 305945) to embed the PrincipIL 'Study Within a Trial' (SWAT) sub-study.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/ Department of Health (DH)/ Medicines and Healthcare Regulatory Agency (MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects.
- How high the risk is compared to normal standard practice.
- How the risk will be minimised/managed.

This trial has been categorised as a TYPE B, where the level of risk is somewhat higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager (TM). The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

This trial will be carried out at participating National Health Service (NHS) sites within the UK. All sites who are interested in participating will be required to complete a registration form to confirm that they have adequate resources and experience.

Up to 40 sites will be opened in total. All sites will be able to recruit and deliver SACT. It is anticipated that 10 sites, geographically spread across the UK, will deliver PIPAC treatment (PIPAC Sites). The remaining sites will be required to refer patients to PIPAC sites when randomised for PIPAC treatment.

In all sites there will be one named Principal Investigator (PI) for the purposes of the IRAS and overall responsibility, and it will be a local decision as to whether this will be an oncologist or surgeon. Each site will have up to 7 Co-PIs (surgery/oncology for each cancer site and single radiologist) depending on local requirements and preference.

The following documents must be in place and copies sent to PICCOS@cardiff.ac.uk before site initiation.

- Confirmation of Capacity and Capability (C&C) from Research and Development (R&D) department following sharing of local information pack.
- A signed Trial Agreement.
- Current Curriculum Vitae and Good Clinical Practice (GCP) training certificate of the PI.
- Completed Site Delegation Log and Roles and Responsibilities document.
- Full contact details for all host care organisation personnel involved, indicating preferred contact.
- A copy of the most recent approved version of the main trial Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper.
- A copy of the most recent approved version of the Qualitative sub study Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper – where applicable.
- A copy of the most recent approved General Practitioner (GP) letters on host care organisation headed paper.
- A copy of the Withdrawal Consent Form on host care organisation headed paper.
- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses.
- Copy of the certificates from at least two surgeons at site confirming completion of the International Society for Study of Pleura and Peritoneum (ISSPP) course on PIPAC (or equivalent) – applicable to “Recruiting and PIPAC sites” only.

The following will be obtained and provided to site by the PICCOS trial team:

- Favourable opinion of host care organisation/PI from Research Ethics Committee (REC).
- Favourable opinion of Health Research Authority/ Health Care Research Wales (HRA/HCRW).

- MHRA approval.
- Site File (including guidance documentation, SAE forms, etc), PICCOS Pharmacy Manual and PIPAC Manual.
- Pharmacy Site File.

Upon completion of all the above documents, the CTR TM will send written confirmation to the PI/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial equipment and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they have the necessary approvals and become available. It is the responsibility of the CTR to ensure that they obtain confirmation of continued C&C for the new documents.

Site initiation will be by attendance at a PICCOS launch meeting or by teleconference if attendance of key personnel is unfeasible.

8 Participant selection

Participants are eligible for the trial if they meet all of the relevant following inclusion criteria for their disease group and none of the exclusion criteria for their disease group apply. All queries about participant eligibility should be directed to the CTR TM before randomisation. Eligibility waivers will not be permitted.

8.1 Inclusion criteria

All disease groups:

- 1) 16 Years and older
- 2) Visible (measurable or non-measurable) peritoneal lesion(s) on CT imaging as per RECIST v1.1
- 3) ECOG performance status 0–1
- 4) Adequate bone marrow, liver and kidney function (within 7 days prior to randomisation):
 - a) Neutrophil $\geq 1.5 \times 10^9/L$
 - b) White blood cells $\geq 3.0 \times 10^9/L$
 - c) Platelets $\geq 100 \times 10^9/L$
 - d) Haemoglobin ≥ 90 g/l
 - e) Serum bilirubin $\leq 3 \times$ ULN
 - f) ALT/AST $\leq 2.5 \times$ ULN (*if both done, both must meet criteria*)
 - g) Creatinine clearance ≥ 60 mls/min
- 5) Fit enough to receive full dose of SACT in cycle 1 as defined in the protocol.
- 6) Ability to provide informed consent obtained prior to any trial-specific screening procedures.

Colorectal group only:

- 1) PM from histologically proven primary adenocarcinoma of the colorectum

Ovarian group only:

- 1) PM from histologically confirmed primary epithelial ovarian, tubal, or primary peritoneal platinum-resistant (clinical recurrence or persistent disease within 6 months of last chemotherapy)

Stomach group only:

- 1) PM from histologically proven primary adenocarcinoma of stomach or sievert type 3 gastro-oesophageal junction tumour (any HER2 status or CPS).

8.2 Exclusion criteria

All disease groups:

- 1) Any prior malignancy not considered in complete remission for at least 2 years, excluding non-melanoma skin cancer.
- 2) Pregnant or breastfeeding.
- 3) Untreated central nervous system disease or symptomatic central nervous system metastasis, history or evidence of thrombotic or haemorrhagic disorders not considered currently in complete remission.
- 4) Bevacizumab / Aflibercept should not be used in either arm (minimum 4 weeks from any prior bevacizumab / Aflibercept).
- 5) Contraindication to any drug contained in the chemotherapy regimen.
- 6) Medical, geographical, sociological, psychological, or legal conditions that would prevent the patient from completing the trial or signing the informed consent.
- 7) Unresolved bowel obstruction or parenteral nutrition or gastric tube.
- 8) Contraindication to surgery.
- 9) Participating in other oncological trials that may impact on progression free survival.

Colorectal group only:

- 1) Extra-peritoneal metastases except for:
 - a) retroperitoneal lymph nodes < 2cm,
 - b) lung metastases; with < 5 lung metastases none >1cm
- 2) Eligible for and chooses CRS and HIPEC upfront.
- 3) Prior systemic therapy for colorectal cancer in the last 6 months.
- 4) DPYD variant detected.
- 5) MSI high.

Ovarian group only:

- 1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes)
- 2) Parenchymal liver or spleen metastases.
- 3) Malignant pleural effusion.
- 4) Low grade pathology subtype.
- 5) Non-epithelial pathology subtype.
- 6) Peritoneal disease, amenable to surgical resection.
- 7) Radiological suspicion of involved lymph nodes (e.g. radiological features suspicious of malignancy)

Stomach group only:

- 1) Extra-peritoneal metastases (with the exception of retroperitoneal lymph nodes).
- 2) Prior systemic anti-cancer therapy, radiotherapy or surgery for stomach cancer.
- 3) Gastric or duodenal stent in-situ.
- 4) Gastro-oesophageal junction Siewert Type 1 or Type 2 tumour.
- 5) Symptoms and/or radiology suggestive of impending and/or current bowel obstruction.
- 6) Uncontrolled and persistent ascites.
- 7) MSI high.
- 8) DPYD variant detected.

9 Recruitment, screening and registration

9.1 Participant identification

Patients will be identified within registered NHS sites across the UK. Participants will be patients with PM from colorectal, ovarian or stomach cancer deemed potentially eligible at local MDT meetings.

Given the trial population it is anticipated that many of the investigations required to ascertain eligibility will have already been undertaken. All results available to the MDT will be used to conduct initial screening against the inclusion and exclusion criteria. Screening logs should be completed at this stage to include all those patients that fulfil eligibility criteria included those invited but not randomised into the trial. Further screening and final confirmation of eligibility will take place after the patient has agreed to participate and signed the trial Consent Form (CF).

Table 1: Screening requirements

Screening test	Timescale
Medical history and examination	Within 28 days prior to randomisation
Performance status assessment (ECOG)	Within 28 days prior to randomisation
Urine pregnancy test (if woman of childbearing potential (WOCBP))	Within 7 days prior to randomisation
Assessment of concomitant medications	Within 28 days prior to randomisation

CT scan with contrast (thorax, abdomen and pelvis)	Within 28 days prior to randomisation
Bloods (FBC, U&Es, LFTs, bone profile, DPYD testing*)	Within 7 days prior to randomisation with the exception of DPYD testing which can be performed at any time prior to randomisation
MSI*, HER2** and CPS** testing on tumour biopsy	Any time prior to randomisation

* *Applicable to colorectal and stomach groups only*

** *Applicable to stomach group only*

9.2 Screening logs

A screening log of all patients with PM not consented or approached will be kept at each site so that any biases from differential recruitment will be detected. As much detail as possible should be recorded on the screening logs.

When at site, logs may contain identifiable information, but this **must be redacted** prior to being sent to the CTR. The screening log should be sent to PICCOS@cardiff.ac.uk on a monthly basis (see section 25 for further detail on data monitoring/quality assurance).

9.3 Informed consent

The patient's clinician will introduce the trial and offer them the opportunity to discuss it in more detail with a member of the local trial team. The nature of the trial, together with all procedures and risks will be fully explained to each prospective trial participant by one of the Investigators. Full details of the trial, in the form of a printed Participant Information Sheet (PIS), will be provided for the patient to take away and consider.

The participant's written informed consent must be obtained using the trial CF, which follows the PIS. The potential participant should be given sufficient time after the initial invitation to participate before being asked to sign the CF (usually 24 hours). Informed consent must be obtained prior to the potential participant undergoing procedures that are specifically for the purposes of the trial, including any screening procedures described in Section 9.1 which are not done as standard. Initial consent to the main trial must be taken by a medically qualified Investigator delegated the responsibility on the site delegation log by the local PI. Reconsent can be taken by anybody who has been appropriately trained and delegated the responsibility on the site delegation log by the local PI, unless indicated otherwise by the CTR. Guidance on use of remote re-consent for amendments will be given by Sponsor at the time of amendment implementation. Please note, only when written informed consent has been obtained from the patient and they have been randomised into the trial can they be considered a trial participant.

Participants should always be asked to initial next to each statement and sign a CF. One copy should be given to the participant, but the original copy should be kept in the Investigator site file and a further copy should be kept with participant's hospital notes.

Participant specific consent is requested to collect their NHS number to utilise NHS data to monitor long-term health status.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the Investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

Consent for the qualitative sub-study

Participants from selected sites will be approached at a convenient time during the course of their trial treatment by a member of the site research team to discuss this optional sub-study. There is a separate PIS/CF for this sub-study to the main trial documents and this will be provided to the participant if they express an initial interest. If a participant is interested in participating, they will be asked to complete a “Consent to Contact Form” and provide their full name, year of birth, gender, address, email address and telephone number. This completed form should be securely emailed to PICCOS@cardiff.ac.uk. The CTR will then forward this information onto the Qualitative Researcher at the University of Bristol who will contact the participant by telephone, discuss the sub-study further and obtain their consent remotely. This sub study is optional, and participants can still be in the main trial even if they choose not to take part in the sub-study.

9.4 Randomisation

Participants will be randomised via the central PICCOS database. Sites should complete the first part of randomisation Case Report Form (CRF), answering all the questions before submitting the randomisation. Please note, you will need to input patients preferred PIPAC centre at the time of randomisation. Once the randomisation is completed, the database will confirm whether the participant has been allocated to the control or intervention arm. The allocation will be sent via email to those indicated as requiring it by the site. If the patient is allocated to receive PIPAC, the PIPAC site will also be notified.

The randomisation system can be accessed via: <https://redcap.ctr.cardiff.ac.uk/redcap/>

If the online system becomes unavailable for any reason, site staff should contact PICCOS@cardiff.ac.uk and a manual randomisation process will be initiated.

Following randomisation, participants should be provided with a Patient Card to identify them as PICCOS trial participants.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial. Participants who withdraw from the trial will not be replaced by additional recruitment. Withdrawal from the trial should not affect ongoing patient care, and patients should continue to receive best possible standard treatment.

If a participant initially consents but subsequently wishes to withdraw from an aspect(s) of the trial, clear distinction must be made as to what aspect(s) of the trial the participant is withdrawing from. These aspects could be:

- 1) SACT.
- 2) PIPAC alone.
- 3) PIPAC and SACT.
- 4) QoL questionnaires as part of the main trial.
- 5) Trial-specific follow-up assessments / visits (*NB: routine follow-up assessments should continue as usual, and data collected from these can continue to be provided to the CTR unless participant also withdraws from this as per point +6*).
- 6) Collection of data from routine hospital notes (e.g. OS data) that does not require the participant to attend any further hospital visits for trial purposes.
- 7) Qualitative sub-study (if applicable).
- 8) Consent for tissue biopsy(ies) of tumour taken as part of participant's routine care either when they were first diagnosed with colorectal / ovarian / stomach cancer or at a subsequent surgery to be sent to collaborating laboratories for analysis.
- 9) Consent for their NHS number to be used to monitor long term health status.
- 10) All of the above.

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal and as such it will not be deleted. Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the PIS but, in brief: If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts.

A participant may discontinue or be discontinued from trial treatment for the following reasons:

- Intolerance to trial medication.
- Severe surgical complications.

- Withdrawal of consent for treatment by the participant.
- Any alteration in the participant's condition which justifies the discontinuation of the treatment in the Investigator's opinion (other than peritoneal progression, as these constitute an endpoint) e.g., inability to perform laparoscopy.
- Pregnancy.
- Non-compliance.

NB: Any patient in the intervention arm identified as having peritoneal disease progression will have no further PIPAC surgical interventions but should not be considered as having withdrawn from the trial for this reason.

In all instances participants who consent and subsequently withdraw should be asked to complete a PICCOS Participant Withdrawal Consent Form. The information provided on this form should be used to subsequently complete the PICCOS Withdrawal Form on the online database to inform the CTR. The Participant Withdrawal Form should not be submitted to the CTR.

If the patient declines to complete the Participant Withdrawal Form, any discussions held with the patient regarding their withdrawal, and aspect(s) of the trial they no longer wish to continue with should be recorded within the patient notes or other source data. The PICCOS Withdrawal Form should then be completed in the PICCOS database based on information provided by the participant. Any queries relating to potential withdrawal of a participant should be forwarded to PICCOS@cardiff.ac.uk.

10.2 Lost to follow up

Patients will be considered lost to follow-up if they stop attending trial follow-up visits before the primary or secondary outcome data have been collected or the trial has completed data collection.

Missing data will be collected via routine NHS data.

Outcome data from participants who deviate from the protocol will be collected.

11 Trial Intervention

11.1 Treatments

Prior to randomisation, the treating Investigator will select the SACT regimen most appropriate to the individual patient from the options available in the protocol for the patient's disease group.

Following randomisation, treatment should commence within 2 weeks for all groups other than the ovarian intervention arm, for whom first PIPAC should take place within 3 weeks. Once treatment commences, patients should be provided with a Patient Card, to identify them as participants in the PICCOS trial in case of emergency.

Colorectal group treatment

Figure 2 Colorectal group treatment schema

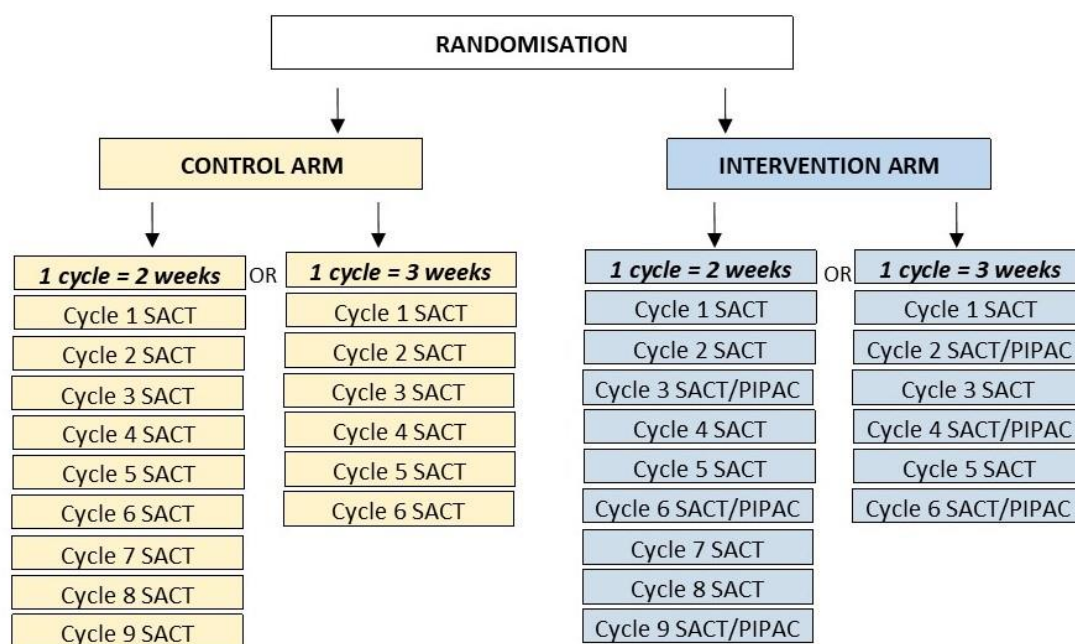


Table 2 Colorectal group dosing schedule

NB: In all cases dose reductions from prior cycles will be maintained

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	SACT	PIPAC chemotherapy
Option 1 = FOLFOX 2 weekly cycles	On day 1 of each cycle: (9 cycles total) <ul style="list-style-type: none"> Oxaliplatin 85mg/m² IV Fluorouracil (5FU) 400mg/m² IV bolus, 5FU 2400mg/m² continuous IV, infusion over 46hrs Sodium Folate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion 	On day 1 of cycles where PIPAC is <u>not</u> given: FOLFOX <ul style="list-style-type: none"> Oxaliplatin 85mg/m² IV 5FU 400mg/m² IV bolus 5FU 2400mg/m² continuous IV infusion over 46hrs Sodium Folate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion On cycles 3, 6, 9 where PIPAC is <u>also</u> given: <ul style="list-style-type: none"> 5FU 2400mg/m² continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC 	On cycles 3, 6 and 9 <ul style="list-style-type: none"> Oxaliplatin 120mg/m² IP (dose reduction to 90mg/m² for frail participants or those with neuropathy as agreed by site oncologist) OR <ul style="list-style-type: none"> Mitomycin C 7.5mg/m² IP (if contraindication to Oxaliplatin) <p>PIPAC should be scheduled day 3 to day 7 of the cycles to ensure a break of 24 hours between finishing the 5FU infusion and having PIPAC. If it is not possible to schedule the 5FU infusion prior to a participant's PIPAC it can be administered 48 hours or more after the PIPAC</p> <p>Subsequent non PIPAC cycles should occur a minimum of 10 days after completion of the 5FU infusion</p>
Option 2 = FOLFOX + Cetuximab 2 weekly cycles	Each cycle: (9 cycles total) <ul style="list-style-type: none"> FOLFOX (as in option 1) Cetuximab 500mg/m² IV (initial dose over 2 hrs, subsequent doses over 1 hour) day 1 	On day 1 of cycles where PIPAC is <u>not</u> given: <ul style="list-style-type: none"> FOLFOX (as in option 1) Cetuximab 500mg/m² IV (initial dose over 2 hrs, subsequent doses over 1 hour) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: <ul style="list-style-type: none"> 5FU 2400mg/m² continuous IV infusion over 46hrs should be administered with pump 	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	SACT	PIPAC chemotherapy
		<p>disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC</p> <ul style="list-style-type: none"> Cetuximab 500mg/m² IV infusion 	
Option 3 = FOLFOX + Panitumumab 2 weekly cycles	<p>Each cycle: (9 cycles total)</p> <ul style="list-style-type: none"> FOLFOX (as in option 1) Panitumumab 6mg/Kg IV day 1 	<p>On day 1 of cycles where PIPAC is <u>not</u> given:</p> <ul style="list-style-type: none"> FOLFOX (as in option 1) Panitumumab 6mg/Kg IV <p>On cycles 3, 6, 9 where PIPAC is <u>also</u> given:</p> <ul style="list-style-type: none"> 5FU 2400mg/m² continuous infusion over 46 hours Panitumumab 6mg/Kg IV infused over 30 to 60 minutes 	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1
Option 4 = FOLFIRI 2 weekly cycles	<p>On day 1 of each 2 week cycle: (9 cycles total)</p> <ul style="list-style-type: none"> Irinotecan 180mg/m² IV infusion 5FU 400mg/m² IV bolus 5FU 2400mg/m² continuous IV infusion over 46hrs Sodium Folate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion 	<p>On day 1 of cycles where PIPAC is <u>not</u> given: FOLFIRI</p> <ul style="list-style-type: none"> Irinotecan 180mg/m² IV infusion 5FU 400mg/m² IV bolus 5FU 2400mg/m² continuous IV infusion over 46hrs Sodium Folate 350mg IV infusion OR calcium folinate 300 or 350mg IV infusion <p>On cycles 3, 6, 9 where PIPAC is <u>also</u> given:</p> <ul style="list-style-type: none"> 5FU 2400mg/m² continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC 	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	SACT	PIPAC chemotherapy
Option 5 = FOLFIRI + Cetuximab 2 weekly cycles	Each cycle: (9 cycles total) <ul style="list-style-type: none"> FOLFIRI (as in option 4) <u>plus</u> Cetuximab 500mg/m² IV day 1 	On day 1 of cycles where PIPAC is <u>not</u> given: <ul style="list-style-type: none"> FOLFIRI (as in option 4) Cetuximab IV 500mg/m² IV (initial dose over 2 hours, subsequent doses over 1 hour) On cycles 3, 6, 9 where PIPAC is <u>also</u> given: <ul style="list-style-type: none"> 5FU 2400mg/m² continuous IV infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC Cetuximab IV 500mg/m² IV infusion 	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1
Option 6 = FOLFIRI + Panitumumab 2 weekly cycles	Each cycle: (9 cycles total) <ul style="list-style-type: none"> FOLFIRI (as in option 4) <u>plus</u> Panitumumab 6mg/Kg IV day 1 	On day 1 of cycles where PIPAC is not given: <ul style="list-style-type: none"> FOLFIRI (as in option 4) Panitumumab 6mg/Kg IV On cycles 3, 6, 9 where PIPAC is <u>also</u> given: <ul style="list-style-type: none"> 5FU infusion 2400mg/m² continuous infusion over 46hrs should be administered with pump disconnection 24 hours pre PIPAC or pump attachment 48 hours after PIPAC Panitumumab 6mg/Kg IV 	Cycles 3, 6 and 9: Oxaliplatin or Mitomycin as in option 1
Option 7 = CAPOX 3 weekly cycles	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none"> Oxaliplatin 130mg/m² IV D1 Capecitabine 1000mg/m² bd for 14 days (days 1-14 of the cycle) PO 	On cycles where PIPAC is <u>not</u> given: <ul style="list-style-type: none"> Oxaliplatin 130mg/m² IV day 1 Capecitabine 1000mg/m² bd for 14 days (days 1-14 of the cycle) PO On cycles where PIPAC is given:	Cycles 2, 4 and 6: <ul style="list-style-type: none"> Oxaliplatin 120mg/m² IP (dose reduction to 90mg/m² for frail participants or those with neuropathy as agreed by site oncologist) OR

Option No. Cycle length	Control arm- Colorectal	Intervention arm- Colorectal	
	SACT	SACT	PIPAC chemotherapy
		<ul style="list-style-type: none"> Capecitabine 1000mg/m² bd for 14 days (days 1-14 of the cycle) PO. <i>Capecitabine should be omitted for 24 hours prior to the PIPAC procedure and for 48 hours afterwards. Missed tablets should not be replaced (thus only 11 days of tablets are required)</i> 	<ul style="list-style-type: none"> Mitomycin C 7.5mg/m² IP (<i>if contraindication to Oxaliplatin</i>) <p>Subsequent non PIPAC cycles should occur a minimum of 6 days after completion of the last capecitabine tablets</p>
<u>In all cases dose reductions from prior cycles will be maintained</u>			

Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.

Ovarian group treatment

Figure 3 Ovarian group treatment schema

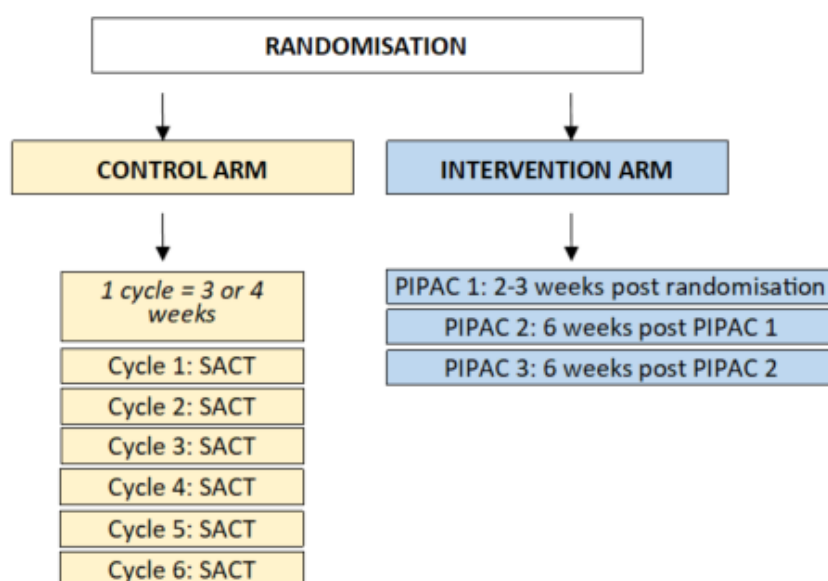


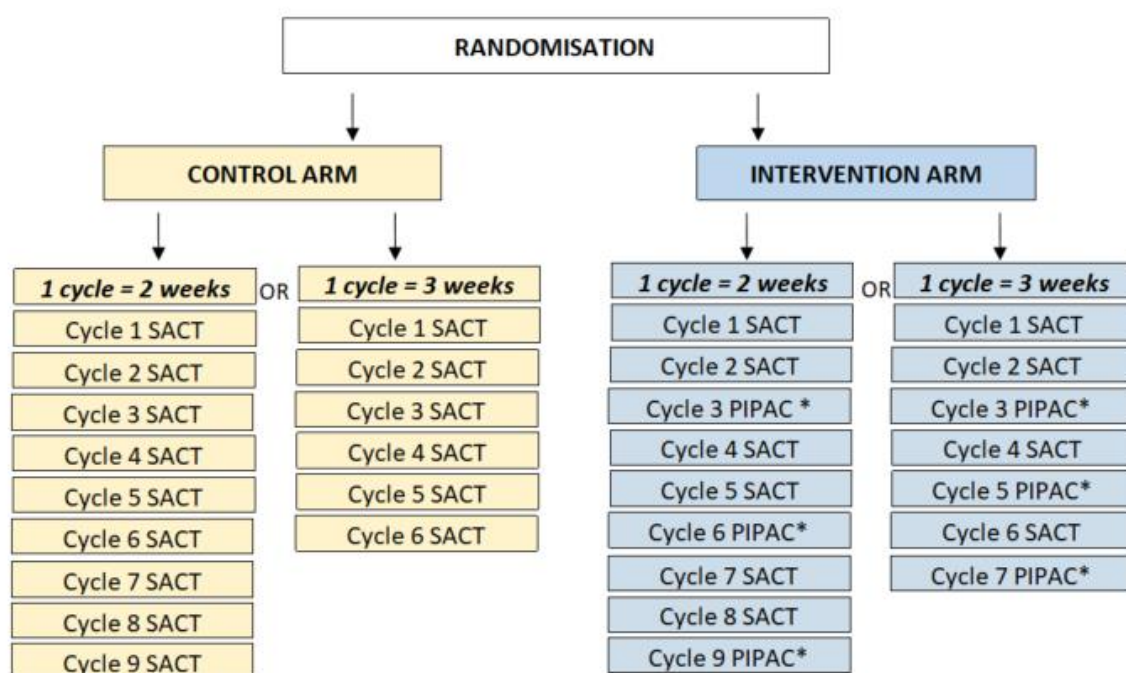
Table 3 Ovarian group dosing schedule

Option No Cycle length	Control arm - Ovarian	Intervention arm- Ovarian	
	SACT	SACT	PIPAC chemotherapy
Option 1 4 weekly cycles	On days 1, 8, 15 of each 4 week cycle: (6 cycles total) • Paclitaxel 80mg/m ² IV infusion over 3 hrs	None	PIPAC 1: 2-3 weeks after randomisation PIPAC 2: PIPAC 1 + 6 weeks PIPAC 3: PIPAC 2 + 6 weeks • Cisplatin 10.5mg/m ² IP • Doxorubicin 2.1mg/m ² IP
Option 2 4 weekly cycles	On day 1 of each 4 week cycle: (6 cycles total) • Liposomal doxorubicin 50mg/m ² IV infusion. Initial dose at 1mg/minute (so 100mg dose over 100 minutes), subsequent doses over 60 minutes	None	As in option 1
Option 3 3 weekly cycles	On days 1, 8 and 15 of each 3 week cycle: (6 cycles total) • Gemcitabine 1000mg/m ² IV infusion	None	As in option 1

Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime in the control arm or have SACT added in, in the intervention arm, at the discretion of their treating PI. If chemotherapy is added to intervention arm, it should be completed 7 days prior to the PIPAC procedure.

Stomach group treatment

Figure 4 Stomach group treatment schema



* +/- nivolumab or trastuzumab (if applicable) on day 2 or 3

*Trastuzumab or Nivolumab (if applicable) should be continued during PIPAC cycles to maintain standard schedule (day 3 of PIPAC cycles)

**** Trastuzumab/Nivolumab maintenance should continue after completion of trial schema as per standard of care (if clinically indicated).

**** Maintenance cytotoxic chemotherapy is not permitted in the gastric arm of the trial

Table 4 Stomach group dosing schedule

NB: In all cases dose reductions from prior cycles will be maintained

Option No, Cycle length	Control arm- Stomach SACT	Intervention arm- Stomach SACT		PIPAC chemotherapy	Comments
HER 2 negative patients:					
Option 1 = FOLFOX 2 weekly cycles	On day 1 of each 2 week cycle: (9 cycles total) <ul style="list-style-type: none">Oxaliplatin 85mg/m² infused IV over 2 to 6 hrs5FU bolus 400mg/m² given as IV infusion over 30 to 60 minutes5FU infusion 2400mg/m² IV continuous infusion over 46hrsSodium Folate 350mg IV OR calcium folinate 300 or 350mg IV infusion over 1 to 2 hours	On day 1 of each 2 week cycle: (76 cycles total) <ul style="list-style-type: none">Oxaliplatin 85mg/m² infused IV over 2 to 6 hrs5FU bolus 400mg/m² given as IV infusion over 30 to 60 minutes5FU infusion 2400mg/m² IV continuous infusion over 46hrsSodium Folate 350mg IV OR calcium folinate 300 or 350mg IV infusion over 1 to 2 hours <i>IV SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9)</i>	Cycles 3, 6 and 9 during PIPAC procedure: <ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP		
Option 2 = CAPOX 3 weekly cycles	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none">Oxaliplatin 130mg/m² via IV infused over 2 to 6 hrs day 1Capecitabine 1000mg/m² bd (PO Days 1-14)	Each 3 week cycle: (4 cycles total) <ul style="list-style-type: none">Oxaliplatin 130mg/m² via IV infused over 2 to 6 hrs, day 1Capecitabine 1000mg/m² bd (PO Days 1-14) <i>IV and oral SACT is OMITTED during PIPAC cycles (i.e. cycle 3,5 and 7)</i>	Cycles 3, 5 and 7 during PIPAC procedure: <ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC	

Option No, Cycle length	Control arm- Stomach	Intervention arm- Stomach		Comments
	SACT	SACT	PIPAC chemotherapy	
Option 3 = CX 3 weekly cycles	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none"> Cisplatin 60mg/m² IV day 1 Capecitabine 1000mg/m² bd (PO days 1-14) 	Each 3 week cycle: (4 cycles total) <ul style="list-style-type: none"> Cisplatin 60mg/m² IV day 1 Capecitabine 1000mg/m² bd (PO Days 1-14) <p><i>IV and oral SACT is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)</i></p>	Cycles 3, 5 and 7 during PIPAC procedure: <ul style="list-style-type: none"> Cisplatin 10.5mg/m² IP Doxorubicin 2.1mg/m² IP 	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC
HER 2 positive patients:				
Option 4 = CXtraz 3 weekly cycles Trastuzumab to be used as per current NICE recommendation	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none"> CX as per option 3 Trastuzumab* IV day 1 Cycle 1 8mg/kg over 90 minutes. Subsequent cycles 6mg/kg over 30 minutes 	On day 1 of each 3 week cycle: (4 cycles total) <ul style="list-style-type: none"> CX as per option 3 Trastuzumab* IV Cycle 1 8mg/kg over 90 minutes. Subsequent cycles 6mg/kg over 30 minutes <p><i>IV and oral Chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7)</i></p> <p>However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC</p>	Cycles 3, 5 and 7 during PIPAC procedure: <ul style="list-style-type: none"> Cisplatin 10.5mg/m² IP Doxorubicin 2.1mg/m² IP 	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC *Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 5 = CAPOXtraz	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none"> CAPOX as in option 2 	Each 3 week cycle: (4 cycles total) <ul style="list-style-type: none"> CAPOX as in option 2 	Cycles 3, 5 and 7 during PIPAC procedure:	Please note a 14 day capecitabine regime (not 21 days) is required to

Option No, Cycle length	Control arm- Stomach SACT	Intervention arm- Stomach		
	SACT	SACT	PIPAC chemotherapy	Comments
3 weekly cycles Trastuzumab to be used as per current NICE recommendation	<ul style="list-style-type: none">Trastuzumab* IV day 1, cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes	<ul style="list-style-type: none">Trastuzumab* IV day 1, cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes IV and oral Chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7) However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC	<ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP	allow a 7 day chemotherapy washout prior to PIPAC *Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 6 = FOLFOXtraz 2 weekly cycles Trastuzumab to be used as per current NICE recommendation	On day 1 of each 2 week cycle: (9 cycles total) <ul style="list-style-type: none">FOLFOX as per option 1 PLUS 3 weekly <ul style="list-style-type: none">Trastuzumab* IV cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes	On day 1 of each 2 week cycle: (6 cycles total) <ul style="list-style-type: none">FOLFOX as per option 1 PLUS 3 weekly <ul style="list-style-type: none">Trastuzumab* IV cycle 1 8mg/kg over 90 minutes, subsequent cycles 6mg/kg over 30 minutes IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 6 and 9) However trastuzumab should be continued throughout PIPAC cycles, given D3 post PIPAC	Cycles 3, 6 and 9 during PIPAC procedure: <ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP	*Trastuzumab should be continued 3 weekly throughout PIPAC. Maintenance trastuzumab may be continued upon completion of planned trial treatment (if clinically indicated)

Option No, Cycle length	Control arm- Stomach SACT	Intervention arm- Stomach		
	SACT	SACT	PIPAC chemotherapy	Comments
Patients eligible for immunotherapy in line with current NICE recommendations (currently HER –2 negative, CPS ≥5)				
Option 7 = CAPOXniv 3 weekly cycles Nivolumab to be used as per current NICE recommendation	Each 3 week cycle: (6 cycles total) <ul style="list-style-type: none">CAPOX as in option 2Nivolumab** 360mg IV over 30 minutes day 1	Each 3 week cycle: (4 cycles total) <ul style="list-style-type: none">CAPOX as in option 2Nivolumab ** 360mg IV day 1 IV and oral chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 3, 5 and 7) However nivolumab should be continued throughout PIPAC cycles, given D3 post PIPAC	Cycles 3, 5 and 7 during PIPAC procedure: <ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC **Nivolumab should be continued 3 weekly throughout PIPAC cycles. Maintenance nivolumab may be continued upon completion of planned trial treatment (if clinically indicated)
Option 8 – FOLFOXniv 2 weekly cycles Nivolumab to be used as per current NICE recommendation	On day 1 of each 2 week cycle: (9 cycles total) <ul style="list-style-type: none">FOLFOX as per option 1Nivolumab** 240mg IV over 30 minutes day 1	On day 1 of each 2 week cycle: (6 cycles total) <ul style="list-style-type: none">FOLFOX as per option 1Nivolumab** 240mg IV day 1 IV chemotherapy is OMITTED during PIPAC cycles (i.e. cycle 4, 7 and 10)	Cycles 3, 6 and 9 during PIPAC procedure: <ul style="list-style-type: none">Cisplatin 10.5mg/m² IPDoxorubicin 2.1mg/m² IP	Please note a 14 day capecitabine regime (not 21 days) is required to allow a 7 day chemotherapy washout prior to PIPAC **Nivolumab should be continued throughout PIPAC cycles. Maintenance nivolumab may be continued upon completion of

Option No, Cycle length	Control arm- Stomach	Intervention arm- Stomach		Comments
	SACT	SACT	PIPAC chemotherapy	
		However Nivolumab should be continued throughout PIPAC cycles, given D3 post PIPAC		planned trial treatment (if clinically indicated)

In all cases dose reductions from prior cycles will be maintained

Note:

- HER-2 directed therapy and immunotherapy allowed within their respective NICE recommendations.
- IV and oral cytotoxic chemotherapy is omitted during PIPAC cycles in the intervention arm.
- If using 3 weekly capecitabine containing regimens, must use 14 days of capecitabine to allow washout period of 1 week before PIPAC.
- Trastuzumab/ Nivolumab (if applicable) should be continued during PIPAC cycles to maintain standard schedule (day 3 post PIPAC).
- If Trastuzumab is delayed, please follow appropriate re-loading guidance.
- In the event that PIPAC does not go ahead on day 1 as planned, a +7 day window is allowed for PIPAC to be given before the next SACT needs to be deferred. If Nivolumab or Trastuzumab are given on day 3 of a deferred PIPAC cycle the site is encouraged to give the Nivolumab or Trastuzumab as close as possible to the date next due (2 weeks later for 2 weekly Nivolumab and 3 weeks later for 3 weekly Nivolumab and Trastuzumab), recognising that this will lead to a disconnection between the cytotoxic SACT and the biological agent.
- Trastuzumab /Nivolumab maintenance should continue after completion of trial schema (if clinically indicated) as per standard of care.
- Maintenance cytotoxic chemotherapy post-completion of trial schema is not permitted in the stomach arm of the trial.
- Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime in listed in the protocol at the discretion of their treating PI.

11.2 Treatment supply and storage (all disease groups)

No specific drug provision is necessary for the trial. All Investigational Medicinal Products (IMPs) and n-IMPs (non-Investigational Medicinal Products) will be obtained through normal hospital supply routes. For SACT IMP and nIMPs these can also be sourced using pre-made bags of chemotherapy outsourced locally.

All IMPs and n-IMPs should be stored as per current Summary Product Characteristics (SmPC). Intraperitoneal (IP) IMPs should be prepared as described in the Protocol and PICCOS Pharmacy Manual. IMPs given as per SmPC (paclitaxel, gemcitabine and liposomal doxorubicin), and all n-IMPs, should be prepared as per SmPC.

Once prepared, drugs to be given IP should be kept at room temperature (other than Mitomycin, which should be stored in the refrigerator) and used within 12 hours (including infusion time) to ensure drug stability. Mitomycin C should be brought to room temperature prior to administration.

Any temperature deviations following dispensing, for both IMPs and nIMPs, should be dealt with as per SmPC and PICCOS Pharmacy Manual.

More information can be found in the PICCOS Pharmacy Manual.

11.3 Treatment prescribing and dispensing (all disease groups)

SACT and PIPAC chemotherapy will be prescribed at the doses described in section 11.134.

SACT will be prepared as per local standard practice.

The trial prescription form will be used to request the trial drug(s) from pharmacy on an individual participant basis. Prescriptions can be completed by staff permitted to do so as per local practice.

Body surface area (BSA) should be calculated using the site's usual method.

Creatinine clearance (CrCl) should be calculated using Cockcroft-Gault or local site formula to assess chemotherapy doses. Ideal body weight should be used when calculating Creatinine Clearance in patients with high BMI.

Dose banding as per NHSE dose banding table is allowed for SACT IMP and nIMP. The NHSE dose banding tables do not apply to doses delivered via PIPAC. However, PIPAC doses can be rounded to nearest whole number.

Dose capping:

- Colorectal group - doses will be capped as per Standard Operating Procedure (SOP) for local chemotherapy unit.
- Ovarian group - doses will be capped at BSA 2m².
- Stomach group - doses will be capped at BSA 2m²

PIPAC chemotherapy will be assembled by a chemotherapy pharmacist on an individual patient basis. This will require preparation of the chemotherapy at the specified dose in the solution specified in Table 5 in a syringe to fit the high-pressure injector pump. Volume of dilution will vary depending on the size and type of injector pump available locally, as this will impact on the syringe size used. Once assembled in the appropriate syringes, the chemotherapy will be placed in a sealed and labelled plastic bag ready for transport to theatre. For labelling requirements see section 5211.14.

Table 5: PIPAC preparation details

PIPAC agent	Dose	Dilution
Oxaliplatin	92mg/m ²	5% dextrose
Mitomycin C	7.5mg/m ²	NaCl 0.9%
Cisplatin	10.5 mg/m ²	NaCl 0.9%
Doxorubicin	2.1 mg/m ²	NaCl 0.9%

11.4 Drug administration

SACT

SACT should be administered according to section 11.1 and as per local practice.

PIPAC chemotherapy

Colorectal group - PIPAC Oxaliplatin or Mitomycin (as applicable) chemotherapy will be supplied from pharmacy in syringes to be delivered in theatres using PIPAC specialist equipment.

Ovarian and Stomach groups - PIPAC Cisplatin and Doxorubicin chemotherapy will be supplied from pharmacy in syringes to be delivered in theatre using PIPAC specialist equipment.

PIPAC procedure – all groups

- After insufflation of a 12 mmHg of capnoperitoneum at 37 °C during laparoscopy, two balloons safety trocars (10 and 12 mm) are inserted into the abdominal wall.
- Ascites is removed and volume documented.
- A laparoscopic nebuliser device is connected to an intravenous high-pressure injector and inserted into the abdomen. Tightness of the abdomen is documented via a zero-flow of CO₂. Safety house may be used to entirely cover the abdomen.
- A continuous suction is performed under the house (if being used) by a surgical smoke extractor providing a second level of security in case of leak during the vaporisation.
- Injection parameters are set at a flow rate of 30 mL/min and a maximum upstream pressure of 200 psi in the high-pressure injector.
- The injection is remote-controlled to minimise theatre staff exposure.
- The PIPAC Manual safety protocol with checklist containing all safety aspects is to be used before and during administration of intraperitoneal chemotherapy.

- After application of chemotherapy the therapeutic capnoperitoneum is maintained for 30 min at a temperature of 37 °C.
- Chemotherapy aerosol is then exhausted over a secure system (Closed Aerosol Waste System (CAWS)).
- Trocars are then removed and laparoscopy ended. No drainage of the abdomen is applied.

The PIPAC procedure is repeated three times as per the schedule in section 11.1 **Error! Reference source not found..**

11.5 Delays

PIPAC

PIPAC can be delayed if patient does not meet minimum criteria for surgery. If PIPAC is delayed for 3 weeks or longer (other than for Covid-19 infection, as noted below), discussions should be had with the PICCOS trial team on whether appropriate to continue treatment.

If a participant in the intervention arm tests positive for Covid-19, PIPAC should be delayed as per local standard practice for surgery.

If PIPAC is delayed, subsequent courses and PIPACs should also be delayed to maintain treatment timelines (i.e. if delayed by 1 week, all subsequent treatments and follow-up visits should be delayed by 1 week, CT scans should be maintained as per schedule of assessments and not moved).

SACT

If a participant tests positive for Covid-19, SACT should be delayed as per local standard practice. If SACT is delayed, subsequent cycles should also be delayed to maintain treatment timelines (i.e. if delayed by 1 week, all subsequent cycles and follow-up visits should be delayed by 1 week, CT scans should be maintained as per schedule of assessments and not moved).

11.6 Dose modification for toxicity

SOC systemic SACT can be modified as permitted within the SmPC and in accordance with local practice. However, full doses as stipulated in the protocol must be given for cycle 1.

A dose reduction to IP Oxaliplatin (Colorectal group PIPAC) from 120,g/m² to 90mg/m² is permitted for participants with neuropathy or who are frail (as per ISSPP PIPAC Consensus Statement, March 2022 (70)) subject to discussion and agreement of site oncologist.

There are no dose modifications for IP Cisplatin, Doxorubicin or Mitomycin.

Safety signals from trial drugs will be regularly monitored throughout the course of the trial. If excessive toxicity is observed from the PIPAC drugs, a protocol amendment to introduce the possibility of a standard dose reduction will be considered.

Colorectal group participants who show toxicity that in the view of their treating Investigator warrants stopping Oxaliplatin, can be treated with Mitomycin at their subsequent scheduled PIPAC cycle.

Ovarian or Stomach group participants who show toxicity that in the view of their treating Investigator warrants stopping either Cisplatin or Doxorubicin can be treated at their subsequent scheduled PIPAC cycle with the other drug alone.

11.7 Management of toxicity and hypersensitivity reactions

Toxicity and hypersensitivity reactions to SACT and PIPAC chemotherapy should be managed as per standard anaphylaxis protocol. Following hypersensitivity reactions, any further surgeries should be discussed with the trial team prior to being undertaken.

11.8 Management of overdose/ underdose

In the event of an overdose/underdose of any drug provided within PICCOS, any further treatment should be withheld and the PICCOS Trial Manager should be notified via a dosing error form being completed and submitted to PICCOS@cardiff.ac.uk within 24 hours of site becoming aware. Treatment should not recommence until advice has been obtained from the Sponsor and CI / disease site lead as required. This does not need to be reported as an adverse event but if the patient experiences a Serious Adverse Event (SAE) that the PI considers may be causally related to the overdose/underdose then this must be clearly stated on a SAE form submitted to the CTR Pharmacovigilance (PV) team. Please see section 14 for more information on reporting SAEs.

If a patient is underdosed due to reasons not related to toxicity then a dosing error form should be completed. If doses are stopped prematurely or otherwise reduced due to toxicity then this is captured on the Course CRF.

11.9 Pre-medication

Pre-medication should be prescribed as per local guidance.

11.10 Prohibited medications and interaction with other drugs

Prohibited medications

Drugs described as contraindicated in the SmPC for each SACT or chemotherapy agent will not be permitted. The most up to date SmPC from www.medicines.org.uk will be used. Treatment with any other anti-cancer experimental drug/ agent is not permitted for the duration of the trial.

Bevacizumab and Aflibercept is prohibited to be given whilst receiving trial treatment and for 4 weeks after completion of trial treatment. Please note a 4-week washout period should be allowed prior to randomisation as per trial exclusion criteria.

Medications permitted with caution / procedures

Other medications, as long as they are not anti-cancer or experimental drugs/ agents, will be permitted in line with the SmPC for each drug. The most up to date SmPC from www.medicines.org.uk will be used.

In the event of a possible disease response to the point that reductive surgery may be an option for the patient, this will be permitted.

11.11 Permitted concomitant medications

GCSF (Granulocyte colony-stimulating factor) should be prescribed as per local guidance and should be used as required.

11.12 Supportive care

Supportive medications should be prescribed as per local guidance and should be used as required.

11.13 Accountability procedures

Since the trial will use standard chemotherapies already available at pharmacy, there will be no trial specific drug delivery to site. Trial specific per-patient accountability logs should be maintained for all IMPs (no trial specific accountability records will be required for nIMPs). The PICCOS trial team will provide a template, but local templates can be used within the trial provided all required information is collected.

Any drug recalls should be actioned as per local practice.

For further information, refer to the PICCOS Pharmacy Manual.

11.14 Drug labelling

All IMPs- Oxaliplatin (IP), Mitomycin (IP), Cisplatin (IP), Doxorubicin (IP), Paclitaxel (IV), Liposomal Doxorubicin (IV), Gemcitabine (IV): IP syringes/ IV bags should be labelled with full information regarding the trial in accordance with EU Good Manufacturing Process (GMP) Annex 13, as per Sponsor provided labels.

nIMPs- Capecitabine (PO), Oxaliplatin (IV), Calcium folinate (IV), Nivolumab (IV), Sodium folinate (folinic acid) (IV), Trastuzumab (IV), 5FU (IV), Irinotecan (IV), Cisplatin (IV), Cetuximab (IV) and Panitumumab (IV): There is no requirement to add trial specific labels to packs of these drugs.

All labels are included in the Pharmacy File provided by CTR upon site activation. For further information refer to the PICCOS Pharmacy Manual.

11.15 Drug disposal

SACT

Unused SACT drugs should be disposed of as per local practice.

PIPAC chemotherapy

Prepared chemotherapy delivered to surgery for use in PIPAC procedures but not used for any reason should be returned to pharmacy for disposal according to local practice. The gas inside the abdomen at the end of the PIPAC procedure will require disposal as per the PIPAC Manual. It will be evacuated from the abdomen via a closed system (CAWS). All consumables and waste from theatre after PIPAC has been performed will be packed and labelled as per local guidelines for chemotherapy waste/ PIPAC Manual.

12 Sample management

Participants are asked to consent to collection of Formalin Fixed Paraffin Embedded (FFPE) tumour blocks, and provision of these to the PICCOS trial. FFPE tumour samples will be from initial diagnostic cancer biopsy and, for those in the intervention arm, routine biopsies taken at PIPAC surgeries.

All samples should be stored locally/ in local biobanks until requested by the PICCOS trial team. All sites are encouraged to collect these samples, but this is not currently mandatory.

13 Trial procedures

13.1 Assessments

Schedule of Assessments vary depending on disease type and SACT regime to be given. The Appendix (section 16.1) includes all schedules.

Baseline assessments- all participants

Table 7: summarises the assessments which should be performed prior to commencing any trial treatment along with the required timeframes.

Table 6: Baseline Assessments

Assessment	Timepoint
Assessment of tumour markers (CEA for colorectal / CA125 for ovarian group)	Within 4 weeks prior to day 1 of cycle 1
Ethnicity documentation	After trial consent but prior to first cycle of SACT or PIPAC
EORTC QLQ-C30	After trial consent but prior to first cycle of SACT or PIPAC

Assessments prior to each cycle of SACT

Table 7 summarises the assessments which should be performed prior to SACT cycle within the timeframes described. Where a participant has their screening bloods done within 2 weeks of starting SACT these do not need to be repeated at cycle 1. With the exception of bloods, where screening assessments fit within the timeframes included in table 7 there is no requirement to repeat the assessment pre cycle1 of SACT.

Table 7: Assessments required prior to each SACT cycle

Assessment	Timepoint
Physical assessment (including height, weight)	Within 72 hours, or as per local practice
Vital signs (including blood pressure, heart rate)	Within 72 hours, or as per local practice
Bloods (including FBC, U&Es, Mg ²⁺ , LFTs, bone profile)	Within 72 hours, or as per local practice
Adverse Events (AE)/ SAEs	During the PV reporting period
Concomitant medications	Within 72 hours, or as per local practice
ECOG performance status assessment	Within 72 hours, or as per local practice, at Weeks 9, 12 and 18 only
Assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	Within 72 hours, or as per local practice

Assessment prior to each PIPAC

Table 8 summarises the pre-operative assessments which should be carried out prior to PIPAC at the timeframes described. These assessments can be conducted at either the site where the participant has their SACT or their PIPAC procedure (if these are different) and data entered onto the PICCOS database accordingly. *If patients do not meet the criteria for undergoing PIPAC procedure, or are receiving treatment with any medicine that may affect the safety of PIPAC (prohibited concomitant medications- see section 11.10), they should not travel to the PIPAC centre and the surgery should be rearranged.*

Where a participant's screening assessment fit within the timeframes included in table 8 there is no requirement to repeat the assessment pre PIPAC 1.

Table 8 Assessments required prior to PIPAC

Assessment	Timepoint
Physical assessment (including height, weight)	Within 72 hours prior to PIPAC
Vital signs (including blood pressure, heart rate)	Within 72 hours prior to PIPAC
Bloods (including FBC, U&Es, Mg ²⁺ , LFTs, Cr, bone profile)	Within 72 hours prior to PIPAC
ECG (<i>dependent on pre-op assessment requirements</i>)	Within 72 hours prior to PIPAC
AEs/ SAEs	Within 72 hours prior to PIPAC
Concomitant medications	Within 72 hours prior to PIPAC
Urine pregnancy test (WOCBP only)	Within 72 hours prior to PIPAC
ECOG performance status assessment	Within 72 hours prior to PIPAC
Assessment of tumour marker (CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients)	Prior to PIPAC 3 only

Conversation with PIPAC centre if patient has ascites re: suitability for PIPAC/ if requires tap prior to travel	Minimum of 3 days prior to PIPAC
--	----------------------------------

Assessments 30 days after each PIPAC.

30 days after each PIPAC procedure the site RN will call the participant and review their medical notes to collect information on the nature and grade of any surgical complications (Clavien Dindo classification) that have happened in the 30 days since the respective PIPAC procedure. Any AEs/SAEs will also be reported as applicable.

CT scans

CT scans should be performed at the timepoints noted below regardless of delays to SACT and/or PIPAC treatments, but there should always be at least 1 week following a PIPAC procedure to allow time for reduction of post operative inflammation.

Each group should have their scans booked within the following timepoints:

- Colorectal
 - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
 - 8-10 weeks post-randomisation
 - 19-21 weeks post-randomisation
- Ovarian
 - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
 - 10-12 weeks post-randomisation
 - 18-20 weeks post-randomisation
- Stomach
 - Baseline (should be within 6 weeks prior to randomisation, ideally within 4 weeks)
 - 8-10 weeks post-randomisation
 - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th and thereafter: every 2 months +/- 2 weeks for the first year after the end of trial treatment, thereafter every 3 months (or as per local SOC) until end of trial. Trial specific CT scans (with RECIST measurements for peritoneal disease reported on the CRFs) will stop at the time of peritoneal disease progression as per RECIST (V1.1).

QoL questionnaires (EORTC QLQ-C30)

QoL questionnaires (EORTC QLQ C30 – version 3) should be completed in line with CT scans, at the following timepoints:

- Colorectal
 - Baseline (after consent, and prior to treatment starting)
 - 8-10 weeks post-randomisation
 - 19-21 weeks post-randomisation
- Ovarian
 - Baseline (after consent, and prior to treatment starting)
 - 10-12 weeks post-randomisation
 - 18-20 weeks post-randomisation
- Stomach
 - 1st - Baseline (after consent, and prior to treatment starting)
 - 2nd - 8-10 weeks post-randomisation
 - 3rd - 19-21 weeks post randomisation (2 weekly group) or 20-22 weeks post randomisation (3 weekly group)

All groups: 4th, 5th and 6th questionnaires:

- 4th - 2 months after CT scan number 3
- 5th - 6 months after CT scan number 3
- 6th - 10 months after CT scan number 3

PIPAC procedure

The dose prescription and management plan will be recorded clearly in the participant's medical records.

Consent for the PIPAC procedure is to be obtained using the standard NHS CF prior to each surgery. Patients should be informed of the following possible risks:

- Risks associated with PIPAC treatment and delivery of intraperitoneal chemotherapy including but not limited to: wound infections and toxicity (see trial PIS for further details)
- Operative risks
- General anaesthetic risks

Table 9 should be followed to assess whether PIPAC can be given to a participant.

Table 9: Requirements to be met prior to PIPAC

Do Not Give PIPAC Unless	Contraindications to PIPAC
<ul style="list-style-type: none"> • Creatinine and CrCl within normal range • Bilirubin <30 micromol/L • WBC $\geq 3.0 \times 10^9/L$ • Neutrophils $\geq 1.5 \times 10^9/L$ • Platelets $\geq 100 \times 10^9/L$ • No red blood cell fragmentation seen if manual blood film deemed necessary 	<ul style="list-style-type: none"> • Hypersensitive or idiosyncratic reaction to, or any of the components of, the IP chemotherapy product in the past • Coagulation disorders and increased bleeding tendency • Prolonged QT interval on ECG

PIPAC should be administered as described in the PIPAC Manual provided by the PICCOS trial. Dosing and schedule for intraperitoneal drugs delivery should be as per section 11.1. PIPAC can be delayed if required, as described in section 11.5.

PIPAC is the administration of an aerosolised anti-cancer treatment within the abdominal cavity. The equipment required to do this includes a laparoscopic nebuliser and an injector which together constitute the drug delivery system. There are several CE marked nebulisers and injectors with the required regulatory approval to deliver drugs in this way and only these will be permitted for use during the PICCOS trial.

The PICCOS PIPAC Manual describes the health and safety requirements that must be implemented in theatre. PIPAC has been rigorously tested in numerous international jurisdictions and found to be completely safe if applied responsibly. Safety measures are necessary to comply with health and safety at work laws and regulations. These include laminar airflow and closed aerosol waste management (71). Whilst laminar airflow is recommended for use during PIPAC, alternative advanced operating theatre ventilation systems may be used subject to the approval of the PICCOS TMG.

PIPAC sites will have undergone the ISSPP approved 2-day PIPAC team training course. They will have carried out simulated procedures, dry runs and initial cases will be preceptored by experienced PIPAC surgeons. Standardised and well-tested checklists are utilised throughout the procedure and completeness will be checked at monitoring visits.

Monitoring during surgery

Participants will be closely monitored during the delivery of PIPAC in keeping with standard trust policy outlining care for patients under general anaesthesia. The Consultant Anaesthetist will monitor the participant remotely by telemetry and all staff will be outside the operating theatre while PIPAC is being delivered with the exception of the treating consultants who may be required to enter theatres if there are problems with PIPAC delivery or if an emergency occurs. All staff members will comply with trust policy regarding the delivery of chemotherapy.

Post-surgery procedure

Participants will be monitored as per local protocols post abdominal surgery, particularly monitoring the patient for immediate complications such as bleeding and infection. Any signs of toxicity will be documented in the participant's medical notes using CTCAE, reported as AEs/SAEs (as applicable) and the patients' symptoms will be appropriately managed. Surgical complications will also be recorded in medical records and on the Toxicity CRF using the Clavien-Dindo scale (up to 30 days post each PIPAC procedure).

Guidance for post operative ward staff on caring for patients after PIPAC is included in the PIPAC Manual.

13.2 Follow-up

All participants will be followed up to the point of peritoneal disease progression as per RECIST (v1.1) or a minimum of six months post-randomisation whichever comes first. Ongoing assessments will end for all patients when the last patient randomised has completed six months of follow up from their randomisation date or for the timeframes specified below. After the end of treatment, participants will have a telephone call from the site RN every 2 months in the first year and then 3 monthly thereafter just prior to each CT scan to review progress and collect follow up data as per Table 10.

Table 10: Follow-up Assessments

Assessment	Timepoint
AEs/ SAEs	For up to 30 days post end of trial treatment only
Documentation of bowel obstruction since last trial visit/follow up phone call (admissions to hospital or the cause of prolonged hospitalisation – record on Toxicity CRF) – <i>RN from site to call participants to obtain this information prior to each CT scan in the follow up period</i>	Every 2 months (+/- 2 weeks) for the first year following the 3 rd CT scan then every 3 months thereafter or as per local SOC for CT scanning frequency until peritoneal disease progression as per RECIST (v1.1) or end of trial
CT scan (chest, abdomen and pelvis)	Every 2 months (+/- 2 weeks) for the first year following the 3 rd CT scan then every 3 months thereafter (or as per local SOC) until peritoneal disease progression as per RECIST (v1.1) or end of trial
Blood test - CA125 for ovarian patients, CEA for colorectal patients, not applicable to stomach patients	Same timepoints as for CT scans until peritoneal disease progression as per RECIST (v1.1) or end of trial
QoL questionnaire (EORTC QLQ-30)	2 months after end of treatment, then 4 monthly thereafter (+/- 2 weeks) until death or end of trial
Documentation on whether the participant is suitable for curative surgery	Every follow up visit/phone call (every 2 months in the first year of follow up and every 3 months thereafter)
Details of further treatment for colorectal / ovarian or stomach cancer (as applicable) – document type of	Every 2 months (+/- 2 weeks) in first year after EOT, 3 monthly thereafter until

treatment given and number of lines (courses) of each. <i>(Information collected by RN at phone call and upon review of medical notes)</i>	progressive disease as per RECIST (v1.1) or end of trial
Concomitant Medications	For up to 30 days post end of trial treatment only (i.e. same period as AEs/SAEs)

13.3 Payment

Participants receiving PIPAC will be eligible for reimbursement for travel based on a mileage rate of 45p/mile. This is to be claimed by the participants through their local NHS organisation and the recruiting site will be reimbursed by the Sponsor as per site agreement. Sites should discuss with the CTR options available to cover alternative transport options or accommodation costs.

13.4 Disease response assessment

CT scans should be performed with contrast, and should cover the abdomen, thorax and pelvis as per the timelines described in section 13.1.

CT scans should be reviewed and assessed by the site Radiologist using RECIST V1.1 (Section 29.3). A PICCOS specific RECIST assessment form has been designed to capture and assess peritoneal metastases. All baseline RECIST assessments must include visible measurable or non-measurable lesions from the peritoneum. If further metastases are seen outside of the peritoneum, these should be captured at the end of the form but do not require formal evaluation.

Disease response will be evaluated for peritoneal and extra-peritoneal disease separately, and overall, as per the primary and secondary endpoints.

As pseudo-progression is possible within this population, any increases in lesion size (LS) (within the peritoneum) should be confirmed by a second CT scan at the next planned timepoint before any treatment changes occur. Any new lesions should be classed as definite progression and treatment changes may be required.

In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made. For participants with ovarian malignancy receiving PIPAC, extraperitoneal progression during treatment will lead to an assessment in regard to the addition of SACT.

14 Pharmacovigilance

The PI is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by a medically qualified Investigator (delegated this duty on site delegation log) at the participating site to the CTR PV and Safety Specialist. This includes SAEs related to IMPs and nIMP.

SAEs are reportable immediately following informed consent and should be reported until 30 days after the end of trial treatment.

14.1 Definitions

Table 11: SAE definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an IMP which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - <ul style="list-style-type: none"> • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition*** <p>Following a PIPAC procedure, anything that keeps the participant in hospital for ≥48 hours immediately after the procedure should be reported as an SAE.</p>
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Trial specific SAE reporting requirements

Events requiring reporting

In addition to the SAE reporting requirements defined in Table 11, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Following a PIPAC procedure, anything that keeps the participant in hospital for ≥ 48 hours immediately after the procedure should be reported as an SAE.

Events that do not require reporting

For the purposes of this trial the following events will not require reporting as SAEs. These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

- Hospitalisation for PIPAC procedure, only prolonged hospitalisation requires reporting (as per section 14.2).
- Disease progression.
- Death due to disease progression- if this occurs, the death CRF must be completed.

14.3 Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

Table 12: Colorectal Causality

IMPs: Mitomycin (IP), Oxaliplatin (IP)

nIMPs: Oxaliplatin (IV), Sodium folinate (IV), Calcium folinate (IV), 5-FU (IV), Capecitabine (PO), Irinotecan (IV), Cetuximab (IV), Panitumumab (IV)

Procedures: Laparoscopic surgery

Table 13: Ovarian Causality

IMPs: Cisplatin (IP), Doxorubicin (IP), Paclitaxel (IV), Liposomal Doxorubicin (IV), Gemcitabine (IV)

nIMPs: None

Procedures: Laparoscopic surgery

Table 14: Stomach Causality

IMPs: Cisplatin (IP), Doxorubicin (IP)
nIMPs: Cisplatin (IV), Nivolumab (IV), Sodium folinate (folinic acid) (IV), Calcium Folate (IV), Trastuzumab (IV), Oxaliplatin (IV), 5FU (IV), Capecitabine (PO)
Procedures: Laparoscopic surgery

The PI (or another delegated medically qualified doctor from the trial team) and CI (or another medically qualified doctor from the TMG) will assess each SAE to determine the causal relationship:

Table 15: SAE relationship

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the PI (or delegate) cannot be downgraded by the CI (or delegate), and in the case of disagreement both opinions will be provided.

14.4 Expectedness

The CI (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current to RSI for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented AE constitute unexpected events. Fatal and life-threatening SARs should not be considered expected (unless explicitly stated in the RSI and approved by the MHRA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The tables below list the RSIs that should be referenced:

Table 16: Colorectal RSI

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Mitomycin C (IP)	Mitomycin 2mg powder for solution for injection/ infusion or intravesical use Accord Healthcare Ltd	Section 14.4
Oxaliplatin (IP)	Oxaliplatin 5mg/ml concentrate for solution for infusion Ranbaxy (UK) Ltd, a Sun Pharmaceutical Company	Section 14.4

Table 17: Ovarian RSI

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Cisplatin (IP)	Cisplatin 1mg/ml Sterile Concentrate Hospira UK Ltd	Section 14.4
Doxorubicin (IP)	Doxorubicin Solution for Injection Pfizer Ltd	Section 14.4
Paclitaxel (IV)	Paclitaxel 6mg/ml concentrate for solution for infusion Seacross Pharmaceuticals Ltd	Section 14.4
Liposomal Doxorubicin (IV)	Doxorubicin pegylated liposomal 2mg/ml concentrate for solution for infusion (Doxorubicin hydrochloride) Accord Healthcare Ltd	Section 14.4

Gemcitabine (IV)	Gemcitabine 1000mg, powder for solution for infusion Ranbaxy (UK) Ltd, a Sun Pharmaceutical Company	Section 14.4
------------------	--	--------------

Table 18: Stomach RSI

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Cisplatin (IP)	Cisplatin 1mg/ml Sterile Concentrate, Hospira UK Ltd	Section 14.4
Doxorubicin (IP)	Doxorubicin Solution for Injection Pfizer Ltd	Section 14.4

Table 19: Laparoscopic surgery RSI

Side effect	
Damage to bowel, bladder, ureter, uterus or major blood vessels which require immediate repair	Bruising
Failure to gain entry	Shoulder-tip pain
Hernia at site of entry	Wound gaping
Thromboembolic complications	Infection
Death	Extra procedures: Laparotomy Repair of damage to bowel, bladder, uterus or blood vessels Blood transfusion

RSI on any CTR trial will be reviewed regularly according to CTR procedures.

14.5 Reporting procedures

Participating site responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, year of birth and initials. The participant's name or other personal identifiers should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address: CTR-Safety@Cardiff.ac.uk

SAEs should be reported from the time of randomisation, throughout the treatment period up to, and including 30 days after the participant receives their last dose of trial treatment (IMP / NIMP or PIPAC laparoscopic surgery). SARs (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow-up as defined in the protocol.

SAEs in oncology trials should be graded using the CTCAE v5.0.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An AE/AR
- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF as described in Section 17.2.

The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 30 days after the participant receives their last dose of IMP. SARs should continue to be reported until the end of follow-up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the CI (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA and REC.

14.6 SUSAR reporting

Cardiff and Vale University Health Board (C&V) is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and REC) as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If the SUSAR report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life threatening and non-life threatening.

Any additional, relevant information must be reported within a further 15 days.

N.B. There is no requirement for the CTR to report SUSARs to nIMPs to the MHRA except in the following instances:

- If the AR is suspected to be linked to an interaction between a nIMP and IMP, and is serious and unexpected, CTR should report as a SUSAR due to the interaction with the IMP
- If a SUSAR is suspected and might be linked to either a nIMP or an IMP and cannot be attributed to only one of these
- If the adverse reaction due to the nIMP is likely to affect the safety of trial participants then CTR should report it to the Sponsor, MHRA and REC in accordance with the relevant SOP for reporting Urgent Safety Measures (USM)

14.7 Safety reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA Clinical Trial Authorisation (CTA) approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually, following submission of the DSUR, throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.8 Contraception and pregnancy

Contraception

The IMPs (listed above) in this trial have a demonstrated or suspected human teratogenicity/fetotoxicity. WOCBP entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least six months after the last dose of IMP (or 7 months if treated with the nIMP Trastuzumab (Herceptin)). A highly effective method of contraception is considered as having a failure rate of less than 1%. Some acceptable contraception methods are listed below;

- combined oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
 - oral
 - injectable
 - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*
- sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

**These contraception methods are considered to be low user dependency.*

Male participants with a WOCBP partner should use condom during treatment and at least until six months after the last dose of IMP. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy

without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within PICCOS SAE reporting periods (30 days following last administration of trial treatment). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP RSI must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

14.9 Urgent Safety Measures (USMs)

An USM is an action that the Sponsor, CI or PI may carry out in order to protect the participants of a trial against any immediate hazard to their health or safety. Any USMs relating to this trial must be notified to the MHRA and REC immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15. Statistical considerations

15.1 Randomisation

Site staff who are delegated the role of randomisation will log onto a central web-based platform (see section 9.4), to enter eligible patients into the trial, who will be randomised in a 1:1 ratio to either SOC or PIPAC.

Allocation will be minimised by the PIPAC centre to ensure there is not a disparity in per patient resource costs between sites and balanced on prognostic factors to avoid bias. Within each disease site, the first patient will be allocated at random, and then minimisation with a 20% random element will be used to allocate the next participant to the treatment which reduces the overall imbalance across all prognostic factors.

15.2 Sample Size

In each of our three disease areas we are using a randomised phase II screening design to detect whether PIPAC shows enough activity to warrant further assessment in confirmatory phase III trials. The 1:1 randomisation allows PIPAC (with or without SACT) to be compared to a concurrent control group who will receive SACT. Each trial is powered to detect a Hazard Ratio (HR) of 0.55, as we will need to see a large effect size at this phase II stage to warrant further investigation. Using a high power

of 90% means that we have a high chance of detecting a true improvement in PFS, but since confirmatory trials would be required, a 20% probability of a false positive is acceptable in this setting. A one-sided test is also employed because we only need to demonstrate an improvement in our primary outcome at this stage. In each disease setting, we have assumed that the published median PFS estimates will be a suitable estimate for the peritoneal-specific PFS, since PM will be selected as target lesions in all patients, and we are confident that PM are the driver of progression events in our target population. The artmenu package in Stata 17 was used to calculate the sample size.

Colorectal

In an individual patient data (IPD) meta-analysis of 1,375 colorectal patients with PM, PFS was estimated to be 6 months with standard care(5). There is no randomised data on the effect of PIPAC on PFS or OS in colorectal cancer patients. To demonstrate that PIPAC has enough activity in this group to warrant further phase III investigation, we need to show improvement in median PFS to 11 months (HR 0.55, 20% one-sided significance, 90% power). This requires 51 PFS events and 66 patients recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 78 to allow for early dropouts due to not being fit for PIPAC.

Ovarian

Median PFS is estimated at 3.4 months with standard care(7). There is no randomised data on the expected PFS in the PIPAC group. To demonstrate PIPAC has activity in this group we need to show an improvement in PFS to 6 months (HR 0.55 20% one-sided significance, 90% power). This requires 52 events and 58 patients recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 66 to allow for early dropouts due to not being fit for PIPAC.

Stomach

PFS is estimated at 5 months in the SOC arm, which is close to that assumed by the French PIPAC phase II trial in stomach cancer(72). To demonstrate PIPAC has activity in this group we need to show an improvement in PFS to 9 months (HR 0.55, 20% one-sided significance, 90% power). This requires 52 events in 63 patients, recruited over 2.5 years, with an additional 6-month follow-up at the end of recruitment. This is inflated to 72 to allow for early dropouts due to not being fit for PIPAC.

15.3 Missing, unused & spurious data

If a patient is missing RECIST data for the primary endpoint (peritoneal PFS), due the RECIST assessment being unavailable or unevaluable, then participants will be censored at the date of their last evaluable RECIST assessment, unless they die prior to missing their second follow-up RECIST assessment, in which case the date of death will be used. If a patient has no evaluable RECIST assessment and have not died prior to their 2nd follow-up RECIST assessment, they will be censored at day 1.

Missing data from the QLQ-C30 will be treated as follows, if at least half of the items from a multi-item scale are missing, assume the missing items have an average value of the items that are present, for cases where more than half of an item scale is missing, or a single arm is missing these will remain as missing.

Full details for handling missing or unevaluable data for primary and secondary endpoints will be provided in the Statistical Analysis Plan (SAP).

15.4 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.5 Termination of the trial

We will evaluate feasibility of randomisation using the hypothesis testing traffic light method (73), alongside stipulating minimum numbers to be recruited by 18 months into the trial. In the first 85 eligible patients invited for randomisation within each cancer type, if $\geq 30\%$ patients are randomised, we will continue to recruit to the required sample sizes, if $< 15\%$ are randomised, we will declare recruitment is not feasible, if randomisation is between 15-30%, we will continue but consider any adaptations we could make to improve recruitment. Using this method requires at least 13 of the first 85 invited participants to consent to randomisation in each disease site. This will include speaking to sites as to why recruitment is barrier and reviewing the following: the way patients are approached and invited to the trial; the participant information sheet; eligibility criteria. We would also consider the option of stepping up the publicity surrounding the trial. Throughout the trial we will make every effort to ensure sites have access to the PICCOS team and are receiving the right support.

15.6 Inclusion of analysis

We will include all randomised participants in the analysis of peritoneal progression free survival and overall progression free survival on an intention to treat basis, censoring patients with no evaluable RECIST assessments at day 1. Patients with no PFS events will be censored at the date of their last CT scan if the RECIST assessment is evaluable. All participants will be included in the overall survival analysis, patients with no death events will be censored at the date last reported to be alive by the site.

The feasibility population consists of all randomised patients who are potentially eligible and are given the PIS and invited to take part in the PICCOS trial.

A per-protocol analysis population will exclude participants who do not receive any chemotherapy, and PIPAC patients who do not receive PIPAC. The per protocol analysis will also exclude participants who have a protocol violation affecting analysis.

The safety dataset will include all participants who received any chemotherapy or PIPAC as part of the trial.

16 Analysis

16.1 Main analysis

The feasibility of randomisation will be assessed by a tabulation of the number of potentially eligible patients invited to take part and given the PIS, and the number of those who give their consent to be randomised. This will be broken down by the first 85 patients approached and overall. The reasons for declining to consent to randomisation will also be included in the tabulation.

Analysis of primary and secondary endpoints will be performed for each disease area separately, and since this is a phase II trial, there will be no adjustment to account for multiplicity of testing. Analysis will be performed on an intention to treat basis, when the required number of peritoneal PFS events (from the sample size) have been recorded in each disease and following a minimum 6-month follow-up. PFS date will be derived from CT scan dates, not visit dates. The primary analysis will be based on the results of a centralised review of CT scans.

Patients who have not progressed in the peritoneum or died at the time of analysis will be censored at the time of the latest evaluable RECIST assessment. Patients who progress or die after missing at least two RECIST assessments will be censored at the last RECIST assessment. Patients with no RECIST assessments evaluable for peritoneal disease will be censored at day 1 unless they die within two RECIST visits of baseline (16 weeks). Peritoneal PFS will be estimated using the Kaplan–Meier method and will be described in terms of median PFS per arm. The log-rank test, stratified by prognostic factors, will be used to compare progression-free survival distributions in the two trial arms. A one-sided p-value will be calculated, if this is less than 0.2 and the outcome favours the PICCOS treatment group, then we will consider there to be sufficient statistical evidence of activity in the PICCOS arm to warrant further investigation. We will use multivariable Cox regression to estimate the adjusted HR and one-sided 80% upper confidence interval, adjusted for key prognostic factors such as PCI (if the proportional hazards assumption is not violated). If there is evidence of non-proportional hazards, then we will calculate the restricted mean survival times in each group.

Cox regression will be used to estimate the HR and associated 95% confidence intervals for the secondary time-to-event endpoints of overall PFS and overall survival, but no formal log-rank tests will be performed for these. Overall PFS (peritoneal and extra-peritoneal disease combined) will consider any evidence of disease progression from both peritoneal and extra-peritoneal lesions.

The peritoneal specific overall response rate and the peritoneal specific disease control rate will be calculated for each group with 95% confidence intervals.

The mean difference in global health scores between groups will be summarised at the end of treatment QoL timepoint. The median global health scores from the QLQ-c30 will be calculated with the inter-quartile range (IQR) at each QoL time point and summarised graphically with boxplots over time for each group. The following functional scales will also be summarised as for global health score above, physical functioning, role functioning and emotional functioning. Single symptom items of pain and fatigue will be summarised as above.

The worst grade reported at any point during the trial of any treatment toxicity, or surgical complications affecting at least 5% of participants will be tabulated by grade for each arm. The overall number of episodes of neutropenic sepsis and bowel obstruction will also be summarised.

The outcome of PIPAC procedure will also be summarised, including the number of patients with one, two or three successful procedures, the number of cases of failed abdominal entry, and the number of participants with stomach or colorectal tumours who become eligible for curative surgery following PIPAC. The reasons for failure of procedure will be summarised.

The full plan for analysis will be detailed in the SAP. We plan to share data from the PICCOS trial to evaluate PIPAC in meta-analysis for each disease setting.

16.2 Sub-group & interim analysis

No formal subgroup analysis is planned. Interim analysis will be performed to assess the feasibility outcomes as described above.

17 Data Management

Source Data is defined as “All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.” There is only one set of source data at any time for any data element, as defined in site source data agreement.

17.1 Data collection

Patient randomisation and data collection will take place via electronic online database. Further information can be found in the PICCOS site manual.

17.2 Completion of CRFs

Data recording for this trial will be via web-based systems. These are secure encrypted systems which comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018 standards. After a site has supplied the CTR trial team with a completed delegation log and completed all other processes required to open for recruitment, each user at the site will be emailed a link to activate their account and a username by which they can access these systems in combination with a password set by the user.

The randomisation system can be accessed via: <https://redcap.ctr.cardiff.ac.uk/redcap/>

The data entry system can be accessed via: <https://redcap.ctr.cardiff.ac.uk/redcap/>

Sites will be provided with a guide on using these systems.

Data is expected to be entered by sites within four weeks after the scheduled visit/assessment. If a participant misses a visit/assessment but relevant data is available, for example from a hospital visit

unrelated to the trial, this data should be provided. Data queries will be flagged on RedCAP by the CTR trial team; unresolved queries and overdue forms will be flagged via email to the site on a regular basis.

Participants who are seen at a “PIPAC site” that is different to their “Recruiting site” will have data entered on their CRF by staff at the “Recruiting site” and the “PIPAC site” as applicable to the relevant activities that are undertaken at the respective sites and as delegated to individual staff members on the “Recruiting site’s” PICCOS Delegation Log by the Recruiting site PI.

17.3 Quality of Life questionnaires

Completed paper EORTC QLQ-C20 questionnaires containing the participant’s trial ID, month and year of birth, initials and date of completion can either be scanned in at site and securely emailed to PICCOS@cardiff.ac.uk via FastFile (or another encrypted service) or photocopied, the original kept in the participant file at site and a copy returned to the CTR using the Freepost labels contained within the Investigator Site File (ISF) and ‘Confidential’ marked on the envelope.

18 Translational research

Details of planned future translational research will be added in a substantial amendment once funding has been secured.

19 Qualitative sub-study

The Bristol Biomedical Research Centre (BRC) Surgical and Orthopaedic Innovation theme have established research methods to understand patient experiences of new procedures and/or devices as they are being developed, evaluated, and introduced into clinical practice and to understand how the procedure itself develops(74). These will be embedded into the PICCOS trial to meet the sub-study objectives:

- i. Explore stakeholder perspectives and experiences of PIPAC treatment, including its impact on symptoms and QoL.
- ii. Investigate if there are QoL issues that are unique to patients with PM treated with PIPAC.
- iii. Determine if existing validated patient-reported scales and items measure QoL issues specific to patients with PM treated with PIPAC.
- iv. Dependent on the findings for objective (iii); develop a new scale or item to measure PIPAC-specific QoL issues.

This work will potentially have three phases. Data collection and analysis will proceed in tandem, and the need to collect additional data and/or sample additional participants will be informed by the findings identified in each stage:

Phase 1: Stakeholder interviews and audio-recording consultations

Qualitative research methods provide an opportunity to elicit and characterise patients' experiences of their treatment (75,76), as well as capturing health professionals' experiences of patient care and management (77). One-to-one, semi structured interviews will be conducted to explore views and experiences of PIPAC. We will also investigate if there appear to be any unique QoL issues experienced by patients with PM undergoing and following PIPAC treatment, and if so, what these are. Participants will be purposively sampled to include a range of healthcare professionals (clinical specialty, experience of PIPAC and roles in patient care) and patients receiving PIPAC treatment or SOC (in the colorectal, ovarian and stomach groups). Patients will be interviewed over a range of timepoints (maximum of two) to understand if experiences differ over time and recovery.

Healthcare professionals with experience of delivering and caring for patients during and after PIPAC treatment will be identified and approached directly by the Bristol qualitative research team. Additional interviewees will be identified by the snowball technique, in which healthcare professionals provide the names of other colleagues who could be interviewed. Healthcare professionals may be invited to take part in multiple interviews as their experience of PIPAC develops. Eligible patients will be identified by the clinical team. All potential participants will be provided with a relevant PIS, given the opportunity to ask questions about the qualitative sub-study and informed, through discussions and sub-study materials, that participation in the sub-study is voluntary and does not affect their participation in the main trial.

Patients and healthcare professionals will be asked to consent to taking part in the sub-study.

Patients who are willing to be contacted for an interview will have their details sent securely by email to the Bristol qualitative team research via CTR to allow contact. Interviews will be undertaken by phone, in person or on-line (depending on participant preference and logistical/practical circumstances) and conducted by a qualitative researcher in the Bristol BRC Surgical and Orthopaedic Innovation theme. Interviews will last approximately 30-45 minutes and will be arranged at a time and date convenient for the participant. Separate topic guides will be developed for healthcare professionals and patients, to ensure that discussions within each group cover the same basic issues but with sufficient flexibility to allow new issues of importance to the informants to emerge.

Interviews will be digitally recorded on encrypted audio-recording devices. These data will be transcribed and imported into qualitative software for analysis (e.g. Nvivo). Transcripts will be analysed thematically using constant comparison techniques (78). Data collection and analysis will proceed in parallel, with emerging findings informing further sampling (theoretical sampling) and data collection. Data collection will ultimately continue until additional data are not adding anything new to the analytical framework and theoretical saturation is felt to have been achieved. Comparisons will be made between the interview data (reported QoL issues) and the published literature (issues that are reported in colon, ovarian and stomach patients and are generic aspects of QoL (e.g. fatigue) or clinical outcomes (e.g. survival), to identify the presence of any PIPAC specific issues.

Phase 2: Targeted literature search and review of existing measurement instruments

Dependent on the findings from Phase 1, Phase 2 will identify existing validated patient-reported outcome measures that address the relevant issues using a literature search. If no existing review of the quality (i.e. reliability, validity and responsiveness) of the available measurement instruments is available, their quality will be assessed using COSMIN methodology. If any unique issues are identified in Phase 1 and are not captured in existing patient-reported outcome measures, then a new scale and/or item will be developed using standard European Organisation for Research and Treatment of Cancer (EORTC) methods for item development in Phase 3.

Phase 3 (dependent on previous phases): Developing a new scale or item

Phase 3 will operationalise any unique issues identified in Phase 1 (if they are not covered in existing measures) into questions (items) for completion by patients with PM undergoing PIPAC treatment. The item(s) will be specific for PIPAC treatment, across disease sites (Colon, Ovarian and Stomach) and will not include generic aspects of QoL (e.g. fatigue) or clinical outcomes (e.g. survival). Items will be pre-tested with a sample of PM patients participating in the trial and iteratively refined to ensure comprehensibility, comprehensiveness, relevance and acceptability to patients.

Phase 4 (dependent on previous phases): Validation of new scale or item

Validation of the new scale or item is required before it can be used in a trial. Data for this purpose can be collected in the PICCOS trial by asking trial participants to complete the scale/item (at baseline and in follow up). Psychometric testing or reliability and validity testing will be required. This will be led by the statistics team at the CTR.

Data management

Upon initial consent to the sub-study, participants will be given a unique identifying (ID) number. All subsequent data collected for the sub-study will be labelled by this ID number and data will not include any identifiable information. The sub-study ID number will be linked to personal information (e.g. names and contact details) in a key breaker document which will be encrypted, password protected and stored securely on the University of Bristol servers.

Digital audio files, recorded using encrypted audio-recorders (supplied by the University of Bristol), will be transferred securely to and retained by the University of Bristol. Transfer will be performed using an encrypted electronic data transfer system to ensure safe and secure transfer of digital data. All digital data will be stored securely on the University of Bristol servers, adhering to University of Bristol's data storage policies.

Audio files will be transcribed by an approved, professional transcriber who holds a contract with Cardiff University. Transcripts will be de-identified (i.e. will not include any personal information) to mitigate the risk that participants are identified. Only authorised members of the research team will have access to the audio recordings and transcripts. The transcripts and the audio recordings will be stored in separate locations on University of Bristol servers. The transcript data may be used as part of publications, teaching and presentations at meetings. All quotes will be pseudonymised so that participants cannot be identified. Information about how the data are stored and used is provided in the information sheets for patients and healthcare professionals, and individuals will be asked to confirm they understand how their data will be used as part of the consent process.

20 Protocol/GCP non-compliance

The PI should report any non-compliance to the trial protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it.

21 End of trial definition

The treatment phase will be followed by a non-interventional follow-up period which will continue for at least 6 months after the last participant is randomised.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the final follow-up collection, which will be at least 6 months after final patient is randomised.

Sponsor must notify the MHRA and REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The Trial Master File (TMF) and Trial Statistical File (TSF) containing essential documents will be archived at an approved external storage facility for a minimum of 15 years after completion of the trial. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The PI is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

The TMF and ISF containing essential documents will be kept for a minimum of 15 years after completion of trial. Documents (paper and electronic) will be retained in a secure location during and after the trial has finished.

A label stating the required retention time should be placed on the inside front cover of the medical records for trial participants. Each PI at any participating site will archive the essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement.

Essential documents pertaining to the trial shall not be destroyed without permission from the sponsor.

23 Regulatory considerations

23.1 CE Mark

PIPAC is the administration of an aerosolised anti-cancer treatment within the abdominal cavity. The equipment required to do this includes a laparoscopic nebuliser and an injector which together constitute the drug delivery system. There are several CE marked nebulisers and injectors with the required regulatory approval to deliver drugs in this way and only these will be permitted for use during the PICCOS trial.

23.2 CTA

This trial has CTA from the UK Competent Authority: MHRA.

23.3 Ethical and governance approval

This protocol has a favourable opinion from a REC that is legally “recognised” by the UK Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. Confirmation of C&C of the host care organisation must be obtained before recruitment of participants within that host care organisation.

23.4 Amendments

The CI will seek advice from C&V R&D office prior to submission of amendments to the relevant bodies. The CI will seek approval for any substantial amendments to the protocol or other trial documents from HRA/HCRW and MHRA/REC (if applicable). The NHS R&D Office(s) will need to confirm C&C prior to implementation. Amendments to the protocol or other trial documents will not be implemented prior to these approvals being granted. Non substantial amendments should be notified to the HRA/HCRW and REC for information and may also need to be reviewed and accepted by R&D departments before they can be implemented in practice at site(s).

Any major amendments to this protocol will be approved by the MHRA, REC and HCRW. Minor amendments may only be approved by REC and HCRW.

23.5 Data protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the UK GDPR and Data Protection Act 2018. Participants will be identified using their unique trial identification number and data will be stored alongside the participants initials and full date of birth.

Participants NHS numbers will be securely stored:

- at the Sponsor organisation to facilitate the logistical organisation of PIPAC surgical procedures.
- at the CTR separate to the main trial data to allow long term monitoring of health status.

The data custodian and the translational sample custodian for this trial is C&V.

23.6 Indemnity

This is a NHS-sponsored research trial, and the NHS indemnity scheme therefore applies. If there is negligent harm during the trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

Claims from participants for harm arising from their participation in the clinical trial will be managed in accordance with standard NHS claims procedures for which NHS indemnity schemes will apply.

23.7 Trial sponsorship

The sponsor of this trial is C&V. It is the role of the sponsor to confirm that there are proper arrangements to initiate, manage, monitor, and finance a trial. The sponsor will not play a role in the trial design, conduct, data analysis and interpretation, manuscript writing, or the dissemination of results; this will be the responsibility of the CI, CTR trial team and TMG, either as an employee of the sponsor organisation or with a delegated responsibility.

The sponsor has responsibility for overall oversight of the trial. The role of the Sponsor is to ensure the trial is run safely and effectively by requiring the following:

- Proportionate peer review.
- Provision of all appropriate, valid supporting documentation at the point of application.
- Clear definition of roles and responsibilities of organisations and individuals, signed off prior to the trial commencing.
- Appropriate level of monitoring and audit.
- A risk assessment process to identify any potential risks to the organisation or the health, safety, and well-being of researchers and research participants.
- Involvement of patients and/or the public in trial design, where appropriate.
- The CIs suitability to fulfil their role, through relevant experience and appropriate training.
- Dissemination of trial findings in an appropriate manner.

The Sponsor, through their R&D department, has a veto on overall approval for the trial.

The funder's role is to finance the trial and to receive a trial report. The trial is being sponsored by C&V with responsibilities delegated to participating centres as per the site agreements.

Sponsor has also delegated responsibilities to the CTR as per the agreements. CTR will also ensure that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments

- Conditions and principles of GCP
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- UK GDPR and Data Protection Act 2018
- The Human Tissue Act 2004
- Other regulatory requirements as appropriate
- NIHR Terms and Conditions

23.8 Funding

The PICCOS trial has been funded by the NIHR EME. Funder reference NIHR151274.

The qualitative sub study is partly funded by the NIHR EME grant and additional funds are being sought for the remainder.

Funding application is pending for translation sample collection and analysis.

23.9 Participant payments

Due to the travel required by participants receiving PIPAC within the PICCOS trial, they will be eligible for reimbursement. This will be up to £45 per participant, per PIPAC. This is calculated as an average of 100 miles round trip paid at the standard NIHR mileage rate of 45p/mile. Sites may use some discretion as long as the average across participants does not exceed this amount.

24 Trial management

The sponsor is responsible for uploading the end of trial summary results to EudraCT as per the commission's guidelines on posting and publication of result-related information.

24.1 TMG

The PICCOS TMG will consist of CTR members, surgical and oncology leads from each disease group, research fellows and patient representatives for each disease group. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

The TMG will meet at least every 3 months. The TMG will monitor progress of the trial including recruitment and retention rates, screening logs, safety reporting and other items which may vary depending on the timepoint of the trial. The TMG will also review any data or sample requests received by the PICCOS trial.

A Patient Advisory Group (PAG) will discuss patient relevant issues and outcomes of these discussions will be fed back to the TMG.

Additional safety reviews will be performed from the point that the first participant taking Nivolumab in the stomach group intervention arm has their first PIPAC to the last date of the pharmacovigilance reporting period for the first 4 participants who have Nivolumab and PIPAC. The toxicity profiles (AEs and SAEs) will be reviewed for these 4 participants within the TMG meetings.

24.2 Trial Steering Committee (TSC)

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter. The TSC will meet at least annually and will monitor and review key elements of trial progress including recruitment, Independent Data Monitoring Committee (IDMC) recommendations, and overall management of the trial.

24.3 IDMC

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter. The IDMC will meet at least annually and will review recruitment, safety and efficacy of the PICCOS trial and provide recommendations to the TSC and TMG.

25 Quality Control and Assurance

25.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PICCOS trial. Moderate monitoring levels will be employed and are fully documented in the trial monitoring plan. An appropriately trained PIPAC surgeon will monitor the first PIPAC case at each site to ensure they are being performed as per ISSPP training.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.2 Central review of radiology

All CT scans performed in the trial will be uploaded to the Cimar platform by site staff prior to central review for the primary endpoint of pPFS.

Access to the Cimar platform will be issued upon this duty being assigned by the PI to site staff on the Site Delegation Log. Scans should be pseudonymised at site prior to upload, leaving only participant trial ID, date of birth, male/female and data and time of scan present. Central review will be performed by one member from a Central Review Panel unless there is a discrepancy between the site Radiologist and the Central Reviewers assessment, whereby review by another member of the panel will take place and a consensus opinion obtained.

25.3 Audits & inspections

The trial may be subject to inspection and audit by C&V R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the trial to ensure compliance with the relevant data protection legislation.

The trial is participant to inspection by the MHRA as the regulatory body. The trial may also be participant to inspection and audit by C&V under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

26 Publication policy

All publications and presentations relating to the trial will be authorised by the TMG.

27 Milestones

Recruitment will last ~2.5 years in PICCOS. The last patient will be followed up for 6 months after their randomisation date. Analysis / close down will last a further 6 months.

28 References

1. Glimelius B, Ekström K, Hoffman K, Graf W, Sjöden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Annals of Oncology*. 1997 Feb;8(2):163–8.
2. Chu DZJ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer*. 1989 Jan 15;63(2):364–7.
3. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies. *Cancer*. 2000 Jan 15;88(2):358–63.
4. CRUK. Cancer Statistics for the UK [Internet]. [cited 2022 Aug 12]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk>
5. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol*. 2016 Dec;17(12):1709–19.
6. Blagden SP, Nicum S. A source of hope for platinum-resistant ovarian cancer? *The Lancet*. 2021 Jan;397(10271):254–6.
7. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial. *Journal of Clinical Oncology*. 2014 May 1;32(13):1302–8.
8. Davis A, Tinker A v., Friedlander M. “Platinum resistant” ovarian cancer: What is it, who to treat and how to measure benefit? *Gynecol Oncol*. 2014 Jun;133(3):624–31.
9. Thomassen I, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. *Int J Cancer*. 2014 Feb 1;134(3):622–8.
10. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. *New England Journal of Medicine*. 2008 Jan 3;358(1):36–46.
11. Dedrick RL, Flessner MF. Pharmacokinetic Problems in Peritoneal Drug Administration: Tissue Penetration and Surface Exposure. *JNCI Journal of the National Cancer Institute*. 1997 Apr 2;89(7):480–7.

12. Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol.* 2003 May;4(5):277–83.
13. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Interventional procedure overview of pressurised intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis [Internet]. 2019 Mar [cited 2022 Aug 12]. Available from: <https://www.nice.org.uk/guidance/ipg681/documents/overview>
14. Tate SJ, Torkington J. Pressurized intraperitoneal aerosol chemotherapy: a review of the introduction of a new surgical technology using the IDEAL framework. *BJS Open.* 2020 Apr;4(2):206–15.
15. Baggaley AE, Lafaurie GBRC, Tate SJ, Boshier PR, Case A, Prosser S, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): updated systematic review using the IDEAL framework. *British Journal of Surgery.* 2022 Dec 13;110(1):10–8.
16. Case A, Gwynne S, Kihara S, Peters C, Prosser S. Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for gastric cancer with peritoneal metastases: A systematic review by the UK PIPAC Collaborative. *PROSPERO.* 2021.
17. Naskretski A, Jones S, Owens G. Pressurised Intraperitoneal Aerosolised Chemotherapy (PIPAC) for metastatic ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma: a systematic review by the UK PIPAC Collaborative. *PROSPERO.* 2021.
18. Lurvink RJ, Rovers KP, Nienhuijs SW, Creemers GJ, Burger JWA, de Hingh IHJ. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) in patients with colorectal peritoneal metastases—a systematic review. *J Gastrointest Oncol.* 2021 Apr;12(S1):S242–58.
19. Reymond MA, Hu B, Garcia A, Reck T, Köckerling F, Hess J, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. *Surg Endosc.* 2000 Jan;14(1):51–5.
20. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. *Surg Endosc.* 2012 Jul 12;26(7):1849–55.
21. Solass W, Herbet A, Schwarz T, Hetzel A, Sun JS, Dutreix M, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. *Surg Endosc.* 2012 Mar 1;26(3):847–52.
22. Khosrawipour V, Khosrawipour T, Diaz-Carballo D, Förster E, Zieren J, Giger-Pabst U. Exploring the Spatial Drug Distribution Pattern of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). *Ann Surg Oncol.* 2016 Apr 9;23(4):1220–4.

23. Khosrawipour V, Khosrawipour T, Kern AJP, Osma A, Kabakci B, Diaz-Carballo D, et al. Distribution pattern and penetration depth of doxorubicin after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a postmortem swine model. *J Cancer Res Clin Oncol*. 2016 Nov 2;142(11):2275–80.
24. Bellendorf A, Khosrawipour V, Khosrawipour T, Siebigteroth S, Cohnen J, Diaz-Carballo D, et al. Scintigraphic peritoneography reveals a non-uniform 99mTc-Per technetate aerosol distribution pattern for Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) in a swine model. *Surg Endosc*. 2018 Jan 22;32(1):166–74.
25. Khosrawipour V, Diaz-Carballo D, Ali-Haydar A, Khosrawipour T, Falkenstein TA, Wu D, et al. Cytotoxic effect of different treatment parameters in pressurized intraperitoneal aerosol chemotherapy (PIPAC) on the in vitro proliferation of human colonic cancer cells. *World J Surg Oncol*. 2017 Dec 10;15(1):43.
26. Shariati M, Lollo G, Matha K, Descamps B, Vanhove C, van de Sande L, et al. Synergy between Intraperitoneal Aerosolization (PIPAC) and Cancer Nanomedicine: Cisplatin-Loaded Polyarginine-Hyaluronic Acid Nanocarriers Efficiently Eradicate Peritoneal Metastasis of Advanced Human Ovarian Cancer. *ACS Appl Mater Interfaces*. 2020 Jun 22;acsami.0c05554.
27. MIKOLAJCZYK A, KHOSRAWIPOUR V, SCHUBERT J, CHAUDHRY H, PIGAZZI A, KHOSRAWIPOUR T. Particle Stability During Pressurized Intra-peritoneal Aerosol Chemotherapy (PIPAC). *Anticancer Res*. 2018 Aug 30;38(8):4645–9.
28. Keck HS, Weinreich FJ, Shegokar R, Königsrainer A, Reymond MA, Nadiradze G. Experimental evaluation of icodextrin delivery as pressurized aerosol (PIPAC): Antiadhesive and cytotoxic effects. *European Journal of Surgical Oncology*. 2021 Jun;47(6):1434–40.
29. Mikolajczyk A, Khosrawipour V, Schubert J, Grzesiak J, Chaudhry H, Pigazzi A, et al. Effect of Liposomal Doxorubicin in Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC). *J Cancer*. 2018;9(23):4301–5.
30. Seitenfus R, Ferreira PRW, Santos GO dos, Alves RJV, Kalil AN, Barros ED de, et al. A prototype single-port device for pressurized intraperitoneal aerosol chemotherapy. Technical feasibility and local drug distribution. *Acta Cir Bras*. 2017 Dec;32(12):1056–63.
31. Park SJ, Lee EJ, Lee HS, Kim J, Park S, Ham J, et al. Development of rotational intraperitoneal pressurized aerosol chemotherapy to enhance drug delivery into the peritoneum. *Drug Deliv*. 2021 Jan 1;28(1):1179–87.
32. Kakchekeeva T, Demtröder C, Herath NI, Griffiths D, Torkington J, Solaß W, et al. In Vivo Feasibility of Electrostatic Precipitation as an Adjunct to Pressurized

- Intraperitoneal Aerosol Chemotherapy (ePIPAC). *Ann Surg Oncol*. 2016 Dec 2;23(S5):592–8.
33. van de Sande L, Rahimi-Gorji M, Giordano S, Davoli E, Matteo C, Detlefsen S, et al. Electrostatic Intraperitoneal Aerosol Delivery of Nanoparticles: Proof of Concept and Preclinical Validation. *Adv Healthc Mater*. 2020 Aug 16;9(16):2000655.
 34. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal Chemotherapy of Peritoneal Carcinomatosis Using Pressurized Aerosol as an Alternative to Liquid Solution: First Evidence for Efficacy. *Ann Surg Oncol*. 2014 Feb 5;21(2):553–9.
 35. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and Hepatic Toxicities After Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). *Ann Surg Oncol*. 2013 Jul 3;20(7):2311–6.
 36. Solaß W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Occupational Health and Safety Aspects. *Ann Surg Oncol*. 2013 Oct 14;20(11):3504–11.
 37. Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Pleura Peritoneum*. 2017 Aug 28;2(3):121–8.
 38. Roussin F, Taibi A, Canal-Raffin M, Cantournet L, Durand-Fontanier S, Druet-Cabanac M, et al. Assessment of workplace environmental contamination and occupational exposure to cisplatin and doxorubicin aerosols during electrostatic pressurized intraperitoneal aerosol chemotherapy. *European Journal of Surgical Oncology*. 2021 Nov;47(11):2939–47.
 39. Ndaw S, Hanser O, Kenepkian V, Vidal M, Melczer M, Remy A, et al. Occupational exposure to platinum drugs during intraperitoneal chemotherapy. *Biomonitoring and surface contamination*. *Toxicol Lett*. 2018 Dec;298:171–6.
 40. Tempfer CB, Hartmann F, Hilal Z, Reznicek GA. Intraperitoneal cisplatin and doxorubicin as maintenance chemotherapy for unresectable ovarian cancer: a case report. *BMC Cancer*. 2017 Dec 6;17(1):26.
 41. Tempfer CB, Solass W, Buerkle B, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in a woman with pseudomyxoma peritonei: A case report. *Gynecol Oncol Rep*. 2014 Dec;10:32–5.
 42. Rotolo S, Ferracci F, Santullo F, Lodoli C, Inzani F, Abatini C, et al. Systemic chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC): A case report of a multimodal treatment for peritoneal metastases of pancreatic origin. *Int J Surg Case Rep*. 2020;77:S75–8.

43. Graversen M, Detlefsen S, Pfeiffer P, Lundell L, Mortensen MB. Severe peritoneal sclerosis after repeated pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC OX): report of two cases and literature survey. Clin Exp Metastasis. 2018 Mar 28;35(3):103–8.
44. Siebert M, Alyami M, Mercier F, Gallice C, Villeneuve L, Bérard F, et al. Severe hypersensitivity reactions to platinum compounds post-pressurized intraperitoneal aerosol chemotherapy (PIPAC): first literature report. Cancer Chemother Pharmacol. 2019 Mar 3;83(3):425–30.
45. Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, et al. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). European Journal of Surgical Oncology (EJSO). 2015 Oct;41(10):1379–85.
46. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Reznicek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018 Jul;150(1):23–30.
47. Dumont F, Passot C, Raoul JL, Kepenekian V, Lelièvre B, Boisdron-Celle M, et al. A phase I dose-escalation study of oxaliplatin delivered via a laparoscopic approach using pressurised intraperitoneal aerosol chemotherapy for advanced peritoneal metastases of gastrointestinal tract cancers. Eur J Cancer. 2020 Nov;140:37–44.
48. Robella M, de Simone M, Berchiolla P, Argenziano M, Borsano A, Ansari S, et al. A Phase I Dose Escalation Study of Oxaliplatin, Cisplatin and Doxorubicin Applied as PIPAC in Patients with Peritoneal Carcinomatosis. Cancers (Basel). 2021 Mar 3;13(5):1060.
49. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond M -A. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Disease. 2016 Apr 2;18(4):364–71.
50. de Simone M, Vaira M, Argenziano M, Berchiolla P, Pisacane A, Cinquegrana A, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Oxaliplatin, Cisplatin, and Doxorubicin in Patients with Peritoneal Carcinomatosis: An Open-Label, Single-Arm, Phase II Clinical Trial. Biomedicines. 2020 Apr 30;8(5):102.
51. Ellebæk SB, Graversen M, Detlefsen S, Lundell L, Frstrup CW, Pfeiffer P, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) of peritoneal metastasis from gastric cancer: a descriptive cohort study. Clin Exp Metastasis. 2020 Apr 30;37(2):325–32.

52. Kurtz F, Struller F, Horvath P, Solass W, Bösmüller H, Königsrainer A, et al. Feasibility, Safety, and Efficacy of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastasis: A Registry Study. *Gastroenterol Res Pract*. 2018 Oct 24;2018:1–8.
53. Sgarbura O, Hübner M, Alyami M, Eveno C, Gagnière J, Pache B, et al. Oxaliplatin use in pressurized intraperitoneal aerosol chemotherapy (PIPAC) is safe and effective: A multicenter study. *European Journal of Surgical Oncology*. 2019 Dec;45(12):2386–91.
54. Račkauskas R, Baušys A, Lukšta M, Jurgaitis J, Paškonis M, Strupas K. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal malignancy: initial experience of the first program in the Baltic countries. *World J Surg Oncol*. 2021 Dec 10;19(1):236.
55. Tempfer CB, Celik I, Solass W, Buerkle B, Pabst UG, Zieren J, et al. Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: Preliminary clinical experience. *Gynecol Oncol*. 2014 Feb;132(2):307–11.
56. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. *Gynecol Oncol*. 2015 May;137(2):223–8.
57. Siebert M, Alyami M, Mercier F, Gallice C, Villeneuve L, Laplace N, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in association with systemic chemotherapy and bevacizumab, evaluation of safety and feasibility. A single center comparative study. *European Journal of Surgical Oncology*. 2021 Jan;47(1):139–42.
58. Gockel I, Jansen-Winkel B, Haase L, Rhode P, Mehdorn M, Niebisch S, et al. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Gastric Cancer Patients with Peritoneal Metastasis (PM): Results of a Single-Center Experience and Register Study. *J Gastric Cancer*. 2018;18(4):379.
59. Alyami M, Bonnot PE, Mercier F, Laplace N, Villeneuve L, Passot G, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. *European Journal of Surgical Oncology*. 2021 Jan;47(1):123–7.
60. di Giorgio A, Schena CA, el Halabieh MA, Abatini C, Vita E, Strippoli A, et al. Systemic chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC): A bidirectional approach for gastric cancer peritoneal metastasis. *Surg Oncol*. 2020 Sep;34:270–5.
61. Willaert W, van de Sande L, van Daele E, van de Putte D, van Nieuwenhove Y, Pattyn P, et al. Safety and preliminary efficacy of electrostatic precipitation during

- pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable carcinomatosis. *European Journal of Surgical Oncology*. 2019 Dec;45(12):2302–9.
62. Tidadini F, Abba J, Quesada JL, Baudrant M, Bonne A, Foote A, et al. Effect of Pressurized Intraperitoneal Aerosol Chemotherapy on the Survival Rate of Patients with Peritoneal Carcinomatosis of Gastric Origin. *J Gastrointest Cancer*. 2021 Oct 22;
 63. Feldbrügge L, Gronau F, Brandl A, Auer TA, Oeff A, Thuss-Patience P, et al. Systemic Chemotherapy Including Ramucirumab in Combination With Pressurized Intra-Peritoneal Aerosol Chemotherapy Is a Safe Treatment Option for Peritoneal Metastasis of Gastric Cancer. *Front Oncol*. 2021 Apr 12;10.
 64. Sindayigaya R, Dogan C, Demtröder CR, Fischer B, Karam E, Buggisch JR, et al. Clinical Outcome for Patients Managed with Low-Dose Cisplatin and Doxorubicin Delivered as Pressurized Intraperitoneal Aerosol Chemotherapy for Unresectable Peritoneal Metastases of Gastric Cancer. *Ann Surg Oncol*. 2022 Jan 5;29(1):112–23.
 65. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. *Journal of Gastrointestinal Surgery*. 2016 Feb 28;20(2):367–73.
 66. Sgarbura O, Hübner M, Alyami M, Eveno C, Gagnière J, Pache B, et al. Oxaliplatin use in pressurized intraperitoneal aerosol chemotherapy (PIPAC) is safe and effective: A multicenter study. *European Journal of Surgical Oncology*. 2019 Dec;45(12):2386–91.
 67. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). *Pleura Peritoneum*. 2019 Apr 24;1(3):159–66.
 68. Struller F, Horvath P, Solass W, Weinreich FJ, Strumberg D, Kokkalis MK, et al. Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase II study. *Ther Adv Med Oncol*. 2019 Jan 13;11:175883591984640.
 69. Tempfer C, Giger-Pabst U, Hilal Z, Dogan A, Reznicek GA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal carcinomatosis: systematic review of clinical and experimental evidence with special emphasis on ovarian cancer. *Arch Gynecol Obstet*. 2018 Aug 4;298(2):243–57.
 70. Sgarbura O, Eveno C, Alyami M, Bakrin N, Guiral DC, Ceelen W, et al. Consensus statement for treatment protocols in pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Pleura Peritoneum*. 2022 Mar 1;7(1):1–7.

71. Solaß W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Occupational Health and Safety Aspects. *Ann Surg Oncol*. 2013;20(11):3504–11.
72. Eveno C, Jouvin I, Pocard M. PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study. *Pleura Peritoneum*. 2018 Jun 21;3(2).
73. Lewis M, Bromley K, Sutton CJ, McCray G, Myers HL, Lancaster GA. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! *Pilot Feasibility Stud*. 2021 Dec 3;7(1):40.
74. Elliott D, Blencowe NS, Cousins S, Zahra J, Skilton A, Mathews J, et al. Using qualitative research methods to understand how surgical procedures and devices are introduced into NHS hospitals: the Lotus study protocol. *BMJ Open*. 2021 Dec 3;11(12):e049234.
75. Wilburn J, McKenna SP, Twiss J, Kemp K, Campbell S. Assessing quality of life in Crohn's disease: development and validation of the Crohn's Life Impact Questionnaire (CLIQ). *Quality of Life Research*. 2015 Sep 22;24(9):2279–88.
76. Bausewein C, Simon ST, Benalia H, Downing J, Mwangi-Powell FN, Daveson BA, et al. Implementing patient reported outcome measures (PROMs) in palliative care - users' cry for help. *Health Qual Life Outcomes*. 2011;9(1):27.
77. Trujols J, Portella MJ, Iraurgi I, Campins MJ, Siñol N, Cobos JP de L. Patient-reported outcome measures: Are they patient-generated, patient-centred or patient-valued? *Journal of Mental Health*. 2013 Dec 16;22(6):555–62.
78. Clarke V, Braun V. Thematic Analysis. In: *Encyclopedia of Critical Psychology*. New York, NY: Springer New York; 2014. p. 1947–52.
79. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications. *Ann Surg*. 2004 Aug;240(2):205–13.

29 Appendices

29.1 PCI

The PCI quantitatively combines the distribution of tumour throughout 13 abdominopelvic regions with a LS score.

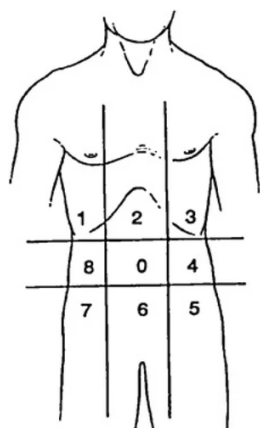
Two transverse and two sagittal planes divide the abdomen into 9 regions (Figure 5). The upper transverse plane is located at the lowest aspect of the costal margin, and the lower transverse plane is placed at the anterior superior iliac spine. The sagittal planes divide the abdomen into three equal sectors. The lines define 9 regions, which are numbered in a clockwise direction with 0 at the umbilicus and 1 defining the space beneath the right hemidiaphragm. Regions 9 through 12 divide the small bowel into upper and lower jejunum and upper and lower ileum. To make the PCI tool more quantitative and reproducible, each region is not only defined by the surface landmarks as previously described but can also be defined by the anatomic structures found in each region (table 20).

LS score refers to the greatest diameter of tumour implants that are distributed on the peritoneal surfaces. LS-0 indicates no implants seen. LS-1 indicates implants less than 0.25 cm. LS-2 indicates implants between 0.25 and 2.5 cm. LS-3 indicates implants greater than 2.5 cm. It refers to the greatest diameter of tumour implants that are distributed on the peritoneal surfaces. Primary tumours or localized recurrences at the primary site that can be removed definitively are excluded from the assessment. If there is confluence of disease matting abdominal or pelvic structures together, this is automatically scored as L-3 even if it is a thin confluence of cancerous implants. The LS are then summated for all abdominopelvic regions.

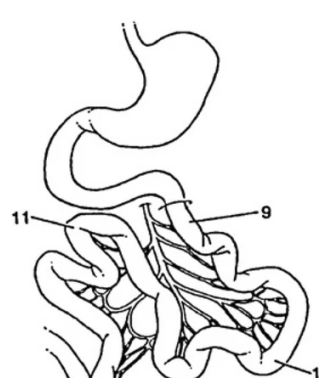
The extent of the disease within all regions of the abdomen and pelvis is indicated by a numerical score from 0 to 39.

Figure 5: PCI

Peritoneal cancer index



Regions	Lesion size	Lesion size score
0 Central	_____	LS 0 No tumour seen
1 Right upper	_____	LS 1 Tumour up to 0.5cm
2 Epigastrium	_____	LS 2 Tumour up to 5.0cm
3 Left upper	_____	LS 3 Tumour > 5.0 or confluence
4 Left flank	_____	
5 Left lower	_____	
6 Pelvis	_____	
7 Right lower	_____	
8 Right flank	_____	
9 Upper jejunum	_____	
10 Lower jejunum	_____	
11 Upper ileum	_____	
12 Lower ileum	_____	



PCI

Table 20: Anatomic structures involved in the 13 abdominopelvic regions of the PCI

Regions	Anatomic structures
0 Central	Midline abdominal incision – entire greater omentum – transverse colon
1 Right upper	Superior surface of the right lobe of the liver – undersurface of the right hemidiaphragm – right retro hepatic space
2 Epigastrium	Epigastric fat pad – left lobe of the liver – lesser omentum – falciform ligament
3 Left upper	Under surface of the left hemidiaphragm – spleen – tail of pancreas – anterior and posterior surfaces of the stomach
4 Left flank	Descending colon – left abdominal gutter
5 Left lower	Pelvic sidewall lateral to the sigmoid colon – sigmoid colon
6 Pelvis	Female internal genitalia with ovaries, tubes and uterus – bladder, Douglas pouch – rectosigmoid colon
7 Right lower	Right pelvic sidewall – caecum – appendix
8 Right flank	Right abdominal gutter – ascending colon
9 Upper jejunum	
10 Lower jejunum	
11 Upper ileum	
12 Lower ileum	

29.2 ECOG

Table 21: ECOG Criteria

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

29.3 RECIST V1.1

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

29.4 Schedule of assessments

Table 22: Colorectal group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Blood test - CEA ²		X (baseline)	X			X	X	X	X	X	X	X
Blood test - DPYD ¹	X											
Urine pregnancy test WOCBP	X											
MSI testing on tumour biopsy ¹	X											
CT scan and upload to CIMAR ³	X			X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ⁴		X (baseline)		X	X	X		X		X		
Administer SACT ⁵			X									
Record concomitant medications	X		X									
Report AEs / SAEs ⁶			X			X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

- 1 MSI testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.
- 2 CEA blood tests to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.
- 3 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry and then 8-10 weeks and 19-21 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.
- 4 QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- 5 SACT is to be administered according to the protocol. Participants who show extraperitoneal disease progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
- 6 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.

Table 23 Colorectal group intervention arm schedule

Activity	Screening	Randomisation	PIPAC treatment cycles			Each non PIPAC cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op assessment ³	Each PIPAC cycle	30 days post PIPAC										
Informed consent	X														
Randomisation		X													
Medical history, pt demographics / ethnicity	X														
Height and weight			X			X									
Vital signs and physical assessment	X		X			X									
ECOG	X		X			X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X			X									
Blood test - magnesium			X			X									
Blood test - CEA ²		X (baseline)	X			X			X	X	X	X	X	X	X
Blood test - DPYD ¹	X														
Urine pregnancy test - WOCBP	X		X												
MSI testing of tumour biopsy ¹	X														
ECG ⁴			X												
CT scan and upload to CIMAR ⁵	X						X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ⁶		X (baseline)					X	X	X		X		X		
PIPAC procedure				X											
Administer SACT ⁷				X		X									
Record concomitant medications	X		X			X									
Report AEs / SAEs ⁸			X	X	X	X			X	X	X	X	X	X	X
Clavien Dindo classification ⁹					X										
PCI scoring ¹⁰				X											

Activity	Screening	Randomisation	PIPAC treatment cycles			Each non PIPAC cycle	8-10 weeks post rand	19-21 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op assessment ³	Each PIPAC cycle	30 days post PIPAC										
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- MSI testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.
- CEA blood tests to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.
- Pre-op assessment to take place within 72 hours prior to PIPAC procedure (can be performed at local recruiting hospital or at hospital where participant will have PIPAC). Results of pre-op assessments to be sent to PIPAC hospital (if applicable). PICCOS RN from the Sponsor will call participants approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure. If patients do not meet the criteria for undergoing PIPAC procedure, they should not travel to the PIPAC centre and the surgery should be rearranged.
- ECG required only if indicated by pre-op assessments.
- CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry, 8-10 weeks and 19-21 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made.
- QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- SACT is to be administered according to the protocol. Note in PIPAC cycles the only permitted SACT are Capecitabine, 5FU infusion (not bolus), Cetuximab and Panitumumab (as applicable). Washout periods included in the protocol should be observed. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
- AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.
- Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification for this time period and report AEs/SAEs as required.
- PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

Table 24 Ovarian group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	10-12 weeks post rand	18-20 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed Consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Blood test - CA125 ¹		X (baseline)	X			X	X	X	X	X	X	X
CT scan and upload to CIMAR ²	X			X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ³		X (baseline)		X	X	X		X		X		
Administer SACT as per protocol ⁴			X									
Record concomitant medications	X		X									
Report AEs / SAEs ⁵			X			X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

- CA125 blood tests to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.
- CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed prior to trial entry, 10-12 weeks and 18-20 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and

thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.

- 3 QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 10-12 weeks post randomisation, 18-20 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- 4 SACT is to be administered according to the protocol. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
- 5 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.

Table 25 Ovarian group intervention arm schedule

Activity	Screening	Randomisation	Each PIPAC treatment cycle			(Each non PIPAC treatment cycle)	10-12 weeks post rand	18-20 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op assessment ²	PIPAC treatment cycle	30 days post PIPAC										
Informed Consent	X														
Randomisation		X													
Medical history, pt demographics/ethnicity	X														
Height and weight			X			(X)									
Vital signs and physical assessment	X		X			(X)									
ECOG	X		X			(X)									
Blood test - FBC, U+Es, LFTs, bone profile	X		X			(X)									
Blood test - magnesium			X			(X)									
Blood test - CA125 ¹		X (baseline)	X			(X)			X	X	X	X	X	X	X
ECG ³			X												
CT scan and upload to CIMAR ⁴	X						X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ⁵		X (baseline)					X	X	X		X		X		
PIPAC procedure				X											
Administer SACT ⁶						(X)									
Record concomitant medications	X		X			(X)									
Report AEs / SAEs ⁷			X	X	X	(X)			X	X	X	X	X	X	X
Clavien Dindo classification ⁹					X										
PCI scoring ¹⁰				X											
CRF completion	X	X	X	X	X	(X)	X	X	X	X	X	X	X	X	X

- 1 CA125 blood test to be performed at baseline, pre each treatment cycle and then at the same timepoints as CT scans in follow up until peritoneal disease progression as per RECIST (v1.1) or end of trial.
- 2 Pre-op assessment to take place within 72 hours prior to PIPAC procedure (can be performed at local recruiting hospital or at hospital where participant will have PIPAC). Results of pre-op assessments to be sent to PIPAC hospital (if applicable). PICCOS RN from the Sponsor will call participant approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure. If participants do not meet the criteria for undergoing PIPAC procedure, they should not travel to the PIPAC centre and the surgery should be rearranged.
- 3 ECG required only if indicated by pre-op assessments.
- 4 CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed at screening, 10-12 weeks and 18-20 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment will be made.
- 5 QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- 6 No SACT is to be given in the ovarian group intervention arm. The exception to this rule is for participants who show extraperitoneal disease progression and have not yet completed 3 PPAC procedures who may have SACT added in at the discretion of their treating PI. If SACT is added, it should be completed 7 days prior to the PIPAC procedure.
- 7 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.
- 8 Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification for this time period and report AEs/SAEs as required.
- 9 PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

Table 26 Stomach group control arm schedule

Activity	Screening	Randomisation	Each treatment cycle	8-10 weeks post rand	19-21 or 20-22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
Informed consent	X											
Randomisation		X										
Medical history, pt demographics/ethnicity	X											
Height and weight			X									
Vital signs and physical assessment	X		X									
ECOG	X		X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X									
Blood test - magnesium			X									
Nlood test - DPYD ¹	X											
MSI, HER2 and CPS testing on tumour biopsy ¹	X											
Urine pregnancy test - WOCBP	X											
CT scan and upload to CIMAR ²	X			X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ³		X (baseline)		X	X	X		X		X		
Administer SACT ⁴			X									
Record concomitant medications	X		X									
Report AEs / SAE ⁵			X			X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X

- MSI, HER2 and CPS testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.
- CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform. CT scans should be performed at screening, and then around 8-10 weeks and 19-21 / 20-22 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment) will be made.

- 3 QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 / 20-22 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- 4 SACT is to be administered according to the protocol. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
- 5 AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.

Table 27 Stomach group intervention arm schedule

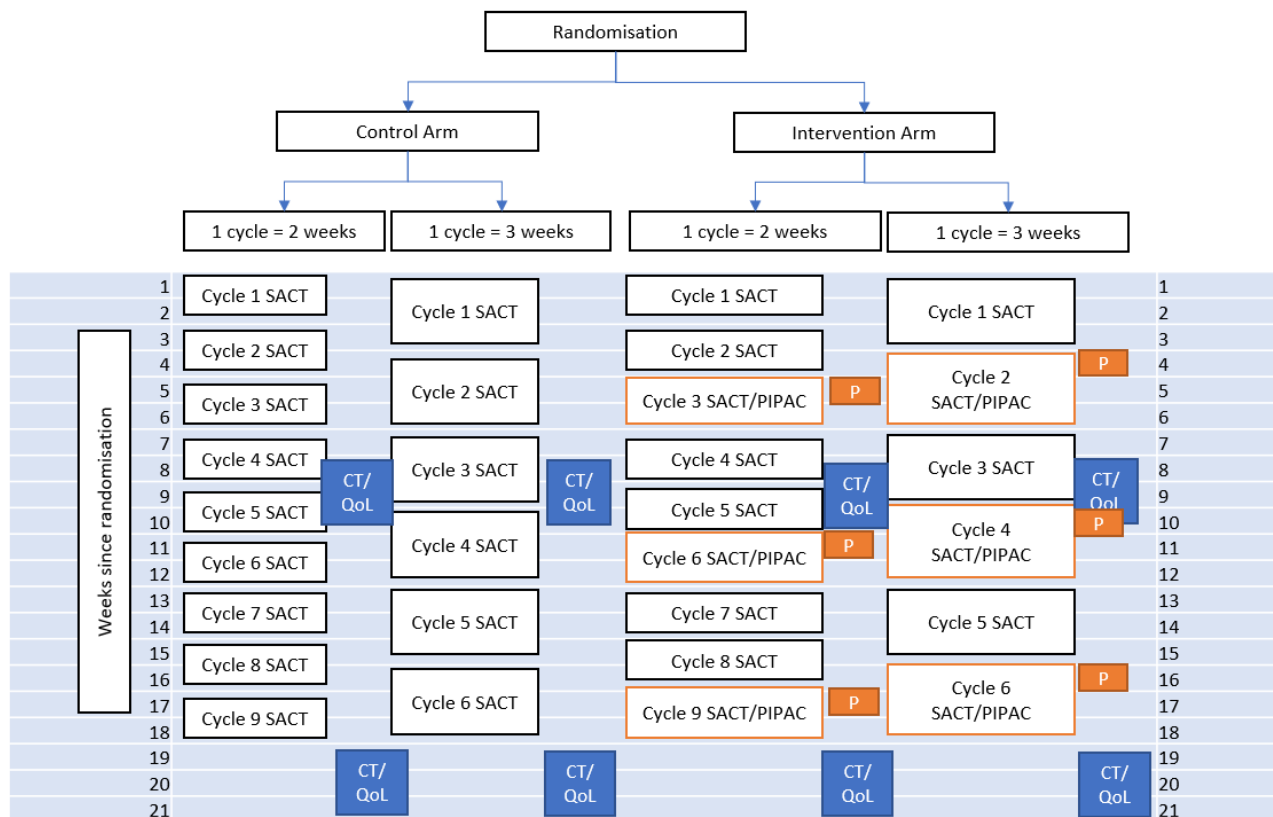
Activity	Screening	Randomi sation	Each PIPAC treatment cycle			Each non PIPAC treatment cycle	8-10 weeks post rand	19-21 or 20- 22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op assessm ent ²	PIPAC treatment cycle	30 days post PIPAC										
Informed Consent	X														
Randomisation		X													
Medical history, pt demographics/ethnicity	X														
Height and weight			X			X									
Vital signs and physical assessment	X		X			X									
ECOG	X		X			X									
Blood test - FBC, U+Es, LFTs, bone profile	X		X			X									
Blood test - magnesium			X			X									
Nlood test – DPYD ¹	X														
MSI, HER2 and CPS testing on tumour biopsy ¹	X														
Urine pregnancy test - WOCBP	X		X												
ECG ³			X												
CT scan and upload to CIMAR ⁴	X						X	X	X	X	X	X	X	X	X
EORTC QLQ-C30 completion ⁵		X (baseline)					X	X	X		X		X		
PIPAC procedure				X											
Administer SACT ⁶				X		X									
Record concomitant medications	X		X			X									
Report AEs / SAEs ⁷			X	X	X	X			X	X	X	X	X	X	X

Activity	Screening	Randomisation	Each PIPAC treatment cycle			Each non PIPAC treatment cycle	8-10 weeks post rand	19-21 or 20-22 weeks post rand	2 months post CT 3	4 months post CT 3	6 months post CT 3	8 months post CT 3	10 months post CT 3	12 months post CT 3	Every 3 months thereafter
			Pre op assessment ²	PIPAC treatment cycle	30 days post PIPAC										
Clavien Dindo classification ⁸					X										
PCI scoring ⁹				X											
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- MSI, HER2 and CPS testing of tumour biopsy and DPYD blood test can take place any time prior to randomisation.
- Pre-op assessment to take place within 72 hours prior to PIPAC procedure (can be performed at local recruiting hospital or at hospital where participant will have PIPAC). Results of pre-op assessments to be sent to PIPAC hospital (if applicable). PICCOS RN from the Sponsor will call participants approximately 24 hours prior to each PIPAC to ensure the participant is ready for their procedure. If patients do not meet the criteria for undergoing the PIPAC procedure, they should not travel to the PIPAC centre and the surgery should be rearranged.
- ECG required only if indicated by pre-op assessments.
- CT scan (with contrast) should cover thorax, abdomen, and pelvis. Pseudonymised copies of CT images should be uploaded to the CIMAR platform, CT scans should be performed at screening, 8-10 weeks and 19-21 / 20-22 weeks after randomisation, regardless of delays and changes to treatment, then every 2 months for the next year and thereafter every 3 months (or as per local SOC) until peritoneal disease progression as per RECIST (V1.1). In cases of progressive extraperitoneal disease (but without progression of peritoneal disease) seen on scans performed during treatment, CT scanning should continue but an assessment will be made by the local/trial team and a decision regarding the appropriateness of continuation or withdrawal of treatment (SACT/PIPAC) will be made.
- QoL (EORTC QLQ-C30) questionnaires to be completed alongside CT scans, at baseline, 8-10 weeks post randomisation, 19-21 / 20-22 weeks post randomisation, and then 2, 6 and 10 months post CT scan 3.
- SACT is to be administered according to the protocol. Note in PIPAC cycles, the only permitted SACT is Nivolumab and Trastuzumab (as applicable). Washout periods included in the protocol should be observed. Participants who show extraperitoneal progression and have not yet completed the treatment period may switch to an alternative SACT regime listed in the protocol at the discretion of their treating PI.
- AEs and SAEs to be reported following informed consent until 30 days after the end of trial treatment. After this, the only AE to be recorded will be the occurrence of bowel obstruction.
- Approximately 30 days after each PIPAC, a RN will call the participant, review their medical notes since their last PIPAC and document the appropriate Clavien Dindo classification for this time period and report AEs/SAEs as required.
- PCI scoring is to be performed by the surgeon during laparoscopic surgery for PIPAC.

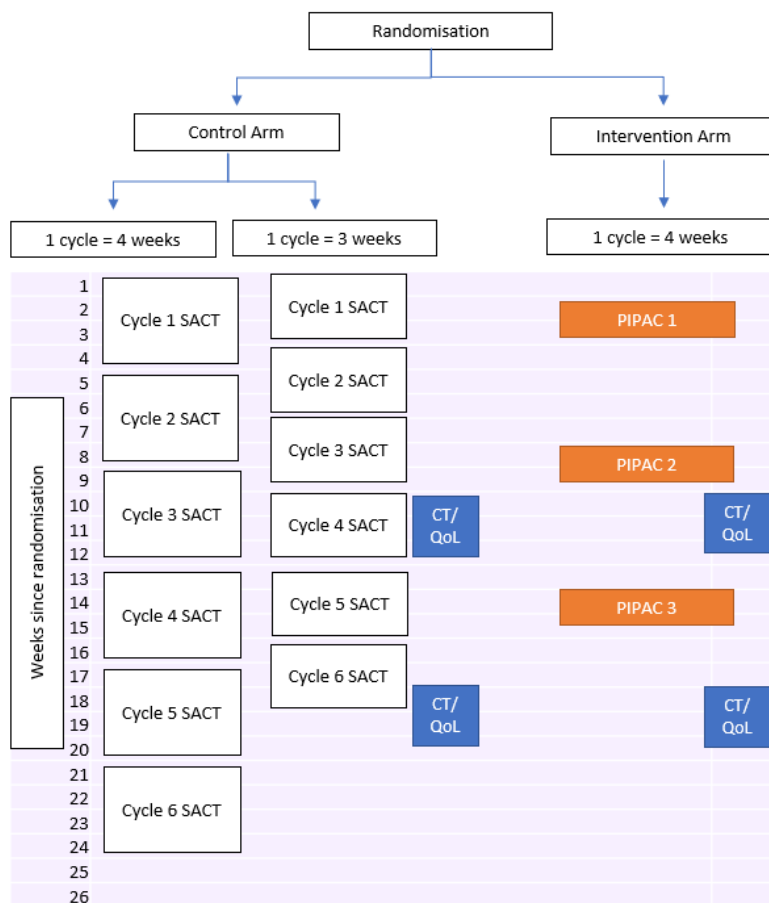
29.5 PIPAC and SACT schedule vs CT scans and QoL questionnaires

Figure 6: Colorectal group



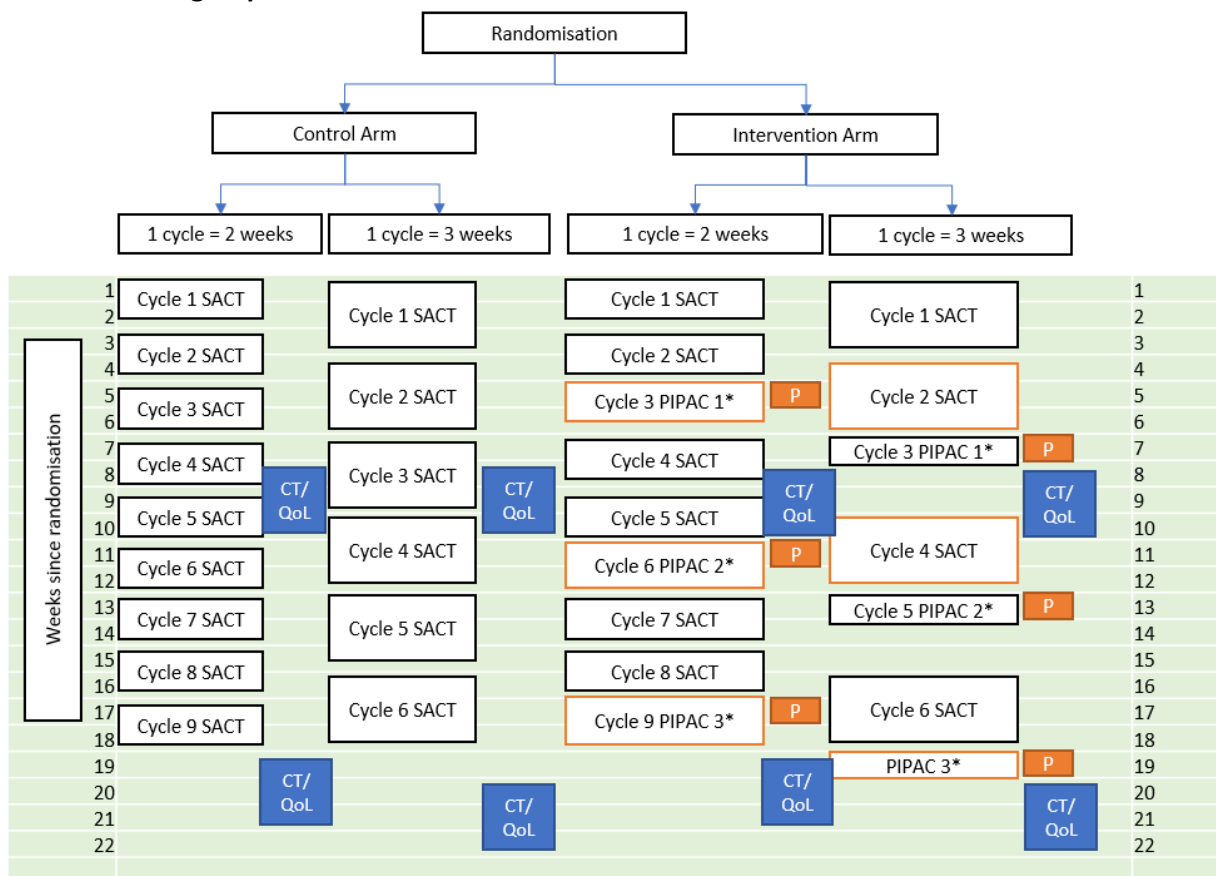
CT scans should be scheduled within the blue window shown, if chemotherapy or PIPAC is delayed, the CT scans should go ahead within the original window, but scans should be avoided within 7 days following a PIPAC procedure.

Figure 7: Ovarian group



CT scans should be scheduled within the blue window shown, if chemotherapy or PIPAC is delayed, the CT scans should go ahead within the original window, but scans should be avoided within 7 days following a PIPAC procedure.

Figure 8: Stomach group



CT scans should be scheduled within the blue window shown, if chemotherapy or PIPAC is delayed, the CT scans should go ahead within the original window, but scans should be avoided within 7 days following a PIPAC procedure.

29.6 Clavien Dindo classification of surgical complications

Table 28: Clavien Dindo classification of surgical complications (79)

Full Scale		Contracted Form	
Grades	Definition	Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	Grade I:	Same as for Full Scale
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Grade II:	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention	Grade III:	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia		
Grade III-b:	intervention under general anesthesia		
Grade IV:	Life-threatening complication (including CNS complications) ‡ requiring IC/ICU-management	Grade IV:	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)		
Grade IV-b:	multi organ dysfunction		
Grade V:	Death of a patient	Grade V:	Same as for Full Scale
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This		

	label indicates the need for a follow-up to fully evaluate the complication.			
--	---	--	--	--

‡ brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.