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Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study)

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ABSTRACT

Introduction

Gastric cancer with peritoneal metastasis has a poor outcome. Only a few studies have specifically investigated this group of patients. Japanese researchers have shown that chemotherapy with intraperitoneal paclitaxel (IPP) and Oral S-1 (tegafur/gimeracil/oteracil) is active and well tolerated. These results have been achieved in a specific genetic pool (Japanese population), using regimens that may not be available in other parts of the world. We have designed this phase I trial to investigate IPP in combination with a standard chemotherapy combination in these patients.

Methods

We use a 3 + 3 expanded cohort dose escalation until a predefined number of dose limiting toxicities are reached. Patients will have an IP catheter placed surgically after trial enrolment. Chemotherapy includes a maximum of six cycles (21 days) of Capecitabine (X) [1000mg/m2 BD days 1-14] + Cisplatin (C) [IV 80mg/m2 day 1] and Intraperitoneal Paclitaxel (IPP) [day 1 and 8] with the following doses; Cohort-1: 10mg/m2, Cohort-2: 20mg/m2, Cohort-3: 30mg/m2. Primary endpoint is to determine the MTD of IPP. Secondary endpoints include determining the safety and tolerability of IPP in combination with C and X, overall response rates, ascites response rate, progression free survival, overall survival and effects on quality of life.

Important inclusion criteria include age ≥ 18 years, HER-2 non-amplified gastric adenocarcinoma with histologic or cytology proven peritoneal involvement and adequate organ function. Exclusion criteria include previous malignancy within 5 years, recent abdominal or pelvic radiation treatment, significant abdominal adhesions or sepsis.

Ethics and dissemination: The study is approved by Southern Adelaide Clinical Human Research Ethics Committee. A manuscript will be prepared for publication on completion of the trial.

Registration: Australia and New Zealand Clinical Trials Registry (ANZCTR) ACTRN12614001063606

Strengths and limitations of the study

Strengths

- Currently, there is limited data to guide treatment in patients with gastric cancer and peritoneal metastases.

- This study investigates a novel treatment: intraperitoneal paclitaxel in combination with standard chemotherapy (capecitabine and cisplatin).
- Based on the results of this study, future studies will be designed to investigate the efficacy of this approach and to improve the outcomes in this population

Limitations

- This is a phase I study and due to small sample size has limitations on providing information on treatment efficacy and clinical outcomes such as survival.
- Not investigating the pharmacokinetics of intraperitoneal paclitaxel is a potential limitation of our study.

Protocol number 007 Protocol version 4.0 21/11/2014

Trial Registration:

a. Trial Identifier (Trial ID) ACTRN12614001063606
Registry Name: Australia and New Zealand Clinical Trials Registry (ANZCTR)
b. Date registered 3/10/2014
Universal Trial Number (UTN) U1111-1159-3914

Ethics Approval: This study is approved by: Southern Adelaide Clinical Human Research Ethics Committee

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Patients and public were not involved in the design of the study.

Competing interest statement: None of the authors declare any competing interests.

Ethics and dissemination: Ethics and dissemination: Study is approved by Southern Adelaide Clinical Human Research Ethics Committee. A manuscript will be prepared for publication on completion of the trial.

Roles and responsibilities:

Contributors:

Names, affiliations, and roles of protocol contributors

Protocol Contributors: All Protocol Contributors were involved in writing the protocol and in Study concept, design and conduct:

Name	Contribution:
1.Sina Vatandoust (1, 2) Corresponding author sina.vatandoust@sa.gov.au	Conception, design, planning, conduct of the study. Writing the manuscript. Final approval of the manuscript. Agreement to be accountable for all aspects of the work
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1 INTRODUCTION

1.1 Gastric Cancer

Gastric cancer is amongst the most common cancers and the second most frequent cause of cancer death worldwide [1]. Whilst responses can be achieved with chemotherapy, the cancer often develops resistance within 6 months. The median survival for the combination chemotherapy regimens including cisplatin and the fluoropyrimidine, capecitabine – which is considered one of the standard systemic chemotherapy regimens for advanced gastric cancer in is 10.5 months [2].

1.2 Peritoneal involvement in Gastric Cancer

Advanced gastric cancer can spread via the trans-coelomic route to involve the peritoneum and ascites often develops as a consequence. There have been few studies looking specifically at this group of patients with malignant ascites or peritoneal disease. Due to lack of measurable disease some of these patients are ineligible for clinical trials. The few studies that have looked at this subgroup of patients have shown poor survival. Some of the regimens studied in this group of patients include modified FOLFOX (fluorouracil, leucovorin and oxaliplatin) leading to 1-year survival of 27.2% [3], and sequential MTX/5FU (methotrexate and fluorouracil) leading to 1-year survival of 16% [4].

1.3 Paclitaxel in Advance Gastric Cancer

In advanced gastric cancer, including cases with malignant ascites, paclitaxel has shown good response rates [5]. The response rate to paclitaxel monotherapy has been reported to be 17% to 28% [6-9]. Combination chemotherapy regimens using paclitaxel have also been studied in a number of phase II studies [Table – 1].

Regimen [reference]	**RR**	**PFS (months)**	**OS (months)**
Paclitaxel + Platinum [10-16]	22 - 46%	2.9 – 6	7.5-13.8
Paclitaxel + Fluoropyrimidine [17-21]	32 - 66%	3 – 9	9.9-14
Paclitaxel + Fluoropyrimidine + Platinum [22-25]	51 - 66%	4 - 9	6 -14
RR: Response rate, PFS: Progression free survival, Median Overall Survival: OS			
Table-1: Combination chemotherapy regimens using paclitaxel in the management of advanced gastric cancer			

1.4 Intraperitoneal Paclitaxel

In ovarian cancer, a phase III randomized trial showed survival advantage for IV paclitaxel plus IP cisplatin and paclitaxel over IV paclitaxel plus cisplatin [26]. Paclitaxel has been shown to have distinct pharmacokinetic advantages when given via an IP route. These include high IP concentration of the drug, as well as a longer half–life in the peritoneal cavity, compared to that observed with IV administration [27]. This makes IP paclitaxel a compelling option for use in patients with peritoneal involvement from advanced gastric cancer.

Recent studies Japan have reported that intraperitoneal (IP) paclitaxel is well tolerated and active in patients with gastric cancer and peritoneal involvement [28]. In a series of 100 patients, the median survival was 23 months, and the 12-month survival was 80% [29]. The chemotherapy regimen used consisted of weekly intravenous (IV) paclitaxel at 50mg/m2 , IP paclitaxel at 20 mg/m2 and oral S1 (tegafur/gimeracil/oteracil) given on a 14 day regimen of 80 mg/m2 per day repeated every 3 weeks. It is of note that S1 may not be available for this indication in other parts of the world.

1.5 Rational for phase I study

The mentioned results have been achieved in a different genetic pool (Japanese population) using regimens that are not available in other parts of the world. We have designed this phase I trial to investigate the Maximum Tolerated Dose of intraperitoneal paclitaxel in combination with one of the standard chemotherapy combinations (cisplatin and capecitabine) in this patient population.

1.6 Justification of IP paclitaxel Dose and Escalation Schedule

The maximum tolerable dose and recommended dose available from previous phase I study by Ishigami et al [28], is certainly informative but because we are suggesting the use of IP paclitaxel in a new combination and in a different genetic pool, these doses may not be accurate. Therefore, we have elected to start the IP paclitaxel from 10 mg/m^2 which is one dose level lower than recommended dose by Ishigami et al. In our study, regardless of the IP paclitaxel, patients receive a standard regimen for their disease, therefore despite the low starting dose of IP paclitaxel, under-treatment is not a concern. The next dose levels are to be increased in 10 mg/m^2 increments to 30 mg/m^2, unless the MTD is achieved.

METHODS

2 AIM AND OBJECTIVES

Primary objective

1) To determine the Maximum Tolerated Dose (MTD) of IP paclitaxel in patients with advanced gastric cancer and peritoneal involvement

Secondary objectives

To determine:
2) Rates of toxicities [based on Common Terminology Criteria for Adverse Events (CTCAE version 4.0)][30]
3) Rates of intraperitoneal catheter complications
4) 12-month survival
5) Median survival
6) Progression free survival (based on RECIST 1.1 criteria)[31]
7) Objective Response Rate [Complete Response Rate + Partial Response Rate (based on RECIST 1.1 criteria)]
8) Ascites response (based on imaging)
9) Effects of treatment on quality of life. (based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4))[32]
10) Quality of life. (based on average scores as assessed by the EORTC STO22)[33]
11) Tissue banking for biomarker analysis

3 DESIGN

Open-label, single centre, phase I trial with standard 3 + 3 dose escalation design

4 SUBJECT POPULATION

4.1 Target Population

Subjects with Stage IV gastric cancer with biopsy or cytology proven peritoneal involvement

4.2 Inclusion criteria

1. Age ≥ 18 years
2. A diagnosis of Gastric cancer proven by histopathology and either:
    - Biopsy proven peritoneal metastases OR
    - Cytology consistent with malignant ascites: in which case patient must have ≥ 1 area of metastasis apart from the ascites.
3. Subject must not have received previous chemotherapy for metastatic gastric cancer
    - Previous adjuvant chemotherapy for gastric cancer is allowed
4. Adequate bone marrow function (platelets > 100 x 10^9/L, Absolute Neutrophil Count > 1.5 x 10^9/L)
5. Adequate liver function (Serum bilirubin ≤ 1.5 Upper Limit Normal (ULM) and transaminases ≤ 3 ULN,)
6. Adequate renal function (Serum creatinine ≤ 1.5 UNL or creatinine clearance (CRCL) ≥ 50ml/min (using Cockcroft-Gault Equation)
7. negative pregnancy test for female patients if of potential child bearing age
8. Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0, 1 or 2
9. Staging CT scan of chest/abdomen/pelvis within 30 days of registration
10. Study treatment both planned and able to start within 30 days of registration
11. Willing and able to comply with all study requirements, including treatment (able to swallow tablets), and required assessments
12. Signed, written informed consent

4.3 Exclusion criteria

1. Contraindications to investigational chemotherapy regimen including allergies to any of the chemotherapy medications
2. Any comorbidities or conditions that the investigator considers the patient should not participate in the study
3. Life expectancy of less than 3 months.
4. History of another malignancy within 5 years prior to registration. Patients with a past history of adequately treated cervical carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or superficial transitional cell carcinoma of the

bladder are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment.

5. Significant intercurrent illness that will interfere with the chemotherapy during the trial such as:
    a. Known Human Immunodeficiency Virus (HIV) infection
    b. Active infection
    c. Myocardial infarction within the previous 6 months or significant cardiac disease resulting in an inability to tolerate the intravenous fluid load as required for administration of cisplatin
    d. Severe lung disease which in the investigator's opinion would limit the patient's ability to tolerate large volumes of intra-abdominal fluids.
6. Peripheral neuropathy of any grade (based on CTCAE version 4.0)
7. Clinically significant sensori-neural hearing impairment or tinnitus which may be exacerbated by cisplatin (Audiometric abnormalities without corresponding clinical deafness will not be grounds for exclusion).
8. Previous abdominal or pelvic radiation treatment.
    a. Recent (<4 weeks) abdominal or pelvic radiation treatment; Patients who have received palliative radiation to gastric/oesophageal area are not excluded if total radiation received is less than 30 Gy and radiation is completed more than 4 weeks prior to commencing study treatments.
9. Significant intra-abdominal adhesions as determined by the surgeon at time of staging laparoscopy.
10. Active intra-abdominal sepsis
11. Medical or psychiatric condition that compromises the ability of patients to give informed consent.
12. Pregnancy, lactation, or inadequate contraception. Women must be postmenopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a barrier method of contraception during treatment and for the subsequent three months after treatment.

4.4 Screening

Written informed consent (supplementary file 1) must be signed and dated by the subject, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

Entry to this study is conditional on confirmation of tumour peritoneal involvement through either biopsy or cytology. Patients must have a staging CT scan of chest/abdomen/pelvis within 30 days of registration.

4.5 Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. Subjects must be registered before starting study treatment. Treatment should be planned to start within 28 days after registration. Registration should be done after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility, and signed the completed registration form. Once the registration process has been completed, the subject will be assigned a subject study number.

5 TREATMENT PLAN

IP paclitaxel is the study intervention in this trial; IV cisplatin and oral capecitabine are required standard concomitant interventions.

5.1 Administration of study treatments

5.1.1 IP CATHETER

IP catheter insertion:
Patients will have an IP catheter placed surgically after trial enrolment. The Intra-Peritoneal Catheter is placed surgically; under General Anaesthesia. The port should be secured to the anterior abdominal wall or the costal margin to enable easy access. The catheter should be tunnelled through the rectus sheath and muscle and secured to minimise the risk of an ascitic leak.

Possible Adverse Effects of IP catheter:

- Infection
- Abdominal pain,
- Development of intra-abdominal adhesions,
- Risk of organ perforation
- IP Catheter Blockage: In the event that the catheter is blocked and is not opened with conservative management including flushing with normal saline or simple manoeuvring, then this will be considered a rate limiting toxicity and the catheter will be removed

5.1.2 Endoscopic Biopsy

At the time of the surgery for IP catheter insertion, 4 endoscopic biopsies of the primary gastric tumour should be taken as well as biopsies of the peritoneal disease. These biopsy specimens are to be stored as fresh tissue in RNAlater® in separate containers for any and all later molecular analyses.

5.1.3 CHEMOTHERAPY

5.1.3.1 **Paclitaxel:**

Preparation for intraperitoneal administration: Paclitaxel, at the appropriate dose will be diluted in 250 - 500ml of 0.9% sodium chloride injection or 5% dextrose injection.
Stability: The infusion should be completed within 24 hours of preparation of the solution and any residue discarded. Diluted solutions should be refrigerated if not used immediately to decrease the likelihood of microbial contamination.

5.1.3.2 **Cisplatin:**

Preparation: The 10mg and 50mg vials should be reconstituted with 10 ml or 50ml of sterile water for injection, USP respectively. Each ml of the resulting solution will contain 1mg of cisplatin. Cisplatin should be diluted in 1L of normal saline.
Stability: Infusion should be completed within 24 hours of preparation and any residue discarded.

5.1.3.3 **Capecitabine:**

Preparation: A combination of the 500 mg and 150 mg tablets will be administered to reach the desired dose of 1000 mg/ m2

5.1.4 CHEMOTHERAPY REGIMEN AND DOSES

Each Cycle will be 21 days and includes the following combination:

- **Capecitabine** (oral) 1000 mg/m^2 twice a day, day 1 to 14 every 21 days
- **Cisplatin** at 80 mg/m^2 day (IV), day 2 every 21 days
- **Paclitaxel** will be given on day 1 and day 8 of a 21 day cycle. The dose of paclitaxel will vary depending on the cohort as follows (Table-2)

Cohort	Number of Patients	Paclitaxel dose given on day 1 and day 8 of a 21 day cycle
1	3	10 mg/m^2
2	3	20 mg/m^2
3	6	30 mg/m^2

Table-2: dosing of intraperitoneal paclitaxel based on 3+3 design

- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 1, patients will commence enrolment into Cohort 2.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 2, patients will commence enrolment into Cohort 3.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 3, this cohort will be expanded to 6 patients if maximum tolerated does (MTD) has not been reached. There will be no further dose escalation after Cohort 3.

5.2 Dose modifications

Dose modifications for cisplatin and capecitabine will be based on Eviq guidelines (https://www.eviq.org.au) (supplementary file 2). Adverse events are graded according to CTCAE version 4.0. In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until the adverse event has resolved to G0-1, at the investigator's discretion. Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events with differing recommendations, then the modification that results in the longest delay and lowest dose should be used.

Dose escalations or dose re-escalations after reductions for adverse events are prohibited.

5.2.1 Rechallenge

If patients experience a suspected drug related adverse event, they can interrupt the study medication until the symptoms resolve and then can reintroduce the study medication at same dose. If the reaction reappears then the study medication is to be discontinued permanently.

5.3 Concomitant Medications/Treatments

Include medications and treatments recommended, permitted (including rescue medication) and prohibited before and/or during the trial.

5.3.1 Recommended

The following medications and treatments are recommended in this study:

Each cycle:		
Day 1		
Aprepitant	165 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	The night before and the morning of chemotherapy
Dexamethasone	12 mg (PO)	ONCE a day with or after food
Day 2, 3		
Dexamethasone	8 mg (PO)	ONCE a day with or after food
Day 8		
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	the night before and the morning of chemotherapy
Dexamethasone	20 mg (PO)	the night before and the morning of chemotherapy

5.3.2 Permitted

Anti diarrheal and analgesics are permitted in this study:

5.3.3 Prohibited

The following medications should not be used during this study. Subjects who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair:

- Radiation to Abdomen/Pelvis
- Operations/Procedures involving Abdomen/Pelvis
- Other investigational treatments

5.3.4 Concomitant medication reporting

Concomitant medications will not be recorded during the study.

5.4 Treatment discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease (PD) is documented by a site investigator.
- Unacceptable toxicity as determined by the patient or site investigator
- Delay of day 1 treatment for >21 days due to treatment-related adverse events. For delays >21 days due to reasons other than treatment-related adverse events, please contact the CTC to discuss treatment continuation.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety, e.g. pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in section 5.3.
- Failure to comply with the protocol.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject's medical record.

Follow up of subjects who stop study treatment should continue. All end-of-treatment assessments must be performed within 30 days after the end of study treatment. A safety assessment should be performed to include any adverse events occurring within 30 days after the last dose of study treatment.

5.5 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

6 ASSESSMENT PLAN

6.1 Schedule of assessments

	Screening	**Run-in**	**Baseline**	**On treatment**	**After 3rd cycle**	**End-of-Treatment and 30-day safety assessment**	**Follow-up after treatment**	**End of Study**
	14-28 days prior to registration	Within 14 days prior to registration	Within 7 days prior to registration	Within 3 days prior to: day 1 and day 8 of every cycle	Within 7 days after end of day 8 of 3rd cycle	Within 30 days after end of treatment	Every 12 weeks after end of treatment	2 years after registration
Informed consent	X							
Clinic assessment,	X		X	X		X	X	X
Haematology	X		X	X				
Biochemistry	X		X	X				
Imaging CT	X				X	X	X	
Adverse Events				X				
Endoscopy and Biopsy		X						
IP Catheter insertion		X						
Patient status			X	X		X	X	X
Quality of life assessments			X		X	X	X	X

7 OUTCOMES, ENDPOINTS AND OTHER MEASURES

7.1 Maximum Tolerated Dose (MTD):

7.1.1 **MTD** is defined as the highest dose level at which ≤ 33% of patients experience DLT [34]

7.1.2 **Dose Limiting Toxicities (DLTs)** are defined as:

7.1.2.1 Grade 3 or higher febrile neutropenia,

7.1.2.2 Grade 3 or higher thrombocytopenia with bleeding,

7.1.2.3 Grade 3 or higher neurologic toxicity, (excluding ototoxicity (hearing deficit and tinnitus))

7.1.2.4 Grade 3 or higher non-hematologic toxicities not including fatigue, alopecia, nausea, vomiting, elevated liver transaminases, Palmar Plantar Erythrodysesthesia and other capecitabine related skin toxicity, hearing deficit and tinnitus)

7.1.2.5 Grade 4 neutropenia lasting >7 days,

7.1.2.6 Grade 4 thrombocytopenia,

7.1.2.7 Grade 4 increased liver transaminases.

7.1.3 **Recommended phase 2 dose (RP2D) defined as:** dose equal to the MTD (as defined above), or cohort 3 if the MTD is not reached

7.2 Adverse Events (worst grade according to NCI CTCAE v4.0)

- Rate of toxicities based on CTCAE version 4.0 and the rate of catheter complications. See section 8.1 for the definition of an adverse event (AE), and reporting of Serious Adverse Events (SAEs).
- The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0) will be used to classify and grade the intensity of adverse events after each treatment cycle.
- The investigator's assessment of attribution to the study drug: IP Paclitaxel

7.3 Overall response rate:

Defined as complete response rate plus partial response rate (both defined according to RECIST 1.1

7.4 Progression free survival (disease progression or death)

Progression free survival (PFS) is defined as the interval from date of registration to the date of first evidence of disease progression or death, whichever occurs first. Disease progression is defined according to RECIST 1.1

7.5 Overall survival (death from any cause)

Overall survival is defined as the interval from the date of registration to date of death from any cause, or the date of last known follow-up alive.

7.6 Effects of treatment on quality of life

Based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4) and EORTC STO22

8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device. AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol
-

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not

consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol.

8.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the principal investigators (through FMC Medical Oncology Clinical Trials Unit) within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

The principal investigators must notify the local Human Research Ethics Committees as required.

8.3 Pregnancy

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the principal investigators. The partner should be counselled and followed as described above.

9 STATISTICAL CONSIDERATIONS

This is an open label phase 1 study with a standard 3 + 3 dose escalation design, therefore does not require sample size justification. The dose escalation is continued until the predefined number of DLT is reached.

10 ADMINISTRATIVE ASPECTS

10.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

10.2 Recruitment of participants

Patients attending oncology clinics within the Southern Adelaide Health Services that are potential candidates for the study will be given a patient information sheet by a member of the research team inviting them to participate in the study. Subjects willing to participate will meet with a study investigator to sign a consent form.

10.3 Consent

Involved clinicians will initially approach eligible patients to determine their interest in the study. Potential study subjects will be given a study patient information sheet. The purpose, requirements and risks of the study will be explained in a clear manner. Before witnessing the consent form, the investigator will discuss the study with the potential study subject to ensure that they fully understand the study risks, procedures and requirements.

10.4 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Clinical Trials Unit and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

10.5 Protocol amendments

Changes and amendments to the protocol can only be made by the Principal Investigators. Approval of amendments by the Institutional HREC is required prior to their implementation.

10.6 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the Case Report Forms (CRF). All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated. All study-related documentation will be maintained for 15 years following completion of the study).

10.7 Study Monitoring

Data from this study will be monitored by FMC Medical Oncology Clinical Trials Unit. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness.

10.8 Audit and Inspection

This study may be subject to audit or inspection by representatives of regulatory bodies.

10.9 Publication Policy

The Principal Investigators will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). All publications must receive prior written approval from the Principal Investigators prior to submission.

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12 Appendices:

12.1 Appendix-1: Participant information sheet and Consent form (Supplementary document 1)

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Flinders Medical Centre

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Location	Flinders Medical Centre

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have *Stomach Cancer*. The research project is testing a new treatment for *Stomach Cancer*. The new treatment is called *intraperitoneal paclitaxel*.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of the study is to determine the safe dose of chemotherapy to treat patients with stomach cancer with chemotherapy, some of which is given directly into the abdomen as well as into the vein. This study will also determine how safe this chemotherapy approach is, what side-effects it causes and how it affects quality of life.

There is a gap in our knowledge as to how to best treat patients with stomach cancer who have extension of the disease in the peritoneum (peritoneum is the membrane that forms the lining of the abdominal cavity). Researchers in Japan have used *intraperitoneal paclitaxel* treatment in patients with stomach cancer who had disease extension in the peritoneum and have reported promising results. Nevertheless, the other drugs used by those researchers are different from the standard of care in Australia and also there might be differences in the way stomach cancer behaves in different populations from different backgrounds.
Intraperitoneal paclitaxel has been given safely to people with other types of cancer and is part of a standard treatment for patients with cancer of the ovary or peritoneum.
With the results of this study we will be able to design a larger study to define the effectiveness of this treatment option.
The drugs used in this study consist of two drugs (*capecitabine* and *cisplatin*) that are part of the standard treatment for patients with advanced stomach cancer, and a the third drug called *paclitaxel which* is registered in Australia to be used in other cancers (both through intravenous catheter or directly into abdomen)

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Paclitaxel is approved in Australia to treat cancer of ovary and peritoneum, breast cancer and cancer of the lung. *However it is not approved to treat Stomach cancer. Therefore, it is an experimental treatment for Stomach Cancer. This means that it must be tested to see if it is an effective treatment for Stomach Cancer.*

This research has been initiated by the study doctor, Associate Professor Chris Karapetis and Dr Tim Bright

This research has been funded by the Medical Oncology Clinical Research Unit of the Flinders Medical Centre.

3 What does participation in this research involve?

The consent form will be signed prior to any study assessments being performed.

First we need to make sure about the diagnosis and the extent of the disease: this will include: physical examination, some routine blood tests to check your blood count and your kidney and liver function, a CT scan (of chest abdomen and pelvis) and an endoscopy. (all of these tests are usually done as part of standard work up prior to starting treatment for stomach cancer.)

This study does not involve the use of placebo

Before you participate in this study, you will need to have a catheter placed in your abdomen. This small tube – called intraperitoneal port - will allow the doctors to give you the chemotherapy directly into the abdomen. This tube can be put in when you are having your endoscopy. However, your doctor may decide to put it in at a later date. The port is inserted in the operating theatre. You will be given a general anaesthetic. Your doctor or nurse will give you more

information on what you need to do to prepare for the procedure. You may be allowed to go home on the same day of the procedure if there are no complications.

You will need to see your treating doctor before each cycle of chemotherapy. At this visit, a physical examination will be performed. Before each visit with the treating doctor you will have a blood test.

A cycle of treatment is given every 21 days (3 weeks). You will get a maximum of 6 cycles of treatment.

During your chemotherapy you will be treated with 3 different drugs, they are *capecitabine* tablets (The tablets are taken TWICE a day with a glass of water within 30 minutes after the end of a meal), these tablets are taken for the first two weeks (day 1 to 14) of each chemotherapy cycle.

The second drug is *cisplatin* (given by a drip into a vein, this takes around 4 hours) and is given once every 21 days on day 2. You will need to have fluids given into the vein for several hours, before and after cisplatin and this will mean you may have to stay in hospital for one night. You will also be given medication to prevent nausea and vomiting.

The third drug is *paclitaxel*, this drug will be given into your abdomen through an intraperitoneal port on days 1 and 8 of each cycle, this will take 4 hours. Intraperitoneal chemotherapy will be given to you by a nurse who has been trained to give this treatment. Before this treatment begins you will have fluids and anti-sickness medication by a drip. You will also get medications into the vein beforehand to prevent any allergic reactions. You will also need to empty your bladder. Once the treatment begins you will be on bed rest and you will need to ask for a bedpan if required. The skin over the port site is cleaned with an antiseptic lotion. A needle is inserted through the skin into the port and fluids and chemotherapy will be given. The amount of time required for this treatment will vary depending on the volume of fluids and the chemotherapy that is being given. When the chemotherapy is finished, the needle will be removed. You will then be required to change your position in bed every 15 minutes for 1 hour. When the hour has passed it is important that you get up out of bed and move around. The intraperitoneal port will be removed by your doctor after completing the study.

You will have repeat CT scans of chest abdomen and pelvis after 9 weeks into the treatment and after completing the treatment course. The frequency of the scans is not different than what is routinely used in patients receiving standard chemotherapy treatment for stomach cancer.

During the follow-up period, you will be required to see your treating doctor for a check-up every 3 months up to a maximum of two years. During each visit you will be asked questions about your symptoms and will be examined by your doctor. A routine blood test and repeat CT scan will be done prior to the visit. After the mentioned follow-up period, further follow up plan will be decided by your doctor. .

You will be asked to complete a questionnaire on your quality of life at certain time points during the study; at the start of treatment, after the 3rd cycle and at the end of treatment at the end of the treatment (after 6 cycles) and then every 3 months during your follow up visits. These questionnaires will take about 15 - 20 minutes to complete.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visit.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

- No specific Lifestyle restrictions are required e.g. physical restrictions, participation in sport
- No specific Dietary restrictions are required
- Some of your regular medication may interact with chemotherapy drugs; your doctor will ask you about your regular medications and will advise you accordingly
- You cannot donate blood

5 Other relevant information about the research project

This study will be running in Flinders Medical Centre. Patients will be joining the study in groups of 3, and given a specific dose of intraperitoneal paclitaxel; depending on the side effects and how well they tolerate the dose, the next group of patients will receive a similar or different dose. The study has been designed this way to define the appropriate dose of this drug for patients with stomach cancer.

- Depending on the results a further study based on the doses suggested by this study will be designed to investigate the effectiveness of this treatment approach in similar patients.

Researchers from different departments (surgical department and medical oncology department)w ill be working together in this project

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Flinders Medical Centre

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include using the combination of *capecitabine* and *cisplatin* (same as this study without the intraperitoneal paclitaxel) or palliative and supportive care. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible additional benefits include potential improvement control of the disease especially in the peritoneum, potential improvement in ascites symptoms, potential improvement in delaying disease recurrence, potential improvement in survival or possible development of a more effective treatment approach for future patients.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Intraperitoneal catheter: Most ports are inserted and used throughout treatment without any complications. Complications may include:

- Infection, including infection of the abdominal wall or infection inside the abdominal cavity (this is called 'peritonitis'). Such infections may require hospital admission for antibiotic therapy,
- Abdominal pain,
- Development of intra-abdominal adhesions: Abdominal Adhesions are fibrous bands that form between tissues and organs, often as a result of injury during surgery. The most important implication of abdominal adhesions is Adhesion-related twisting and pulling of internal organs which can result in complications such as abdominal pain or intestinal obstruction. Intestinal obstruction can is a medical emergency and can be potentially life threatening.
- Risk of organ perforation

Possible Adverse Effects of Chemotherapy:

- **Nausea and Vomiting**
- **Changes in Sense of Smell and Taste**
- **Chest Pain:** Chest pain is uncommon, but may occur at any time during treatment. If you feel short of breath or develop chest pain call an ambulance, do not delay.
- **Increased Risk of Infection :** If you develop a fever 38oC or higher, have shivers, shakes or feel unwell call an ambulance to take you to the nearest hospital emergency department. Do not delay as this is life-threatening.
- **Low Red Blood Cell Count**
- **Low platelets and Increased Risk of Bleeding**
- **Sore Mouth**
- **Diarrhoea**
- **Stomach Pain**
- **Heartburn, difficult and painful swallowing**
- **Feeling Tired**
- **Numbness and Tingling in Fingers and Toes**

- **Ringing in the ears and loss of hearing:** Changes in hearing, such as ringing in the ears and hearing loss, may happen. If you develop hearing changes, tell your doctor.
- **Impaired Kidney Function**
- **Hand Foot Syndrome :** Your skin may become red, hot and tender. Small blisters can form and your skin may peel.
- **Hair Loss:** Hair loss may start within a few weeks of beginning treatment.
- **Nail Damage**
- **Poor concentration :** Memory changes and being unable to concentrate are common but generally improve once treatment is completed.
- **Yellowing of the skin and eyes:** Yellowing of your skin and eyes are uncommon. It is caused by the drugs affecting your liver. You will have regular blood tests to check your liver function. If you notice your urine is a dark colour or the whites of your eyes look yellow tell your doctor or nurse.

Possible Adverse Effects of intraperitoneal Chemotherapy:

- **Risks:**

During treatment with chemotherapy directly into the abdomen the following concerning side effects may occur,

  - Increased abdominal pressure,
  - Increased abdominal pain
  - Increased abdominal bloating

- **You may also experience the following side effects**
  - Diarrhoea
  - Nausea
  - Vomiting

With medication and appropriate counselling, most side effects can be prevented or reduced.

The effects of *intraperitoneal paclitaxel* on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 3 months after the last dose of study medication.
Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 3 months after completion of the research project. You should discuss methods of effective contraception with your study doctor.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

Chemotherapy may cause temporary or permanent sterility. Please discuss this with your study doctor if you have any concerns about future fertility.

Having a drug injected or blood (or tissue sample) taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

These days, whilst anaesthesia is generally very safe there are some risks associated with anaesthesia. The most common problems associated with anaesthesia are feeling unwell or vomiting, bruising at the site of injections, sore throat or hoarse voice. Most patients do not have these problems. If these problems do happen, they usually get better very quickly. Damage to teeth may occur, but this is rare. The risk of brain damage or death due to anaesthesia is very rare.

The risk of problems from anaesthesia increases for patients who are having more major surgery, those with medical problems and those that require difficult anaesthetic procedures. If you have any concerns about these issues, you should discuss them with the study team.

10 What will happen to my test samples?

During the assessment procedures before enrolling into the study and after you have signed the consent form; an endoscopy will be performed by your doctor. During the endoscopy 4 small tissue samples will be taken from the cancer in the stomach and also small tissue samples will be taken from the cancer in the peritoneum. These samples will be stored for future analyses to see if there are any markers that can predict different response to treatment. All the tissue samples will be held in Flinders Medical Centre

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing

15 What happens when the research project ends?

You will be followed up for a maximum of 2 years after completing the study, after that your doctor will discuss further follow up plans with you.

After completing this study, treatment with intraperitoneal paclitaxel will not be available. When further treatment is indicated your medical oncologist will advise you on the treatment options.

It is usual for a number of years to elapse before definitive results of this type of study are available. These are published in medical journals that are available to the public. You should feel free to ask your doctor about this.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All the information will be kept in medical oncology clinical trials unit in flinders medical centre Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by *A/Prof Chris Karapetis and Dr Tim Bright*

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to *Flinders Medical Centre*

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Flinders Medical Centre*

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on *08 8204 8997* or any of the following people:

Clinical contact person

Name	
Position	
Telephone	
Email	

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	
Telephone	
Email	

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact (Single Site -Research Governance Officer)

Name	
Position	
Telephone	
Email	

Consent Form - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *Flinders Medical Centre* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of tissue samples obtained previously from my *routine biopsy or surgery* for the purposes of additional testing for *Molecular testing*

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Flinders Medical Centre*

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Supplementary File 2

Specific dose modifications for cisplatin and capecitabine

Haematological toxicity

ANC x 10^9/L (on day of chemotherapy)	
0.5 to less than 1.5	Delay treatment until recovery
less than 0.5	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Platelets x10^9/L (at any stage of the cycle)	
50 to less than 100	Delay treatment until recovery
less than 50	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles

Renal impairment

eGFR (Cockcroft Gault) (mL/min)*	
greater than or equal to 70	No dose modifications necessary
50 to less than 70	Reduce cisplatin by 25%
30 to less than 50	Reduce capecitabine by 25% and cisplatin by 50%
less than 30	Withhold treatment

Hepatic impairment

Hepatic dysfunction	
Mild	No dose modifications necessary
Moderate	Reduce capecitabine by 25%
Severe	Reduce capecitabine by 50%
Treatment related Grade 3 or 4 Hyperbilirubinaemia	Delay treatment until toxicity resolves to Grade 2 or less

Peripheral neuropathy

CTC grading	
Grade 2, Grade 3 or Grade 4	Omit cisplatin

Mucositis & stomatitis

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce cisplatin and capecitabine by 25% 3rd occurrence: Reduce cisplatin and capecitabine by 50% 4th occurrence: Omit cisplatin and capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce cisplatin and capecitabine by 50% 2nd occurrence: Omit cisplatin and capecitabine

Diarrhoea

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Hand and foot syndrome (Palmar-plantar erythrodysesthesia syndrome)

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction

	2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	3

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	N/A

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Data access	#29	Statement of who will have access to the final trial dataset,	16

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8

BMJ Open

Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study)

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	gastric cancer, intraperitoneal paclitaxel, cisplatin, capecitabine

Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study)

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AUSTRALIA

Keywords
Gastric cancer, Intraperitoneal Paclitaxel, Cisplatin, Capecitabine

Word Count
4435

ABSTRACT

Introduction

Gastric cancer with peritoneal metastasis has a poor outcome. Only a few studies have specifically investigated this group of patients. Japanese researchers have shown that chemotherapy with intraperitoneal paclitaxel (IPP) and Oral S-1 (tegafur/gimeracil/oteracil) is active and well tolerated. These results have been achieved in a specific genetic pool (Japanese population), using regimens that may not be available in other parts of the world. We have designed this phase I trial to investigate IPP in combination with a standard chemotherapy combination in these patients.

Methods

We use a 3 + 3 expanded cohort dose escalation until a predefined number of dose limiting toxicities are reached. Patients will have an IP catheter placed surgically after trial enrolment. Chemotherapy includes a maximum of six cycles (21 days) of Capecitabine (X) [1000mg/m2 BD days 1-14] + Cisplatin (C) [IV 80mg/m2 day 1] and Intraperitoneal Paclitaxel (IPP) [day 1 and 8] with the following doses; Cohort-1: 10mg/m2, Cohort-2: 20mg/m2, Cohort-3: 30mg/m2. Primary endpoint is to determine the MTD of IPP. Secondary endpoints include determining the safety and tolerability of IPP in combination with C and X, overall response rates, ascites response rate, progression free survival, overall survival and effects on quality of life.

Important inclusion criteria include age ≥ 18 years, HER-2 non-amplified gastric adenocarcinoma with histologic or cytology proven peritoneal involvement and adequate organ function. Exclusion criteria include previous malignancy within 5 years, recent abdominal or pelvic radiation treatment, significant abdominal adhesions or sepsis.

Ethics and dissemination: The study is approved by Southern Adelaide Clinical Human Research Ethics Committee. A manuscript will be prepared for publication on completion of the trial.

Registration: Australia and New Zealand Clinical Trials Registry (ANZCTR) ACTRN12614001063606

Strengths and limitations of the study

- Currently, there is limited data to guide treatment in patients with gastric cancer and peritoneal metastases.
- This study investigates a novel treatment: intraperitoneal paclitaxel in combination with standard chemotherapy (capecitabine and cisplatin).
- Based on the results of this study, future studies will be designed to investigate the efficacy of this approach and to improve the outcomes in this population
- Not investigating the pharmacokinetics of intraperitoneal paclitaxel is a potential limitation of our study.

Trial Registration:

a. Trial Identifier (Trial ID) ACTRN12614001063606
Registry Name: Australia and New Zealand Clinical Trials Registry (ANZCTR)
b. Date registered 3/10/2014
Universal Trial Number (UTN) U1111-1159-3914
Protocol number 007 Protocol version 4.0 21/11/2014

Coordinating Centre:

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Name and contact information for the trial sponsor:

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1 INTRODUCTION

1.1 Gastric Cancer

Gastric cancer is amongst the most common cancers and the second most frequent cause of cancer death worldwide [1]. Whilst responses can be achieved with chemotherapy, the cancer often develops resistance within 6 months. The median survival for the combination chemotherapy regimens including cisplatin and the fluoropyrimidine, capecitabine – which is considered one of the standard systemic chemotherapy regimens for advanced gastric cancer is 10.5 months [2].

1.2 Peritoneal involvement in Gastric Cancer

Advanced gastric cancer can spread via the trans-coelomic route to involve the peritoneum and ascites often develops as a consequence. There have been few studies looking specifically at this group of patients with malignant ascites or peritoneal disease. Due to lack of measurable disease some of these patients are ineligible for clinical trials. The few studies that have looked at this subgroup of patients have shown poor survival. Some of the regimens studied in this group of patients include modified FOLFOX (fluorouracil, leucovorin and oxaliplatin) leading to 1-year survival of 27.2% [3], and sequential MTX/5FU (methotrexate and fluorouracil) leading to 1-year survival of 16% [4].

1.3 Paclitaxel in Advance Gastric Cancer

In advanced gastric cancer, including cases with malignant ascites, paclitaxel has shown good response rates [5]. The response rate to paclitaxel monotherapy has been reported to be 17% to 28% [6-9]. Combination chemotherapy regimens using paclitaxel have also been studied in a number of phase II studies [Table – 1].

Table – 1: Combination chemotherapy regimens using paclitaxel in advanced gastric cancer

Regimen [reference]	RR	PFS (months)	OS (months)
Paclitaxel + Platinum [10-16]	22 - 46%	2.9 – 6	7.5-13.8
Paclitaxel + Fluoropyrimidine [17-21]	32 - 66%	3 – 9	9.9-14
Paclitaxel + Fluoropyrimidine + Platinum [22-25]	51 - 66%	4 - 9	6 -14
RR: Response rate, PFS: Progression free survival, Median Overall Survival: OS			

1.4 Intraperitoneal Paclitaxel

In ovarian cancer, a phase III randomized trial showed survival advantage for IV paclitaxel plus IP cisplatin and paclitaxel over IV paclitaxel plus cisplatin [26]. Paclitaxel has been shown to have distinct pharmacokinetic advantages when given via an IP route. These include high IP concentration of the drug, as well as a longer half–life in the peritoneal cavity, compared to that observed with IV administration [27]. This makes IP paclitaxel a compelling option for use in patients with peritoneal involvement from advanced gastric cancer.

Studies in Japan have reported that intraperitoneal (IP) paclitaxel is well tolerated and active in patients with gastric cancer and peritoneal involvement [28]. In a series of 100 patients, the median survival was 23 months, and the 12-month survival was 80% [29]. The chemotherapy regimen used consisted of weekly intravenous (IV) paclitaxel at 50mg/m2, IP paclitaxel at 20 mg/m2 and oral S1

(tegafur/gimeracil/oteracil) given on a 14 day regimen of 80 mg/m2 per day repeated every 3 weeks. It is of note that S1 may not be available for this indication in other parts of the world.

1.5 Rational for phase I study

The mentioned results have been achieved in a different genetic pool (Japanese population) using regimens that are not available in other parts of the world. We have designed this phase I trial to investigate the Maximum Tolerated Dose of intraperitoneal paclitaxel in combination with one of the standard chemotherapy combinations (cisplatin and capecitabine) in this patient population.

1.6 Justification of IP paclitaxel Dose and Escalation Schedule

The maximum tolerable dose and recommended dose available from previous phase I study by Ishigami et al [28], is certainly informative but because we are suggesting the use of IP paclitaxel in a new combination and in a different genetic pool, these doses may not be accurate. Therefore, we have elected to start the IP paclitaxel from 10 mg/m^2 which is one dose level lower than recommended dose by Ishigami et al. In our study, regardless of the IP paclitaxel, patients receive a standard regimen for their disease, therefore despite the low starting dose of IP paclitaxel, under-treatment is not a concern. The next dose levels are to be increased in 10 mg/m^2 increments to 30 mg/m^2, unless the MTD is achieved.

2 RECENTLY PUBLISHED STUDIES **(This section is not part of the original protocol and has been added to keep the manuscript up-to-date with the literature.)**

In a randomized phase III trial Ishigami et al [30] enrolled patients with gastric cancer with peritoneal metastasis. Patients were randomized to receive intraperitoneal and intravenous paclitaxel plus S-1or S-1 plus cisplatin. In this study, median survival was not significantly different between the two arms.

Yonemura et al [31] showed that neoadjuvant laparoscopic hyperthermic intraperitoneal chemoperfusion with docetaxel and cisplatin and Neoadjuvant Intraperitoneal/Systemic Chemotherapy with S-1, docetaxel and cisplatin can lead to reduced Peritoneal Cancer Index in patients with gastric cancer with peritoneal metastasis.

METHODS

3 AIM AND OBJECTIVES

Primary objective	1) To determine the Maximum Tolerated Dose (MTD) of IP paclitaxel in patients with advanced gastric cancer and peritoneal involvement
Secondary objectives	To determine: 2) Rates of toxicities [based on Common Terminology Criteria for Adverse Events (CTCAE version 4.0)][32] 3) Rates of intraperitoneal catheter complications 4) 12-month survival

5) Median survival
6) Progression free survival (based on RECIST 1.1 criteria)[33]
7) Objective Response Rate [Complete Response Rate + Partial Response Rate (based on RECIST 1.1 criteria)]
8) Ascites response (based on imaging)
9) Effects of treatment on quality of life. (based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4)[34]
10) Quality of life. (based on average scores as assessed by the EORTC STO22)[35]
11) Tissue banking for biomarker analysis

4 DESIGN

Open-label, single centre, phase I trial with standard 3 + 3 dose escalation design

5 SUBJECT POPULATION

5.1 Target Population

Subjects with Stage IV gastric cancer with biopsy or cytology proven peritoneal involvement

5.2 Inclusion criteria

1. Age ≥ 18 years
2. A diagnosis of Gastric cancer proven by histopathology and either:
    - Biopsy proven peritoneal metastases OR
    - Cytology consistent with malignant ascites: in which case patient must have ≥ 1 area of peritoneal metastasis apart from the ascites.
3. Subject must not have received previous chemotherapy for metastatic gastric cancer
    - Previous adjuvant chemotherapy for gastric cancer is allowed
4. Adequate bone marrow function (platelets > 100 x 10^9/L, Absolute Neutrophil Count > 1.5 x 10^9/L)
5. Adequate liver function (Serum bilirubin ≤ 1.5 Upper Limit Normal (ULM) and transaminases ≤ 3 ULN,)
6. Adequate renal function (Serum creatinine ≤ 1.5 UNL or creatinine clearance (CRCL) ≥ 50ml/min (using Cockcroft-Gault Equation)
7. negative pregnancy test for female patients if of potential child bearing age
8. Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0, 1 or 2
9. Staging CT scan of chest/abdomen/pelvis within 30 days of registration
10. Study treatment both planned and able to start within 30 days of registration
11. Willing and able to comply with all study requirements, including treatment (able to swallow tablets), and required assessments
12. Signed, written informed consent

5.3 Exclusion criteria

1. Contraindications to investigational chemotherapy regimen including allergies to any of the chemotherapy medications
2. Any comorbidities or conditions that the investigator considers the patient should not participate in the study
3. Life expectancy of less than 3 months.
4. History of another malignancy within 5 years prior to registration. Patients with a past history of adequately treated cervical carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or superficial transitional cell carcinoma of the bladder are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment.
5. Significant intercurrent illness that will interfere with the chemotherapy during the trial such as:
    a. Known Human Immunodeficiency Virus (HIV) infection
    b. Active infection
    c. Myocardial infarction within the previous 6 months or significant cardiac disease resulting in an inability to tolerate the intravenous fluid load as required for administration of cisplatin
    d. Severe lung disease which in the investigator's opinion would limit the patient's ability to tolerate large volumes of intra-abdominal fluids.
6. Peripheral neuropathy of any grade (based on CTCAE version 4.0)
7. Clinically significant sensori-neural hearing impairment or tinnitus which may be exacerbated by cisplatin (Audiometric abnormalities without corresponding clinical deafness will not be grounds for exclusion).
8. Previous abdominal or pelvic radiation treatment.
    a. Recent (<4 weeks) abdominal or pelvic radiation treatment; Patients who have received palliative radiation to gastric/oesophageal area are not excluded if total radiation received is less than 30 Gy and radiation is completed more than 4 weeks prior to commencing study treatments.
9. Significant intra-abdominal adhesions as determined by the surgeon at time of staging laparoscopy.
10. Active intra-abdominal sepsis
11. Medical or psychiatric condition that compromises the ability of patients to give informed consent.
12. Pregnancy, lactation, or inadequate contraception. Women must be postmenopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a barrier method of contraception during treatment and for the subsequent three months after treatment.

5.4 Screening

Written informed consent (supplementary file 1) must be signed and dated by the subject, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

Entry to this study is conditional on confirmation of tumour peritoneal involvement through either biopsy or cytology. Patients must have a staging CT scan of chest/abdomen/pelvis within 30 days of registration.

5.5 Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. Subjects must be registered before starting study treatment. Treatment should be planned to start within 28 days after registration. Registration should be done after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility, and signed the completed registration form. Once the registration process has been completed, the subject will be assigned a subject study number.

6 TREATMENT PLAN

IP paclitaxel is the study intervention in this trial; IV cisplatin and oral capecitabine are required standard concomitant interventions.

6.1 Administration of study treatments

6.1.1 IP CATHETER

IP catheter insertion:

Patients will have an IP catheter placed surgically after trial enrolment. The Intra-Peritoneal Catheter is placed surgically; under General Anaesthesia. The port should be secured to the anterior abdominal wall or the costal margin to enable easy access. The catheter should be tunnelled through the rectus sheath and muscle and secured to minimise the risk of an ascitic leak.

Possible Adverse Effects of IP catheter:

- Infection
- Abdominal pain,
- Development of intra-abdominal adhesions,
- Risk of organ perforation
- IP Catheter Blockage: In the event that the catheter is blocked and is not opened with conservative management including flushing with normal saline or simple manoeuvring, then this will be considered a rate limiting toxicity and the catheter will be removed

6.1.2 Endoscopic Biopsy

Before the surgery for IP catheter insertion, 4 endoscopic biopsies of the primary gastric tumour should be taken as well as biopsies of the peritoneal disease. These biopsy specimens are to be stored as fresh tissue in RNAlater® in separate containers for any and all later molecular analyses.

6.1.3 CHEMOTHERAPY

6.1.3.1 Paclitaxel:

Preparation for intraperitoneal administration: Paclitaxel, at the appropriate dose will be diluted in 250 - 500ml of 0.9% sodium chloride injection or 5% dextrose injection.
Stability: The infusion should be completed within 24 hours of preparation of the solution and any residue discarded. Diluted solutions should be refrigerated if not used immediately to decrease the likelihood of microbial contamination.

6.1.3.2 Cisplatin:

Preparation: The 10mg and 50mg vials should be reconstituted with 10 ml or 50ml of sterile water for injection, USP respectively. Each ml of the resulting solution will contain 1mg of cisplatin. Cisplatin should be diluted in 1L of normal saline.
Stability: Infusion should be completed within 24 hours of preparation and any residue discarded.

6.1.3.3 Capecitabine:

Preparation: A combination of the 500 mg and 150 mg tablets will be administered to reach the desired dose of 1000 mg/ m2

6.1.4 CHEMOTHERAPY REGIMEN AND DOSES

Each Cycle will be 21 days and includes the following combination:

- **Capecitabine** (oral) 1000 mg/m^2 twice a day, day 1 to 14 every 21 days
- **Cisplatin** at 80 mg/m^2 day (IV), day 2 every 21 days
- **Paclitaxel** will be given on day 1 and day 8 of a 21 day cycle. The dose of paclitaxel will vary depending on the cohort as follows (Table-2)

Table – 2: Dosing of intraperitoneal paclitaxel based on 3+3 design

Cohort	Number of Patients	Paclitaxel dose given on day 1 and day 8 of a 21 day cycle
1	3	10 mg/m^2
2	3	20 mg/m^2
3	6	30 mg/m^2

- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 1, patients will commence enrolment into Cohort 2.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 2, patients will commence enrolment into Cohort 3.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 3, this cohort will be expanded to 6 patients if maximum tolerated does (MTD) has not been reached. There will be no further dose escalation after Cohort 3.

6.2 Dose modifications

Dose modifications for cisplatin and capecitabine will be based on Eviq guidelines (https://www.eviq.org.au) (supplementary file 2). Adverse events are graded according to CTCAE version 4.0. In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until the adverse event has resolved to G0-1, at the investigator's discretion. Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events with differing recommendations, then the modification that results in the longest delay and lowest dose should be used.

Dose escalations or dose re-escalations after reductions for adverse events are prohibited.

6.2.1 Rechallenge

If patients experience a suspected drug related adverse event, they can interrupt the study medication until the symptoms resolve and then can reintroduce the study medication at same dose. If the reaction reappears then the study medication is to be discontinued permanently.

6.3 Concomitant Medications/Treatments

Include medications and treatments recommended, permitted (including rescue medication) and prohibited before and/or during the trial.

6.3.1 Recommended

The following medications and treatments are recommended in this study [Table – 3]:

Table – 3: Recommended medication before chemotherapy

Each cycle:		
Day 1		
Aprepitant	165 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	The night before and the morning of chemotherapy
Dexamethasone	12 mg (PO)	ONCE a day with or after food
Day 2, 3		
Dexamethasone	8 mg (PO)	ONCE a day with or after food
Day 8		
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	the night before and the morning of chemotherapy
Dexamethasone	20 mg (PO)	the night before and the morning of chemotherapy

6.3.2 Permitted

Anti diarrheal and analgesics are permitted in this study:

6.3.3 Prohibited

The following medications should not be used during this study. Subjects who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair:

- Radiation to Abdomen/Pelvis
- Operations/Procedures involving Abdomen/Pelvis
- Other investigational treatments

6.3.4 Concomitant medication reporting

Concomitant medications will not be recorded during the study.

6.4 Treatment discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease (PD) is documented by a site investigator.
- Unacceptable toxicity as determined by the patient or site investigator
- Delay of day 1 treatment for >21 days due to treatment-related adverse events. For delays >21 days due to reasons other than treatment-related adverse events, please contact the CTC to discuss treatment continuation.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety, e.g. pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in section 5.3.
- Failure to comply with the protocol.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject's medical record.

Follow up of subjects who stop study treatment should continue. All end-of-treatment assessments must be performed within 30 days after the end of study treatment. A safety assessment should be performed to include any adverse events occurring within 30 days after the last dose of study treatment.

6.5 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

7 ASSESSMENT PLAN

7.1 Schedule of assessments

Schedule of assessments is outlined in Table -4.

Table – 4: Schedule of assessments

	Screening	**Run-in**	**Baseline**	**On treatment**	**After 3rd cycle**	**End-of-Treatment and 30-day safety assessment**	**Follow-up after treatment**	**End of Study**
	14-28 days prior to registration	Within 14 days prior to registration	Within 7 days prior to registration	Within 3 days prior to: day 1 and day 8 of every cycle	Within 7 days after end of day 8 of 3rd cycle	Within 30 days after end of treatment	Every 12 weeks after end of treatment	2 years after registration
Informed consent	X							
Clinic assessment,	X		X	X		X	X	X
Haematology	X		X	X				
Biochemistry	X		X	X				
Imaging CT	X				X	X	X	
Adverse Events				X				
Endoscopy and Biopsy		X						
IP Catheter insertion		X						
Patient status			X	X		X	X	X
Quality of life assessments			X		X	X	X	X

8 OUTCOMES, ENDPOINTS AND OTHER MEASURES

8.1 Maximum Tolerated Dose (MTD):

8.1.1 **MTD** is defined as the highest dose level at which ≤ 33% of patients experience DLT [36]

8.1.2 **Dose Limiting Toxicities (DLTs)** are defined as:

8.1.2.1 Grade 3 or higher febrile neutropenia,

8.1.2.2 Grade 3 or higher thrombocytopenia with bleeding,

8.1.2.3 Grade 3 or higher neurologic toxicity, (excluding ototoxicity (hearing deficit and tinnitus))

8.1.2.4 Grade 3 or higher non-hematologic toxicities not including fatigue, alopecia, nausea, vomiting, elevated liver transaminases, Palmar Plantar Erythrodysesthesia and other capecitabine related skin toxicity, hearing deficit and tinnitus)

8.1.2.5 Grade 4 neutropenia lasting >7 days,

8.1.2.6 Grade 4 thrombocytopenia,

8.1.2.7 Grade 4 increased liver transaminases.

8.1.3 **Recommended phase 2 dose (RP2D) defined as:** dose equal to the MTD (as defined above), or cohort 3 if the MTD is not reached

8.2 Adverse Events (worst grade according to NCI CTCAE v4.0)

- Rate of toxicities based on CTCAE version 4.0 and the rate of catheter complications. See section 8.1 for the definition of an adverse event (AE), and reporting of Serious Adverse Events (SAEs).
- The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0) will be used to classify and grade the intensity of adverse events after each treatment cycle.
- The investigator's assessment of attribution to the study drug: IP Paclitaxel

8.3 Overall response rate:

Defined as complete response rate plus partial response rate (both defined according to RECIST 1.1

8.4 Progression free survival (disease progression or death)

Progression free survival (PFS) is defined as the interval from date of registration to the date of first evidence of disease progression or death, whichever occurs first. Disease progression is defined according to RECIST 1.1

8.5 Overall survival (death from any cause)

Overall survival is defined as the interval from the date of registration to date of death from any cause, or the date of last known follow-up alive.

8.6 Effects of treatment on quality of life

Based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4) and EORTC STO22

9 SAFETY REPORTING

9.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device. AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol
-

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent

with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol.

9.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the principal investigators (through FMC Medical Oncology Clinical Trials Unit) within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

The principal investigators must notify the local Human Research Ethics Committees as required.

9.3 Pregnancy

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the principal investigators. The partner should be counselled and followed as described above.

10 STATISTICAL CONSIDERATIONS

This is an open label phase 1 study with a standard 3 + 3 dose escalation design, therefore does not require sample size justification. The dose escalation is continued until the predefined number of DLT is reached.

11 ADMINISTRATIVE ASPECTS

11.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

11.2 Recruitment of participants

Patients attending oncology clinics within the Southern Adelaide Health Services that are potential candidates for the study will be given a patient information sheet by a member of the research team inviting them to participate in the study. Subjects willing to participate will meet with a study investigator to sign a consent form.

11.3 Consent

Involved clinicians will initially approach eligible patients to determine their interest in the study. Potential study subjects will be given a study patient information sheet. The purpose, requirements and risks of the study will be explained in a clear manner. Before witnessing the consent form, the investigator will discuss the study with the potential study subject to ensure that they fully understand the study risks, procedures and requirements.

11.4 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Clinical Trials Unit and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

11.5 Protocol amendments

Changes and amendments to the protocol can only be made by the Principal Investigators. Approval of amendments by the Institutional HREC is required prior to their implementation.

11.6 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the Case Report Forms (CRF). All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated. All study-related documentation will be maintained for 15 years following completion of the study).

11.7 Study Monitoring

Data from this study will be monitored by FMC Medical Oncology Clinical Trials Unit. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness.

11.8 Audit and Inspection

This study may be subject to audit or inspection by representatives of regulatory bodies.

11.9 Publication Policy

The Principal Investigators will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). All publications must receive prior written approval from the Principal Investigators prior to submission.

12 Appendices: Supplementary File 1 and Supplementary File 2

FOOTNOTES

Contributors:

SV, TFB, ACR, DIW, JAB and CSK were involved in study conception, design, planning, and conduct of the study and manuscript writing. SHSG was involved in writing the manuscript. MNA was involved in conduct of the study and writing manuscript. All authors were involved in final approval of the manuscript. All authors agreed to be accountable for all aspects of the work.

Funding: There are no funders to report for this submission

Patient and Public Involvement:

Patients and public were not involved in the design of the study.

Competing interest statement: None of the authors declare any competing interests.

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Flinders Medical Centre

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Location	Flinders Medical Centre

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have *Stomach Cancer*. The research project is testing a new treatment for *Stomach Cancer*. The new treatment is called *intraperitoneal paclitaxel*.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of the study is to determine the safe dose of chemotherapy to treat patients with stomach cancer with chemotherapy, some of which is given directly into the abdomen as well as into the vein. This study will also determine how safe this chemotherapy approach is, what side-effects it causes and how it affects quality of life.

There is a gap in our knowledge as to how to best treat patients with stomach cancer who have extension of the disease in the peritoneum (peritoneum is the membrane that forms the lining of the abdominal cavity). Researchers in Japan have used *intraperitoneal paclitaxel* treatment in patients with stomach cancer who had disease extension in the peritoneum and have reported promising results. Nevertheless, the other drugs used by those researchers are different from the standard of care in Australia and also there might be differences in the way stomach cancer behaves in different populations from different backgrounds.
Intraperitoneal paclitaxel has been given safely to people with other types of cancer and is part of a standard treatment for patients with cancer of the ovary or peritoneum.
With the results of this study we will be able to design a larger study to define the effectiveness of this treatment option.
The drugs used in this study consist of two drugs (*capecitabine* and *cisplatin*) that are part of the standard treatment for patients with advanced stomach cancer, and a the third drug called *paclitaxel which* is registered in Australia to be used in other cancers (both through intravenous catheter or directly into abdomen)

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Paclitaxel is approved in Australia to treat cancer of ovary and peritoneum, breast cancer and cancer of the lung. *However it is not approved to treat Stomach cancer. Therefore, it is an experimental treatment for Stomach Cancer. This means that it must be tested to see if it is an effective treatment for Stomach Cancer.*

This research has been initiated by the study doctor, Associate Professor Chris Karapetis and Dr Tim Bright

This research has been funded by the Medical Oncology Clinical Research Unit of the Flinders Medical Centre.

3 What does participation in this research involve?

The consent form will be signed prior to any study assessments being performed.

First we need to make sure about the diagnosis and the extent of the disease: this will include: physical examination, some routine blood tests to check your blood count and your kidney and liver function, a CT scan (of chest abdomen and pelvis) and an endoscopy. (all of these tests are usually done as part of standard work up prior to starting treatment for stomach cancer.)

This study does not involve the use of placebo

Before you participate in this study, you will need to have a catheter placed in your abdomen. This small tube – called intraperitoneal port - will allow the doctors to give you the chemotherapy directly into the abdomen. This tube can be put in when you are having your endoscopy. However, your doctor may decide to put it in at a later date. The port is inserted in the operating theatre. You will be given a general anaesthetic. Your doctor or nurse will give you more

information on what you need to do to prepare for the procedure. You may be allowed to go home on the same day of the procedure if there are no complications.

You will need to see your treating doctor before each cycle of chemotherapy. At this visit, a physical examination will be performed. Before each visit with the treating doctor you will have a blood test.

A cycle of treatment is given every 21 days (3 weeks). You will get a maximum of 6 cycles of treatment.

During your chemotherapy you will be treated with 3 different drugs, they are *capecitabine* tablets (The tablets are taken TWICE a day with a glass of water within 30 minutes after the end of a meal), these tablets are taken for the first two weeks (day 1 to 14) of each chemotherapy cycle.

The second drug is *cisplatin* (given by a drip into a vein, this takes around 4 hours) and is given once every 21 days on day 2. You will need to have fluids given into the vein for several hours, before and after cisplatin and this will mean you may have to stay in hospital for one night. You will also be given medication to prevent nausea and vomiting.

The third drug is *paclitaxel*, this drug will be given into your abdomen through an intraperitoneal port on days 1 and 8 of each cycle, this will take 4 hours. Intraperitoneal chemotherapy will be given to you by a nurse who has been trained to give this treatment. Before this treatment begins you will have fluids and anti-sickness medication by a drip. You will also get medications into the vein beforehand to prevent any allergic reactions. You will also need to empty your bladder. Once the treatment begins you will be on bed rest and you will need to ask for a bedpan if required. The skin over the port site is cleaned with an antiseptic lotion. A needle is inserted through the skin into the port and fluids and chemotherapy will be given. The amount of time required for this treatment will vary depending on the volume of fluids and the chemotherapy that is being given. When the chemotherapy is finished, the needle will be removed. You will then be required to change your position in bed every 15 minutes for 1 hour. When the hour has passed it is important that you get up out of bed and move around. The intraperitoneal port will be removed by your doctor after completing the study.

You will have repeat CT scans of chest abdomen and pelvis after 9 weeks into the treatment and after completing the treatment course. The frequency of the scans is not different than what is routinely used in patients receiving standard chemotherapy treatment for stomach cancer.

During the follow-up period, you will be required to see your treating doctor for a check-up every 3 months up to a maximum of two years. During each visit you will be asked questions about your symptoms and will be examined by your doctor. A routine blood test and repeat CT scan will be done prior to the visit. After the mentioned follow-up period, further follow up plan will be decided by your doctor. .

You will be asked to complete a questionnaire on your quality of life at certain time points during the study; at the start of treatment, after the 3rd cycle and at the end of treatment at the end of the treatment (after 6 cycles) and then every 3 months during your follow up visits. These questionnaires will take about 15 - 20 minutes to complete.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visit.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

- No specific Lifestyle restrictions are required e.g. physical restrictions, participation in sport
- No specific Dietary restrictions are required
- Some of your regular medication may interact with chemotherapy drugs; your doctor will ask you about your regular medications and will advise you accordingly
- You cannot donate blood

5 Other relevant information about the research project

This study will be running in Flinders Medical Centre. Patients will be joining the study in groups of 3, and given a specific dose of intraperitoneal paclitaxel; depending on the side effects and how well they tolerate the dose, the next group of patients will receive a similar or different dose. The study has been designed this way to define the appropriate dose of this drug for patients with stomach cancer.

Depending on the results a further study based on the doses suggested by this study will be designed to investigate the effectiveness of this treatment approach in similar patients.

Researchers from different departments (surgical department and medical oncology department)w ill be working together in this project

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Flinders Medical Centre

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include using the combination of *capecitabine* and *cisplatin* (same as this study without the intraperitoneal paclitaxel) or palliative and supportive care. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible additional benefits include potential improvement control of the disease especially in the peritoneum, potential improvement in ascites symptoms, potential improvement in delaying disease recurrence, potential improvement in survival or possible development of a more effective treatment approach for future patients.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Intraperitoneal catheter: Most ports are inserted and used throughout treatment without any complications. Complications may include:

- Infection, including infection of the abdominal wall or infection inside the abdominal cavity (this is called 'peritonitis'). Such infections may require hospital admission for antibiotic therapy,
- Abdominal pain,
- Development of intra-abdominal adhesions: Abdominal Adhesions are fibrous bands that form between tissues and organs, often as a result of injury during surgery. The most important implication of abdominal adhesions is Adhesion-related twisting and pulling of internal organs which can result in complications such as abdominal pain or intestinal obstruction. Intestinal obstruction can is a medical emergency and can be potentially life threatening.
- Risk of organ perforation

Possible Adverse Effects of Chemotherapy:

- **Nausea and Vomiting**
- **Changes in Sense of Smell and Taste**
- **Chest Pain:** Chest pain is uncommon, but may occur at any time during treatment. If you feel short of breath or develop chest pain call an ambulance, do not delay.
- **Increased Risk of Infection :** If you develop a fever 38oC or higher, have shivers, shakes or feel unwell call an ambulance to take you to the nearest hospital emergency department. Do not delay as this is life-threatening.
- **Low Red Blood Cell Count**
- **Low platelets and Increased Risk of Bleeding**
- **Sore Mouth**
- **Diarrhoea**
- **Stomach Pain**
- **Heartburn, difficult and painful swallowing**
- **Feeling Tired**
- **Numbness and Tingling in Fingers and Toes**

- **Ringing in the ears and loss of hearing:** Changes in hearing, such as ringing in the ears and hearing loss, may happen. If you develop hearing changes, tell your doctor.
- **Impaired Kidney Function**
- **Hand Foot Syndrome :** Your skin may become red, hot and tender. Small blisters can form and your skin may peel.
- **Hair Loss:** Hair loss may start within a few weeks of beginning treatment.
- **Nail Damage**
- **Poor concentration :** Memory changes and being unable to concentrate are common but generally improve once treatment is completed.
- **Yellowing of the skin and eyes:** Yellowing of your skin and eyes are uncommon. It is caused by the drugs affecting your liver. You will have regular blood tests to check your liver function. If you notice your urine is a dark colour or the whites of your eyes look yellow tell your doctor or nurse.

Possible Adverse Effects of intraperitoneal Chemotherapy:

- **Risks:**

During treatment with chemotherapy directly into the abdomen the following concerning side effects may occur,

  - Increased abdominal pressure,
  - Increased abdominal pain
  - Increased abdominal bloating

- **You may also experience the following side effects**
  - Diarrhoea
  - Nausea
  - Vomiting

With medication and appropriate counselling, most side effects can be prevented or reduced.

The effects of *intraperitoneal paclitaxel* on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 3 months after the last dose of study medication.
Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 3 months after completion of the research project. You should discuss methods of effective contraception with your study doctor.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

Chemotherapy may cause temporary or permanent sterility. Please discuss this with your study doctor if you have any concerns about future fertility.

Having a drug injected or blood (or tissue sample) taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

These days, whilst anaesthesia is generally very safe there are some risks associated with anaesthesia. The most common problems associated with anaesthesia are feeling unwell or vomiting, bruising at the site of injections, sore throat or hoarse voice. Most patients do not have these problems. If these problems do happen, they usually get better very quickly. Damage to teeth may occur, but this is rare. The risk of brain damage or death due to anaesthesia is very rare.

The risk of problems from anaesthesia increases for patients who are having more major surgery, those with medical problems and those that require difficult anaesthetic procedures. If you have any concerns about these issues, you should discuss them with the study team.

10 What will happen to my test samples?

During the assessment procedures before enrolling into the study and after you have signed the consent form; an endoscopy will be performed by your doctor. During the endoscopy 4 small tissue samples will be taken from the cancer in the stomach and also small tissue samples will be taken from the cancer in the peritoneum. These samples will be stored for future analyses to see if there are any markers that can predict different response to treatment. All the tissue samples will be held in Flinders Medical Centre

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing

15 What happens when the research project ends?

You will be followed up for a maximum of 2 years after completing the study, after that your doctor will discuss further follow up plans with you.

After completing this study, treatment with intraperitoneal paclitaxel will not be available. When further treatment is indicated your medical oncologist will advise you on the treatment options.

It is usual for a number of years to elapse before definitive results of this type of study are available. These are published in medical journals that are available to the public. You should feel free to ask your doctor about this.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All the information will be kept in medical oncology clinical trials unit in flinders medical centre Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by *A/Prof Chris Karapetis and Dr Tim Bright*

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to *Flinders Medical Centre*

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Flinders Medical Centre*

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on *08 8204 8997* or any of the following people:

Clinical contact person

Name	
Position	
Telephone	
Email	

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	
Telephone	
Email	

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact (Single Site -Research Governance Officer)

Name	
Position	
Telephone	
Email	

Consent Form - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *Flinders Medical Centre* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of tissue samples obtained previously from my *routine biopsy or surgery* for the purposes of additional testing for *Molecular testing*

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Flinders Medical Centre*

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Supplementary File 2

Specific dose modifications for cisplatin and capecitabine

Haematological toxicity

ANC x 10^9/L (on day of chemotherapy)	
0.5 to less than 1.5	Delay treatment until recovery
less than 0.5	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Platelets x10^9/L (at any stage of the cycle)	
50 to less than 100	Delay treatment until recovery
less than 50	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles

Renal impairment

eGFR (Cockcroft Gault) (mL/min)*	
greater than or equal to 70	No dose modifications necessary
50 to less than 70	Reduce cisplatin by 25%
30 to less than 50	Reduce capecitabine by 25% and cisplatin by 50%
less than 30	Withhold treatment

Hepatic impairment

Hepatic dysfunction	
Mild	No dose modifications necessary
Moderate	Reduce capecitabine by 25%
Severe	Reduce capecitabine by 50%
Treatment related Grade 3 or 4 Hyperbilirubinaemia	Delay treatment until toxicity resolves to Grade 2 or less

Peripheral neuropathy

CTC grading	
Grade 2, Grade 3 or Grade 4	Omit cisplatin

Mucositis & stomatitis

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce cisplatin and capecitabine by 25% 3rd occurrence: Reduce cisplatin and capecitabine by 50% 4th occurrence: Omit cisplatin and capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce cisplatin and capecitabine by 50% 2nd occurrence: Omit cisplatin and capecitabine

Diarrhoea

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Hand and foot syndrome (Palmar-plantar erythrodysesthesia syndrome)

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction

	2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	3

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	N/A

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Data access	#29	Statement of who will have access to the final trial dataset,	16

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8

BMJ Open

Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study):study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026732.R2
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	gastric cancer, intraperitoneal paclitaxel, cisplatin, capecitabine

Phase I open label trial of Intraperitoneal Paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and Peritoneal metastases (IPGP study): study protocol

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Keywords
Gastric cancer, Intraperitoneal Paclitaxel, Cisplatin, Capecitabine

Word Count
4440

ABSTRACT

Introduction

Gastric cancer with peritoneal metastasis has a poor outcome. Only a few studies have specifically investigated this group of patients. Japanese researchers have shown that chemotherapy with intraperitoneal paclitaxel (IPP) and Oral S-1 (tegafur/gimeracil/oteracil) is active and well tolerated. These results have been achieved in a specific genetic pool (Japanese population), using regimens that may not be available in other parts of the world. We have designed this phase I trial to investigate IPP in combination with a standard chemotherapy combination in these patients.

Methods

We use a 3 + 3 expanded cohort dose escalation until a predefined number of dose limiting toxicities are reached. Patients will have an IP catheter placed surgically after trial enrolment. Chemotherapy includes a maximum of six cycles (21 days) of Capecitabine (X) [1000mg/m2 BD days 1-14] + Cisplatin (C) [IV 80mg/m2 day 1] and Intraperitoneal Paclitaxel (IPP) [day 1 and 8] with the following doses; Cohort-1: 10mg/m2, Cohort-2: 20mg/m2, Cohort-3: 30mg/m2. Primary endpoint is to determine the MTD of IPP. Secondary endpoints include determining the safety and tolerability of IPP in combination with C and X, overall response rates, ascites response rate, progression free survival, overall survival and effects on quality of life.

Important inclusion criteria include age ≥ 18 years, HER-2 non-amplified gastric adenocarcinoma with histologic or cytology proven peritoneal involvement and adequate organ function. Exclusion criteria include previous malignancy within 5 years, recent abdominal or pelvic radiation treatment, significant abdominal adhesions or sepsis.

Ethics and dissemination: The study is approved by Southern Adelaide Clinical Human Research Ethics Committee. A manuscript will be prepared for publication on completion of the trial.

Registration: Australia and New Zealand Clinical Trials Registry (ANZCTR) ACTRN12614001063606

Strengths and limitations of the study

- Currently, there is limited data to guide treatment in patients with gastric cancer and peritoneal metastases.
- This study investigates a novel treatment: intraperitoneal paclitaxel in combination with standard chemotherapy (capecitabine and cisplatin).
- Based on the results of this study, future studies will be designed to investigate the efficacy of this approach and to improve the outcomes in this population
- Not investigating the pharmacokinetics of intraperitoneal paclitaxel is a potential limitation of our study.

Trial Registration:

a. Trial Identifier (Trial ID) ACTRN12614001063606
Registry Name: Australia and New Zealand Clinical Trials Registry (ANZCTR)
b. Date registered 3/10/2014
Universal Trial Number (UTN) U1111-1159-3914
Protocol number 007 Protocol version 4.0 21/11/2014

Coordinating Centre:

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1 INTRODUCTION

1.1 Gastric Cancer

Gastric cancer is amongst the most common cancers and the second most frequent cause of cancer death worldwide [1]. Whilst responses can be achieved with chemotherapy, the cancer often develops resistance within 6 months. The median survival for the combination chemotherapy regimens including cisplatin and the fluoropyrimidine, capecitabine – which is considered one of the standard systemic chemotherapy regimens for advanced gastric cancer is 10.5 months [2].

1.2 Peritoneal involvement in Gastric Cancer

Advanced gastric cancer can spread via the trans-coelomic route to involve the peritoneum and ascites often develops as a consequence. There have been few studies looking specifically at this group of patients with malignant ascites or peritoneal disease. Due to lack of measurable disease some of these patients are ineligible for clinical trials. The few studies that have looked at this subgroup of patients have shown poor survival. Some of the regimens studied in this group of patients include modified FOLFOX (fluorouracil, leucovorin and oxaliplatin) leading to 1-year survival of 27.2% [3], and sequential MTX/5FU (methotrexate and fluorouracil) leading to 1-year survival of 16% [4].

1.3 Paclitaxel in Advance Gastric Cancer

In advanced gastric cancer, including cases with malignant ascites, paclitaxel has shown good response rates [5]. The response rate to paclitaxel monotherapy has been reported to be 17% to 28% [6-9]. Combination chemotherapy regimens using paclitaxel have also been studied in a number of phase II studies [Table – 1].

Table – 1: Combination chemotherapy regimens using paclitaxel in advanced gastric cancer

Regimen [reference]	RR	PFS (months)	OS (months)
Paclitaxel + Platinum [10-16]	22 - 46%	2.9 – 6	7.5-13.8
Paclitaxel + Fluoropyrimidine [17-21]	32 - 66%	3 – 9	9.9-14
Paclitaxel + Fluoropyrimidine + Platinum [22-25]	51 - 66%	4 - 9	6 -14
RR: Response rate, PFS: Progression free survival, Median Overall Survival: OS			

1.4 Intraperitoneal Paclitaxel

In ovarian cancer, a phase III randomized trial showed survival advantage for IV paclitaxel plus IP cisplatin and paclitaxel over IV paclitaxel plus cisplatin [26]. Paclitaxel has been shown to have distinct pharmacokinetic advantages when given via an IP route. These include high IP concentration of the drug, as well as a longer half–life in the peritoneal cavity, compared to that observed with IV administration [27]. This makes IP paclitaxel a compelling option for use in patients with peritoneal involvement from advanced gastric cancer.

Studies in Japan have reported that intraperitoneal (IP) paclitaxel is well tolerated and active in patients with gastric cancer and peritoneal involvement [28]. In a series of 100 patients, the median survival was 23 months, and the 12-month survival was 80% [29]. The chemotherapy regimen used consisted of weekly intravenous (IV) paclitaxel at 50mg/m2, IP paclitaxel at 20 mg/m2 and oral S1

(tegafur/gimeracil/oteracil) given on a 14 day regimen of 80 mg/m2 per day repeated every 3 weeks. It is of note that S1 may not be available for this indication in other parts of the world.

1.5 Rational for phase I study

The mentioned results have been achieved in a different genetic pool (Japanese population) using regimens that are not available in other parts of the world. We have designed this phase I trial to investigate the Maximum Tolerated Dose of intraperitoneal paclitaxel in combination with one of the standard chemotherapy combinations (cisplatin and capecitabine) in this patient population.

1.6 Justification of IP paclitaxel Dose and Escalation Schedule

The maximum tolerable dose and recommended dose available from previous phase I study by Ishigami et al [28], is certainly informative but because we are suggesting the use of IP paclitaxel in a new combination and in a different genetic pool, these doses may not be accurate. Therefore, we have elected to start the IP paclitaxel from 10 mg/m^2 which is one dose level lower than recommended dose by Ishigami et al. In our study, regardless of the IP paclitaxel, patients receive a standard regimen for their disease, therefore despite the low starting dose of IP paclitaxel, under-treatment is not a concern. The next dose levels are to be increased in 10 mg/m^2 increments to 30 mg/m^2, unless the MTD is achieved.

2 RECENTLY PUBLISHED STUDIES **(This section is not part of the original protocol and has been added to keep the manuscript up-to-date with the literature.)**

In a randomized phase III trial Ishigami et al [30] enrolled patients with gastric cancer with peritoneal metastasis. Patients were randomized to receive intraperitoneal and intravenous paclitaxel plus S-1or S-1 plus cisplatin. In this study, median survival was not significantly different between the two arms.

Yonemura et al [31] showed that neoadjuvant laparoscopic hyperthermic intraperitoneal chemoperfusion with docetaxel and cisplatin and Neoadjuvant Intraperitoneal/Systemic Chemotherapy with S-1, docetaxel and cisplatin can lead to reduced Peritoneal Cancer Index in patients with gastric cancer with peritoneal metastasis.

METHODS

3 AIM AND OBJECTIVES

Primary objective	1) To determine the Maximum Tolerated Dose (MTD) of IP paclitaxel in patients with advanced gastric cancer and peritoneal involvement
Secondary objectives	To determine: 2) Rates of toxicities [based on Common Terminology Criteria for Adverse Events (CTCAE version 4.0)][32] 3) Rates of intraperitoneal catheter complications 4) 12-month survival

5) Median survival
6) Progression free survival (based on RECIST 1.1 criteria)[33]
7) Objective Response Rate [Complete Response Rate + Partial Response Rate (based on RECIST 1.1 criteria)]
8) Ascites response (based on imaging)
9) Effects of treatment on quality of life. (based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4)[34]
10) Quality of life. (based on average scores as assessed by the EORTC STO22)[35]
11) Tissue banking for biomarker analysis

4 DESIGN

Open-label, single centre, phase I trial with standard 3 + 3 dose escalation design

5 SUBJECT POPULATION

5.1 Target Population

Subjects with Stage IV gastric cancer with biopsy or cytology proven peritoneal involvement

5.2 Inclusion criteria

1. Age ≥ 18 years
2. A diagnosis of Gastric cancer proven by histopathology and either:
    - Biopsy proven peritoneal metastases OR
    - Cytology consistent with malignant ascites: in which case patient must have ≥ 1 area of peritoneal metastasis apart from the ascites.
3. Subject must not have received previous chemotherapy for metastatic gastric cancer
    - Previous adjuvant chemotherapy for gastric cancer is allowed
4. Adequate bone marrow function (platelets > 100 x 10^9/L, Absolute Neutrophil Count > 1.5 x 10^9/L)
5. Adequate liver function (Serum bilirubin ≤ 1.5 Upper Limit Normal (ULM) and transaminases ≤ 3 ULN,)
6. Adequate renal function (Serum creatinine ≤ 1.5 UNL or creatinine clearance (CRCL) ≥ 50ml/min (using Cockcroft-Gault Equation)
7. negative pregnancy test for female patients if of potential child bearing age
8. Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0, 1 or 2
9. Staging CT scan of chest/abdomen/pelvis within 30 days of registration
10. Study treatment both planned and able to start within 30 days of registration
11. Willing and able to comply with all study requirements, including treatment (able to swallow tablets), and required assessments
12. Signed, written informed consent

5.3 Exclusion criteria

1. Contraindications to investigational chemotherapy regimen including allergies to any of the chemotherapy medications
2. Any comorbidities or conditions that the investigator considers the patient should not participate in the study
3. Life expectancy of less than 3 months.
4. History of another malignancy within 5 years prior to registration. Patients with a past history of adequately treated cervical carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or superficial transitional cell carcinoma of the bladder are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment.
5. Significant intercurrent illness that will interfere with the chemotherapy during the trial such as:
    a. Known Human Immunodeficiency Virus (HIV) infection
    b. Active infection
    c. Myocardial infarction within the previous 6 months or significant cardiac disease resulting in an inability to tolerate the intravenous fluid load as required for administration of cisplatin
    d. Severe lung disease which in the investigator's opinion would limit the patient's ability to tolerate large volumes of intra-abdominal fluids.
6. Peripheral neuropathy of any grade (based on CTCAE version 4.0)
7. Clinically significant sensori-neural hearing impairment or tinnitus which may be exacerbated by cisplatin (Audiometric abnormalities without corresponding clinical deafness will not be grounds for exclusion).
8. Previous abdominal or pelvic radiation treatment.
    a. Recent (<4 weeks) abdominal or pelvic radiation treatment; Patients who have received palliative radiation to gastric/oesophageal area are not excluded if total radiation received is less than 30 Gy and radiation is completed more than 4 weeks prior to commencing study treatments.
9. Significant intra-abdominal adhesions as determined by the surgeon at time of staging laparoscopy.
10. Active intra-abdominal sepsis
11. Medical or psychiatric condition that compromises the ability of patients to give informed consent.
12. Pregnancy, lactation, or inadequate contraception. Women must be postmenopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a barrier method of contraception during treatment and for the subsequent three months after treatment.

5.4 Screening

Written informed consent (supplementary file 1) must be signed and dated by the subject, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

Entry to this study is conditional on confirmation of tumour peritoneal involvement through either biopsy or cytology. Patients must have a staging CT scan of chest/abdomen/pelvis within 30 days of registration.

5.5 Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. Subjects must be registered before starting study treatment. Treatment should be planned to start within 28 days after registration. Registration should be done after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility, and signed the completed registration form. Once the registration process has been completed, the subject will be assigned a subject study number.

6 TREATMENT PLAN

IP paclitaxel is the study intervention in this trial; IV cisplatin and oral capecitabine are required standard concomitant interventions.

6.1 Administration of study treatments

6.1.1 IP CATHETER

IP catheter insertion:

Patients will have an IP catheter placed surgically after trial enrolment. The Intra-Peritoneal Catheter is placed surgically; under General Anaesthesia. The port should be secured to the anterior abdominal wall or the costal margin to enable easy access. The catheter should be tunnelled through the rectus sheath and muscle and secured to minimise the risk of an ascitic leak.

Possible Adverse Effects of IP catheter:

- Infection
- Abdominal pain,
- Development of intra-abdominal adhesions,
- Risk of organ perforation
- IP Catheter Blockage: In the event that the catheter is blocked and is not opened with conservative management including flushing with normal saline or simple manoeuvring, then this will be considered a rate limiting toxicity and the catheter will be removed

6.1.2 Endoscopic Biopsy

Before the surgery for IP catheter insertion, 4 endoscopic biopsies of the primary gastric tumour should be taken as well as biopsies of the peritoneal disease. These biopsy specimens are to be stored as fresh tissue in RNAlater® in separate containers for any and all later molecular analyses.

6.1.3 CHEMOTHERAPY

6.1.3.1 Paclitaxel:

Preparation for intraperitoneal administration: Paclitaxel, at the appropriate dose will be diluted in 250 - 500ml of 0.9% sodium chloride injection or 5% dextrose injection.
Stability: The infusion should be completed within 24 hours of preparation of the solution and any residue discarded. Diluted solutions should be refrigerated if not used immediately to decrease the likelihood of microbial contamination.

6.1.3.2 Cisplatin:

Preparation: The 10mg and 50mg vials should be reconstituted with 10 ml or 50ml of sterile water for injection, USP respectively. Each ml of the resulting solution will contain 1mg of cisplatin. Cisplatin should be diluted in 1L of normal saline.
Stability: Infusion should be completed within 24 hours of preparation and any residue discarded.

6.1.3.3 Capecitabine:

Preparation: A combination of the 500 mg and 150 mg tablets will be administered to reach the desired dose of 1000 mg/ m2

6.1.4 CHEMOTHERAPY REGIMEN AND DOSES

Each Cycle will be 21 days and includes the following combination:

- **Capecitabine** (oral) 1000 mg/m^2 twice a day, day 1 to 14 every 21 days
- **Cisplatin** at 80 mg/m^2 day (IV), day 2 every 21 days
- **Paclitaxel** will be given on day 1 and day 8 of a 21 day cycle. The dose of paclitaxel will vary depending on the cohort as follows (Table-2)

Table – 2: Dosing of intraperitoneal paclitaxel based on 3+3 design

Cohort	Number of Patients	Paclitaxel dose given on day 1 and day 8 of a 21 day cycle
1	3	10 mg/m^2
2	3	20 mg/m^2
3	6	30 mg/m^2

- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 1, patients will commence enrolment into Cohort 2.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 2, patients will commence enrolment into Cohort 3.
- If no dose limiting toxicity is seen after 3 patients have completed treatment in Cohort 3, this cohort will be expanded to 6 patients if maximum tolerated does (MTD) has not been reached. There will be no further dose escalation after Cohort 3.

6.2 Dose modifications

Dose modifications for cisplatin and capecitabine will be based on Eviq guidelines (https://www.eviq.org.au) (supplementary file 2). Adverse events are graded according to CTCAE version 4.0. In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until the adverse event has resolved to G0-1, at the investigator's discretion. Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events with differing recommendations, then the modification that results in the longest delay and lowest dose should be used.

Dose escalations or dose re-escalations after reductions for adverse events are prohibited.

6.2.1 Rechallenge

If patients experience a suspected drug related adverse event, they can interrupt the study medication until the symptoms resolve and then can reintroduce the study medication at same dose. If the reaction reappears then the study medication is to be discontinued permanently.

6.3 Concomitant Medications/Treatments

Include medications and treatments recommended, permitted (including rescue medication) and prohibited before and/or during the trial.

6.3.1 Recommended

The following medications and treatments are recommended in this study [Table – 3]:

Table – 3: Recommended medication before chemotherapy

Each cycle:		
Day 1		
Aprepitant	165 mg (PO)	60 minutes before chemotherapy
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	The night before and the morning of chemotherapy
Dexamethasone	12 mg (PO)	ONCE a day with or after food
Day 2, 3		
Dexamethasone	8 mg (PO)	ONCE a day with or after food
Day 8		
Fexofenadine	120 mg (PO)	60 minutes before treatment
Ranitidine	150 mg (PO)	the night before and the morning of chemotherapy
Dexamethasone	20 mg (PO)	the night before and the morning of chemotherapy

6.3.2 Permitted

Anti diarrheal and analgesics are permitted in this study:

6.3.3 Prohibited

The following medications should not be used during this study. Subjects who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the Study Chair:

- Radiation to Abdomen/Pelvis
- Operations/Procedures involving Abdomen/Pelvis
- Other investigational treatments

6.3.4 Concomitant medication reporting

Concomitant medications will not be recorded during the study.

6.4 Treatment discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease (PD) is documented by a site investigator.
- Unacceptable toxicity as determined by the patient or site investigator
- Delay of day 1 treatment for >21 days due to treatment-related adverse events. For delays >21 days due to reasons other than treatment-related adverse events, please contact the CTC to discuss treatment continuation.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety, e.g. pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in section 5.3.
- Failure to comply with the protocol.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject's medical record.

Follow up of subjects who stop study treatment should continue. All end-of-treatment assessments must be performed within 30 days after the end of study treatment. A safety assessment should be performed to include any adverse events occurring within 30 days after the last dose of study treatment.

6.5 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

7 ASSESSMENT PLAN

7.1 Schedule of assessments

Schedule of assessments is outlined in Table -4.

Table – 4: Schedule of assessments

	Screening	**Run-in**	**Baseline**	**On treatment**	**After 3rd cycle**	**End-of-Treatment and 30-day safety assessment**	**Follow-up after treatment**	**End of Study**
	14-28 days prior to registration	Within 14 days prior to registration	Within 7 days prior to registration	Within 3 days prior to: day 1 and day 8 of every cycle	Within 7 days after end of day 8 of 3rd cycle	Within 30 days after end of treatment	Every 12 weeks after end of treatment	2 years after registration
Informed consent	X							
Clinic assessment,	X		X	X		X	X	X
Haematology	X		X	X				
Biochemistry	X		X	X				
Imaging CT	X				X	X	X	
Adverse Events				X				
Endoscopy and Biopsy		X						
IP Catheter insertion		X						
Patient status			X	X		X	X	X
Quality of life assessments			X		X	X	X	X

8 OUTCOMES, ENDPOINTS AND OTHER MEASURES

8.1 Maximum Tolerated Dose (MTD):

8.1.1 **MTD** is defined as the highest dose level at which ≤ 33% of patients experience DLT [36]

8.1.2 **Dose Limiting Toxicities (DLTs)** are defined as:

8.1.2.1 Grade 3 or higher febrile neutropenia,

8.1.2.2 Grade 3 or higher thrombocytopenia with bleeding,

8.1.2.3 Grade 3 or higher neurologic toxicity, (excluding ototoxicity (hearing deficit and tinnitus))

8.1.2.4 Grade 3 or higher non-hematologic toxicities not including fatigue, alopecia, nausea, vomiting, elevated liver transaminases, Palmar Plantar Erythrodysesthesia and other capecitabine related skin toxicity, hearing deficit and tinnitus)

8.1.2.5 Grade 4 neutropenia lasting >7 days,

8.1.2.6 Grade 4 thrombocytopenia,

8.1.2.7 Grade 4 increased liver transaminases.

8.1.3 **Recommended phase 2 dose (RP2D) defined as:** dose equal to the MTD (as defined above), or cohort 3 if the MTD is not reached

8.2 Adverse Events (worst grade according to NCI CTCAE v4.0)

- Rate of toxicities based on CTCAE version 4.0 and the rate of catheter complications. See section 8.1 for the definition of an adverse event (AE), and reporting of Serious Adverse Events (SAEs).
- The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0) will be used to classify and grade the intensity of adverse events after each treatment cycle.
- The investigator's assessment of attribution to the study drug: IP Paclitaxel

8.3 Overall response rate:

Defined as complete response rate plus partial response rate (both defined according to RECIST 1.1

8.4 Progression free survival (disease progression or death)

Progression free survival (PFS) is defined as the interval from date of registration to the date of first evidence of disease progression or death, whichever occurs first. Disease progression is defined according to RECIST 1.1

8.5 Overall survival (death from any cause)

Overall survival is defined as the interval from the date of registration to date of death from any cause, or the date of last known follow-up alive.

8.6 Effects of treatment on quality of life

Based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (Version 4) and EORTC STO22

9 SAFETY REPORTING

9.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device. AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol
-

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent

with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol.

9.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the principal investigators (through FMC Medical Oncology Clinical Trials Unit) within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

The principal investigators must notify the local Human Research Ethics Committees as required.

9.3 Pregnancy

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the principal investigators. The partner should be counselled and followed as described above.

10 STATISTICAL CONSIDERATIONS

This is an open label phase 1 study with a standard 3 + 3 dose escalation design, therefore does not require sample size justification. The dose escalation is continued until the predefined number of DLT is reached.

11 ADMINISTRATIVE ASPECTS

11.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

11.2 Recruitment of participants

Patients attending oncology clinics within the Southern Adelaide Health Services that are potential candidates for the study will be given a patient information sheet by a member of the research team inviting them to participate in the study. Subjects willing to participate will meet with a study investigator to sign a consent form.

11.3 Consent

Involved clinicians will initially approach eligible patients to determine their interest in the study. Potential study subjects will be given a study patient information sheet. The purpose, requirements and risks of the study will be explained in a clear manner. Before witnessing the consent form, the investigator will discuss the study with the potential study subject to ensure that they fully understand the study risks, procedures and requirements.

11.4 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Clinical Trials Unit and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

11.5 Protocol amendments

Changes and amendments to the protocol can only be made by the Principal Investigators. Approval of amendments by the Institutional HREC is required prior to their implementation.

11.6 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the Case Report Forms (CRF). All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated. All study-related documentation will be maintained for 15 years following completion of the study).

11.7 Study Monitoring

Data from this study will be monitored by FMC Medical Oncology Clinical Trials Unit. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness.

11.8 Audit and Inspection

This study may be subject to audit or inspection by representatives of regulatory bodies.

11.9 Publication Policy

The Principal Investigators will appoint a Writing Committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). All publications must receive prior written approval from the Principal Investigators prior to submission.

12 Appendices: Supplementary File 1 and Supplementary File 2

FOOTNOTES

Contributors:

SV, TFB, ACR, DIW, JAB and CSK were involved in study conception, design, planning, and conduct of the study and manuscript writing. SHSG was involved in writing the manuscript. MNA was involved in the conduct of the study and writing manuscript. All authors were involved in the final approval of the manuscript. All authors agreed to be accountable for all aspects of the work.

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Patient and Public Involvement:

Patients and public were not involved in the design of the study.

Competing interest statement: None of the authors declare any competing interests.

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Flinders Medical Centre

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Location	Flinders Medical Centre

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have *Stomach Cancer*. The research project is testing a new treatment for *Stomach Cancer*. The new treatment is called *intraperitoneal paclitaxel*.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of the study is to determine the safe dose of chemotherapy to treat patients with stomach cancer with chemotherapy, some of which is given directly into the abdomen as well as into the vein. This study will also determine how safe this chemotherapy approach is, what side-effects it causes and how it affects quality of life.

There is a gap in our knowledge as to how to best treat patients with stomach cancer who have extension of the disease in the peritoneum (peritoneum is the membrane that forms the lining of the abdominal cavity). Researchers in Japan have used *intraperitoneal paclitaxel* treatment in patients with stomach cancer who had disease extension in the peritoneum and have reported promising results. Nevertheless, the other drugs used by those researchers are different from the standard of care in Australia and also there might be differences in the way stomach cancer behaves in different populations from different backgrounds.
Intraperitoneal paclitaxel has been given safely to people with other types of cancer and is part of a standard treatment for patients with cancer of the ovary or peritoneum.
With the results of this study we will be able to design a larger study to define the effectiveness of this treatment option.
The drugs used in this study consist of two drugs (*capecitabine* and *cisplatin*) that are part of the standard treatment for patients with advanced stomach cancer, and a the third drug called *paclitaxel which* is registered in Australia to be used in other cancers (both through intravenous catheter or directly into abdomen)

Medications, drugs and devices have to be approved for use by the Australian Federal Government. Paclitaxel is approved in Australia to treat cancer of ovary and peritoneum, breast cancer and cancer of the lung. *However it is not approved to treat Stomach cancer. Therefore, it is an experimental treatment for Stomach Cancer. This means that it must be tested to see if it is an effective treatment for Stomach Cancer.*

This research has been initiated by the study doctor, Associate Professor Chris Karapetis and Dr Tim Bright

This research has been funded by the Medical Oncology Clinical Research Unit of the Flinders Medical Centre.

3 What does participation in this research involve?

The consent form will be signed prior to any study assessments being performed.

First we need to make sure about the diagnosis and the extent of the disease: this will include: physical examination, some routine blood tests to check your blood count and your kidney and liver function, a CT scan (of chest abdomen and pelvis) and an endoscopy. (all of these tests are usually done as part of standard work up prior to starting treatment for stomach cancer.)

This study does not involve the use of placebo

Before you participate in this study, you will need to have a catheter placed in your abdomen. This small tube – called intraperitoneal port - will allow the doctors to give you the chemotherapy directly into the abdomen. This tube can be put in when you are having your endoscopy. However, your doctor may decide to put it in at a later date. The port is inserted in the operating theatre. You will be given a general anaesthetic. Your doctor or nurse will give you more

information on what you need to do to prepare for the procedure. You may be allowed to go home on the same day of the procedure if there are no complications.

You will need to see your treating doctor before each cycle of chemotherapy. At this visit, a physical examination will be performed. Before each visit with the treating doctor you will have a blood test.

A cycle of treatment is given every 21 days (3 weeks). You will get a maximum of 6 cycles of treatment.

During your chemotherapy you will be treated with 3 different drugs, they are *capecitabine* tablets (The tablets are taken TWICE a day with a glass of water within 30 minutes after the end of a meal), these tablets are taken for the first two weeks (day 1 to 14) of each chemotherapy cycle.

The second drug is *cisplatin* (given by a drip into a vein, this takes around 4 hours) and is given once every 21 days on day 2. You will need to have fluids given into the vein for several hours, before and after cisplatin and this will mean you may have to stay in hospital for one night. You will also be given medication to prevent nausea and vomiting.

The third drug is *paclitaxel*, this drug will be given into your abdomen through an intraperitoneal port on days 1 and 8 of each cycle, this will take 4 hours. Intraperitoneal chemotherapy will be given to you by a nurse who has been trained to give this treatment. Before this treatment begins you will have fluids and anti-sickness medication by a drip. You will also get medications into the vein beforehand to prevent any allergic reactions. You will also need to empty your bladder. Once the treatment begins you will be on bed rest and you will need to ask for a bedpan if required. The skin over the port site is cleaned with an antiseptic lotion. A needle is inserted through the skin into the port and fluids and chemotherapy will be given. The amount of time required for this treatment will vary depending on the volume of fluids and the chemotherapy that is being given. When the chemotherapy is finished, the needle will be removed. You will then be required to change your position in bed every 15 minutes for 1 hour. When the hour has passed it is important that you get up out of bed and move around. The intraperitoneal port will be removed by your doctor after completing the study.

You will have repeat CT scans of chest abdomen and pelvis after 9 weeks into the treatment and after completing the treatment course. The frequency of the scans is not different than what is routinely used in patients receiving standard chemotherapy treatment for stomach cancer.

During the follow-up period, you will be required to see your treating doctor for a check-up every 3 months up to a maximum of two years. During each visit you will be asked questions about your symptoms and will be examined by your doctor. A routine blood test and repeat CT scan will be done prior to the visit. After the mentioned follow-up period, further follow up plan will be decided by your doctor. .

You will be asked to complete a questionnaire on your quality of life at certain time points during the study; at the start of treatment, after the 3rd cycle and at the end of treatment at the end of the treatment (after 6 cycles) and then every 3 months during your follow up visits. These questionnaires will take about 15 - 20 minutes to complete.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

You may be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visit.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

4 What do I have to do?

- No specific Lifestyle restrictions are required e.g. physical restrictions, participation in sport
- No specific Dietary restrictions are required
- Some of your regular medication may interact with chemotherapy drugs; your doctor will ask you about your regular medications and will advise you accordingly
- You cannot donate blood

5 Other relevant information about the research project

This study will be running in Flinders Medical Centre. Patients will be joining the study in groups of 3, and given a specific dose of intraperitoneal paclitaxel; depending on the side effects and how well they tolerate the dose, the next group of patients will receive a similar or different dose. The study has been designed this way to define the appropriate dose of this drug for patients with stomach cancer.

Depending on the results a further study based on the doses suggested by this study will be designed to investigate the effectiveness of this treatment approach in similar patients.

Researchers from different departments (surgical department and medical oncology department)w ill be working together in this project

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Flinders Medical Centre

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include using the combination of *capecitabine* and *cisplatin* (same as this study without the intraperitoneal paclitaxel) or palliative and supportive care. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible additional benefits include potential improvement control of the disease especially in the peritoneum, potential improvement in ascites symptoms, potential improvement in delaying disease recurrence, potential improvement in survival or possible development of a more effective treatment approach for future patients.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Intraperitoneal catheter: Most ports are inserted and used throughout treatment without any complications. Complications may include:

- Infection, including infection of the abdominal wall or infection inside the abdominal cavity (this is called 'peritonitis'). Such infections may require hospital admission for antibiotic therapy,
- Abdominal pain,
- Development of intra-abdominal adhesions: Abdominal Adhesions are fibrous bands that form between tissues and organs, often as a result of injury during surgery. The most important implication of abdominal adhesions is Adhesion-related twisting and pulling of internal organs which can result in complications such as abdominal pain or intestinal obstruction. Intestinal obstruction can is a medical emergency and can be potentially life threatening.
- Risk of organ perforation

Possible Adverse Effects of Chemotherapy:

- **Nausea and Vomiting**
- **Changes in Sense of Smell and Taste**
- **Chest Pain:** Chest pain is uncommon, but may occur at any time during treatment. If you feel short of breath or develop chest pain call an ambulance, do not delay.
- **Increased Risk of Infection :** If you develop a fever 38oC or higher, have shivers, shakes or feel unwell call an ambulance to take you to the nearest hospital emergency department. Do not delay as this is life-threatening.
- **Low Red Blood Cell Count**
- **Low platelets and Increased Risk of Bleeding**
- **Sore Mouth**
- **Diarrhoea**
- **Stomach Pain**
- **Heartburn, difficult and painful swallowing**
- **Feeling Tired**
- **Numbness and Tingling in Fingers and Toes**

- **Ringing in the ears and loss of hearing:** Changes in hearing, such as ringing in the ears and hearing loss, may happen. If you develop hearing changes, tell your doctor.
- **Impaired Kidney Function**
- **Hand Foot Syndrome :** Your skin may become red, hot and tender. Small blisters can form and your skin may peel.
- **Hair Loss:** Hair loss may start within a few weeks of beginning treatment.
- **Nail Damage**
- **Poor concentration :** Memory changes and being unable to concentrate are common but generally improve once treatment is completed.
- **Yellowing of the skin and eyes:** Yellowing of your skin and eyes are uncommon. It is caused by the drugs affecting your liver. You will have regular blood tests to check your liver function. If you notice your urine is a dark colour or the whites of your eyes look yellow tell your doctor or nurse.

Possible Adverse Effects of intraperitoneal Chemotherapy:

- **Risks:**

During treatment with chemotherapy directly into the abdomen the following concerning side effects may occur,

  - Increased abdominal pressure,
  - Increased abdominal pain
  - Increased abdominal bloating

- **You may also experience the following side effects**
  - Diarrhoea
  - Nausea
  - Vomiting

With medication and appropriate counselling, most side effects can be prevented or reduced.

The effects of *intraperitoneal paclitaxel* on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 3 months after the last dose of study medication.
Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 3 months after completion of the research project. You should discuss methods of effective contraception with your study doctor.

[For female participants] If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

[For male participants] You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

Chemotherapy may cause temporary or permanent sterility. Please discuss this with your study doctor if you have any concerns about future fertility.

Having a drug injected or blood (or tissue sample) taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

These days, whilst anaesthesia is generally very safe there are some risks associated with anaesthesia. The most common problems associated with anaesthesia are feeling unwell or vomiting, bruising at the site of injections, sore throat or hoarse voice. Most patients do not have these problems. If these problems do happen, they usually get better very quickly. Damage to teeth may occur, but this is rare. The risk of brain damage or death due to anaesthesia is very rare.

The risk of problems from anaesthesia increases for patients who are having more major surgery, those with medical problems and those that require difficult anaesthetic procedures. If you have any concerns about these issues, you should discuss them with the study team.

10 What will happen to my test samples?

During the assessment procedures before enrolling into the study and after you have signed the consent form; an endoscopy will be performed by your doctor. During the endoscopy 4 small tissue samples will be taken from the cancer in the stomach and also small tissue samples will be taken from the cancer in the peritoneum. These samples will be stored for future analyses to see if there are any markers that can predict different response to treatment. All the tissue samples will be held in Flinders Medical Centre

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing

15 What happens when the research project ends?

You will be followed up for a maximum of 2 years after completing the study, after that your doctor will discuss further follow up plans with you.

After completing this study, treatment with intraperitoneal paclitaxel will not be available. When further treatment is indicated your medical oncologist will advise you on the treatment options.

It is usual for a number of years to elapse before definitive results of this type of study are available. These are published in medical journals that are available to the public. You should feel free to ask your doctor about this.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All the information will be kept in medical oncology clinical trials unit in flinders medical centre Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by *A/Prof Chris Karapetis and Dr Tim Bright*

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to *Flinders Medical Centre*

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of *Flinders Medical Centre*

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on *08 8204 8997* or any of the following people:

Clinical contact person

Name	
Position	
Telephone	
Email	

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	
Position	
Telephone	
Email	

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact (Single Site -Research Governance Officer)

Name	
Position	
Telephone	
Email	

Consent Form - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *Flinders Medical Centre* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

By signing this consent section, I agree to the use of tissue samples obtained previously from my *routine biopsy or surgery* for the purposes of additional testing for *Molecular testing*

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to
Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	**Phase I open label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced Gastric cancer and peritoneal metastases**
Short Title	Chemo into the peritoneum for gastric cancer
Protocol Number	007
Project Sponsor	Flinders Centre for Innovation in Cancer, Flinders Medical Centre
Coordinating Principal Investigator	Medical Oncology Clinical Trials Unit
Location	Flinders Medical Centre

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Flinders Medical Centre*

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Supplementary File 2

Specific dose modifications for cisplatin and capecitabine

Haematological toxicity

ANC x 10^9/L (on day of chemotherapy)	
0.5 to less than 1.5	Delay treatment until recovery
less than 0.5	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles
Platelets x10^9/L (at any stage of the cycle)	
50 to less than 100	Delay treatment until recovery
less than 50	Delay treatment until recovery and consider reducing cisplatin and capecitabine by 25% for subsequent cycles

Renal impairment

eGFR (Cockcroft Gault) (mL/min)*	
greater than or equal to 70	No dose modifications necessary
50 to less than 70	Reduce cisplatin by 25%
30 to less than 50	Reduce capecitabine by 25% and cisplatin by 50%
less than 30	Withhold treatment

Hepatic impairment

Hepatic dysfunction	
Mild	No dose modifications necessary
Moderate	Reduce capecitabine by 25%
Severe	Reduce capecitabine by 50%
Treatment related Grade 3 or 4 Hyperbilirubinaemia	Delay treatment until toxicity resolves to Grade 2 or less

Peripheral neuropathy

CTC grading	
Grade 2, Grade 3 or Grade 4	Omit cisplatin

Mucositis & stomatitis

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce cisplatin and capecitabine by 25% 3rd occurrence: Reduce cisplatin and capecitabine by 50% 4th occurrence: Omit cisplatin and capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce cisplatin and capecitabine by 50% 2nd occurrence: Omit cisplatin and capecitabine

Diarrhoea

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction 2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3 or Grade 4	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Hand and foot syndrome (Palmar-plantar erythrodysesthesia syndrome)

CTC grading	
Grade 2	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: No dose reduction

	2nd occurrence: Reduce capecitabine 25% 3rd occurrence: Reduce capecitabine by 50% 4th occurrence: Omit capecitabine
Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce the dose for subsequent cycles as follow: 1st occurrence: Reduce capecitabine by 50% 2nd occurrence: Omit capecitabine

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	3

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	N/A

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Data access	#29	Statement of who will have access to the final trial dataset,	16

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8