Risk-Directed Thromboprophylaxis in Ambulatory Patients with Cancer

This supplement contains the following items:

1. Original protocol, version 1.6 dated 25 May 2018 (first HREC approved protocol including statistical analysis plan)
2. Final protocol, version 3.0 dated 02 July 2019 (final HREC approved protocol including statistical analysis plan and summary of all protocol changes in prior versions).

Targeted thromboprophylaxis in ambulatory patients receiving anticancer therapies for lung or gastrointestinal cancers: an investigator-initiated, open-label, multicentre, randomised, phase 3 trial (TARGET-TP)

Short Title: Target-TP

Protocol Number: TargetTP-1.6

Version 1.6 dated 25 May 2018

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Abbreviations

AE	Adverse event
ATE	Arterial thromboembolism
CEC	Clinical Events Committee – panel of independent experts that conducts central review of trial endpoints in a blinded and unbiased manner, ascertaining whether they meet protocol definitions.
CI	Confidence interval
CT	Computed tomography
DSMB	Data and Safety Monitoring Board – multidisciplinary group established to review accumulating trial data in order to monitor progress of the trial and comprising of members who may be from (or affiliated with) the same institution as the sponsor or investigator but are not part of the trial team.
DVT	Deep vein thrombosis
ECOG	Eastern cooperative oncology group
EOS	End of Study
GI	Gastrointestinal
HIT	heparin induced thrombocytopenia
HR	Hazard Ratio
LMWH	Low molecular weight heparin
LNL	Lower normal limit
NCI CTCAE v4.03	US National Cancer Institute Common Terminology Criteria for adverse events, version 4.03
NNT	Number needed to treat
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PE	Pulmonary embolism
PICF	Patient Information and Consent Form
PFS	Progression free survival
PRO	Patient reported outcomes
P-TP	Pharmacologic thromboprophylaxis
QoL	Quality of Life
RECIST v1.1	Response evaluation criteria in solid tumours version 1.1
SCLC	Small cell lung cancer
TE	Thromboembolism
TP	Thromboprophylaxis
UNL	Upper normal limit
VTE	Venous thromboembolism

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1. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the NHMRC's *National Statement on Ethical Conduct of Research in Humans*, the TGA's *Clinical Trial Handbook*, Good Clinical Practice, the Sponsor's SOPs, and other regulatory requirements as amended.

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

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

For and on behalf of the Study Sponsor:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Principal Investigator 1:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Principal Investigator 2:

Signature: ..... Date: ...../...../.....

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Position: .....

Principal Investigator 3:

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Name (please print): .....

Position: .....

Study Statistician:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

2. PROTOCOL SYNOPSIS

Title	Targeted thromboprophylaxis in ambulatory patients receiving anticancer therapies for lung or gastrointestinal cancers: an investigator-initiated, open-label, multicentre, randomised, phase 3 trial (TARGET-TP)
Short Title	TARGET-TP
Sponsor	Peter MacCallum Cancer Centre
Indication	Ambulatory patients aged 18 years and over, receiving anticancer therapy (chemotherapy, targeted therapy and/or radiotherapy) for the treatment of gastrointestinal or lung cancer, for whom there is no contraindication for pharmacologic thromboprophylaxis (P-TP), and who fulfil all of the other protocol-defined eligibility criteria.
No of sites	5
Study design	Open-label, multicentre, randomised, phase 3 trial to assess the efficacy and safety of enoxaparin P-TP among ambulatory patients with cancer at high risk of TE, receiving anticancer therapy. Approximately 300 patients with gastrointestinal or lung cancer will be assessed for TE risk, based on an established algorithm. According to the algorithm, TE risk will be assessed at baseline (prior to anticancer treatment) and one month after commencing anticancer treatment. Patients classified as high TE risk at baseline (target n=200) will be randomised to enoxaparin P-TP or no P-TP (1:1), in addition to their clinician-directed anticancer therapy. Patients classified as low risk at baseline (expected n=100) will commence anticancer treatment with no P-TP but will be re-assessed one month after commencing anticancer therapy with patients meeting defined risk thresholds upgraded to high TE risk and randomised (1:1) to enoxaparin P-TP for immediate initiation (estimated 10% of low risk cohort). Patients who remain low risk will continue with no P-TP and be monitored for the duration of the study period. The study will commence recruitment at a single site (Peter MacCallum Cancer Centre) in an initial phase, with additional sites planned to open in an expansion phase. It is expected that approximately 100 patients will be recruited in the initial phase, with 200 patients in the expansion phase. **Risk assessment**: High risk if: (i) or (i) or (iii) (i) fibrinogen ≥4g/L + d-dimer ≥0.5mg/L at baseline, or (ii) d-dimer ≥1.5mg/L at baseline, or (iii) d-dimer ≥1.5mg/L at month one.
Background and study rationale	Appropriate P-TP can reduce TE rates in up to 80% of at-risk patients, but must be balanced against potential bleeding complications. Targeting patients and time points in their journey, that are high TE risk, while avoiding intervention in those at lowest risk, will optimise the risk-to-benefit ratio and result in

	greater TE risk reduction with demonstrable survival benefits. The TE risk assessment algorithm has been derived from prospective thrombogenic biomarker studies conducted at Peter MacCallum Cancer Centre. These studies sequentially assessed thromboembolic risk among patients with cancer (multiple myeloma, lung-, and gastrointestinal- cancer) using clinical parameters and thrombogenic biomarkers. The model demonstrated greater potency and specificity in terms of risk stratification, than published models, predicting with regards to TE, NNT 4-6 vs. 15-25 in published risk assessment models and 30-60 in studies for non-targeted interventions. The model has predicted TE with 80-100% sensitivity in gastrointestinal and lung cancer cohorts, compared to sensitivty of 20-25% with application of existing risk models.
Aims and objectives	**Aim:** To assess the efficacy and safety of enoxaparin P-TP among high TE risk ambulatory patients with lung or gastrointestinal cancer, receiving anticancer therapy. **Primary Objectives** 1. To compare incidence of objectively confirmed TE at 6 months after randomisation, among high TE risk patients receiving enoxaparin P-TP versus no P-TP. **Secondary Objectives** 1. To compare incidence of major bleeding or clinically relevant non-major (CRNM) bleeding at 6 months after randomisation, among high TE risk patients receiving enoxaparin P-TP versus no P-TP. 2. To report incidence of adverse events other than bleeding, probably or definitely related to enoxaparin P-TP, from randomisation to two days after last dose of study drug. 3. To compare incidence of objectively confirmed TE at 6 months after enrolment, among high TE risk patients receiving no P-TP versus low TE risk patients receiving no P-TP (risk model sensitivity and specificity) 4. Overall response (OR) to anticancer therapies, Overall Survival (OS) and Progression Free Survival (PFS). 5. Patient reported outcomes related to QoL and P-TP 6. Healthcare resource utilisation costs related to P-TP and TE
Investigational product	7. The investigational product used in the study is enoxaparin (Clexane®), a low molecular weight heparin (LMWH) licenced for use in the prevention of venous TE in surgical patients and medical patients bedridden due to acute illness; not in at-risk ambulatory medical (or cancer) patients. Enoxaparin is the LMWH of choice at Peter MacCallum Cancer Centre.
Cohorts	Low TE risk, no P-TP (approximately 100 patients) High TE risk, randomised to enoxaparin P-TP in 1:1 (approximately 200 patients)
Duration of	Patients will be enrolled in the initiation phase (one site), with continued

follow-up	enrolled in the expansion phase (additional sites) until recruitment target reached. Patients will be followed for minimum 12 months for TE and thrombohaemorrhagic complications, and followed for minimum 24 months for survival outcomes. **Follow-up:** As per standard of care for anticancer treatment with study specific follow-up at months 1, 3, 6, 12, and then yearly until end of study (month 24 for the last enrolled patient). Unscheduled visits will occur at the time of TE or bleeding events.

3. BACKGROUND AND RATIONALE

3.1 Thromboembolism and Cancer

Despite availability of safe and efficacious antithrombotic agents, as well as our vast clinical experience justifying their use, cancer associated TE remains a frequent preventable complication with substantial adverse health and economic consequences.[1-3] It is a negative predictor of survival and leading cause of death, associated with extensive clot burden, post-thrombotic syndrome, higher (2-3 fold) clot recurrence rates, higher (2-6 fold) bleeding complications on anticoagulant therapy, catheter-related complications, increased hospitalisation and impaired quality of life.[4-6] An incident TE event, once a cancer has been diagnosed and treatment started, often denotes a significant clinical hurdle, not only related to the morbidity and mortality associated, but the potential detrimental effect of an interruption or modification in therapy attributable to the event and/or delivery of therapeutic anticoagulation. As such, risk-adapted primary P-TP can have a substantial impact not only on TE reduction, but also disease response, survival, quality of life and healthcare resources.

3.2 Thromboembolism Prevention

Risk stratification and predictive modeling tools are important enablers to facilitate targeted strategies and improve patient outcomes. Appropriate P-TP can reduce TE rates in up to 80% of at-risk patients,[7] but must be balanced against potential bleeding complications. Risk stratification can facilitate this by identifying patients at risk and duration of risk, allowing a personalised risk-directed approach, rather than the broad application in patients with cancer. Targeting patients and time points in their journey that are high TE risk, while avoiding intervention in those at lowest risk, will optimise the risk-to-benefit ratio and result in greater TE risk reduction with demonstrable survival benefits.

Despite continued efforts over more than a decade, current TE risk models [8, 9] lack the necessary precision (19-64% sensitivity) to adequately stratify patients. Moreover, there has been no definitive study to date, that has investigated the use of a relevant and potent risk prediction model, with directed management algorithms, to assess whether this approach can safely and effectively reduce rates of TE, the attributable morbidity and mortality, and improve overall outcomes of patients with cancer.

3.3 Risk assessment model development

At this institution, we have undertaken four studies in three disease groups (multiple myeloma, lung-, and gastrointestinal- cancer), to prospectively and sequentially assess TE risk profile of ambulatory cancer patients using clinical, therapeutic, and thrombogenic biomarkers. From these studies we have derived and cross-validated a TE risk assessment and P-TP guidance algorithm, which will be used for this study. Risk stratification considers cancer treatment and thrombogenic biomarker profile reflecting clot formation potential (fibrinogen and d-dimer). When applied to the gastrointestinal and lung cancer cohorts, the model had more potency, in terms of TE risk stratification, than those previously proposed, predicting NNT 4-6 vs. 15-25 in published studies using risk assessment models, and 30-45 in studies of non-targeted interventions.[10] Our model has predicted TE with 90-100% sensitivity in gastrointestinal and lung cancer cohorts, compared to sensitivty of 20-25% with application of the Khorana TE risk score.[9]

3.4 Safety Considerations

The risk of non-major but clinically relevant bleeding events is higher with LMWH P-TP compared to no P-TP (HR 3.40, 95%CI 1.20-9.63). In a 2016 Cochrane meta-analysis, 102 events were observed among 1543 patients receiving LMWH P-TP, compared to 37 events among 1562 patients receiving no P-TP.[7]

The risk of a major bleeding event for patients receiving LMWH P-TP is low. From the same 2016 Cochrane meta-analysis, a non-significant increased risk of major bleeding was observed for LMWH P-TP versus no P-TP (HR 1.44, 95%CI 0.98-2.11). This analysis included 3378 patients with LMWH P-TP (69 major bleeding events) and 2978 patients with no P-TP (44 major bleeding events).[7]

Differing from the application of P-TP in studies included in this meta-analysis, we will be targeting interventions only to patents at high TE risk, and therefore avoiding intervention and potential bleeding risks in patients at low risk of TE.

Among high TE risk patients, the significant risk of morbidity and mortality associated with TE that occurs in up to 25% of high risk patients, outweighs the small but real increased risk of bleeding complications. Furthermore, intervention will be limited to a short duration where TE risk is highest, minimising long term effects and potential bleeding complications.

3.5 Study Rationale

The described application of P-TP provides a highly targeted and promising prophylactic approach to address a clinically important unmet need, and provide a supportive care tool to improve outcomes for patients with gastrointestinal and lung cancers.

4. TRIAL AIM, OBJECTIVES AND ENDPOINTS

4.1 Aim

To assess the efficacy and safety of P-TP among high TE risk patients with gastrointestinal or lung cancer, receiving anticancer therapy.

4.2 Objectives and Endpoints

Primary Objective	**Endpoint**
Assess the efficacy of enoxaparin primary P-TP	• Objectively confirmed symptomatic or asymptomatic TE (DVT, PE, ATE) at 6 months after randomisation. DVT must be confirmed by ultrasonography, venography or magnetic resonance angiography (cerebral events). PE must be confirmed by spiral CT, CT pulmonary angiography (CTPA) or lung ventilation/perfusion scan. ATE must be confirmed by relevant radiologic imaging, or specifically for myocardial infarct (MI) must meet criteria outlined in the universal definition of MI considering biomarker changes, ischemic symptoms, ECG changes, cardiac imaging abnormalities, and cardiac death.[11]

	Superficial Vein Thrombosis (SVT) will not be considered a TE event, but will be documented if they occur. All TE events will be adjudicated by a committee unaware of randomisation (Clinical Event Committee – CEC).

Secondary Objectives	**Endpoints**
Assess the safety of enoxaparin primary P-TP	• Major bleeding, clinically relevant non-major (CRNM) bleeding, any bleeding (major or CRNM) at 6 months after randomisation, excluding patients on therapeutic anticoagulation. Major bleeding: *clinically* overt bleeding meeting at least one of the following criteria: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.[12] Clinically overt was defined as new onset visible bleeding or signs and symptoms suggestive of bleeding which in the absence of visible bleeding were confirmed by relevant imaging techniques.[11] *CRNM bleeding:* bleeding not meeting criteria for major bleeding but that would be considered relevant and not trivial by a patient and physician.[11] All bleeding events will be adjudicated by a committee unaware of randomisation (Clinical Event Committee – CEC).
Assess the safety of enoxaparin primary P-TP	• Adverse event other than bleeding, probably or definitely related to the study drug, from randomisation to two days after the last dose of study drug.
Assess sensitivity and specificity of TE risk assessment tool	Among patients <u>not</u> receiving enoxaparin P-TP: • TE-positive patients classified as high risk, as a proportion of all TE-positive patients • TE-negative patients classified as low risk, as a proportion of all TE-negative patients Analysis will occur after month 6, the specified time period for primary assessment of TE events, using risk classification assigned at month 1.
Assess the overall response to anticancer therapies, overall survival, and progression free survival.	• Overall response (OR), defined as clinician reported best response to therapy [Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)]. • Duration of response, defined as the time from the date of first response of PR or better until the date of disease progression, for those patients who experience a PR or

	better (death is a censoring event), for those patients who experience a PR or better. • Progression free survival, defined as the time from registration on study to the earliest of date of disease progression or death. • Overall survival, defined as the time from registration on study to date of death.
Assess patient reported outcomes – quality of life and anti-clot treatment	• Patient quality of life survey (SF12 v2.0) for all patients at enrolment and six and twelve months after commencement of anticancer therapy. • Patient response to Anti-Clot Treatment Scale (ACTS), among patients randomised to P-TP at one and three months, and six if applicable, after commencement of anticancer therapy.
Assess healthcare resource utilisation costs directly associated with P-TP and TE	• Cost of P-TP, defined as unit cost of drug for duration of therapy, plus costs associated with P-TP related AE. • Cost of anticoagulation for treatment of TE, defined as unit cost of drug for duration of therapy, plus costs associated with TE event.

5. TRIAL DESIGN

This is a prospective, open-label, randomised controlled study designed to investigate the safety and efficacy of enoxaparin primary P-TP in adult ambulatory care patients with gastrointestinal or lung cancers, at high risk of TE.

Consenting patients presenting for the treatment of gastrointestinal or lung cancer (any line of therapy and including chemotherapy, radiotherapy, immunotherapy, and/or targeted therapy) will be screened for eligibility and, if found to fulfil the eligibility criteria, will be registered in the study.

All patients will undergo TE risk assessment and observational follow-up including sequential assessments of fibrinogen and d-dimer. Patients identified to be at high TE risk will proceed to randomisation for treatment with or without P-TP. Patients identified to be at low TE risk will be observed and then re-assessed one month after commencement of cancer therapy, and if fulfilling requirements for high TE risk, will be randomised to receive P-TP (1:1).

The study will commence recruitment at a single site (Peter MacCallum Cancer Centre) in an initial phase, with up to two additional sites planned to open in an expansion phase. It is expected that approximately 100 patients will be recruited in the initial phase, with 200 patients in the expansion phase.

5.1 Treatment dosing

All high TE risk patients will be randomised to receive P-TP (1:1), as enoxaparin 40mg daily by subcutaneous injection unless meeting any of the below dose modification criteria:

- Creatinine Clearance <30mL/minute: enoxaparin 20mg daily
- Weight <50kg: enoxaparin 20mg daily

- Weight >120kg: enoxaparin 60mg daily
- Platelet count <30 x10^9/L: withhold

5.2 Treatment Duration

For high TE risk patients randomised to the intervention cohort, P-TP will commence at time of completion of risk assessment and continue to at least three months, or at until cancer therapy cessation to a maximum of six months.

For low TE risk patients escalated to high TE risk after on-treatment re-assessment at month one, P-TP will commence as soon as feasible and continue until cancer therapy cessation, to a maximum of six months.

Investigators may prescribe up to three months' supply of study drug (90 x enoxaparin single dose pre-filled syringes) as a single dispensing at the commencement of P-TP, with secondary supply quantity tailored to expected duration of anticancer therapy, not exceeding maximum six months of P-TP.

5.3 Study Duration

Patients will be enrolled over an anticipated period of 12 months and followed from the later date of enrolment or randomisation, for minimum 12 months for thrombohaemorrhagic outcomes and minimum 24 months for survival outcomes. End of study (EOS) is defined as 24 months after commencement of anticancer therapy for the last enrolled patient.

5.4 Patient Withdrawal from Study

Every effort within the bounds of safety and patient choice will be made to have each patient continue within the trial. However, patients may withdraw from the trial at any time and for any reason, without affecting their right for further standard treatment and without their care being affected in any way. The investigator has the right to withdraw a patient for any reason that is in the best interests of the patient, including concurrent illness.

A patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by investigator
- Study termination by sponsor
- Death

5.5 Criteria for Cessation of Study Drug

P-TP will be permanently stopped for any of the following reasons:

- Development of a radiologically confirmed TE requiring full dose anticoagulation
- Any adverse event following which the responsible physician determines that P-TP should be stopped, including any haemorrhage (grade two or above) and haematoma (grade two or above), other adverse event attributable to drug (grade two or above) or if the physician feels that is in the best interest of the participant to stop

- The P-TP interval ended
- If the participant chose to stop

5.6 Criteria for Temporary Suspension of the study

Should a fatal bleeding event occur in a patient receiving P-TP at any time, or a major bleeding event that is solely attributed to P-TP, the study will be temporarily suspended to determine whether causality is attributed to P-TP and whether drug can safely be continued in other patients.

5.7 Criteria for Termination of the Study

The study can be terminated at any time by the Sponsor, the DSMB, TGA or the Ethics Committee (EC) for any reason. The Investigator may be informed of additional procedures to be followed in order to ensure adequate protection of patients.

6. PATIENT SELECTION

The study will enrol consecutive patients presenting for the treatment of gastrointestinal or lung cancer (any line of therapy) at participating trial centres, that meet all the following inclusion criteria and none of the exclusion criteria.

6.1 Inclusion criteria

All of the following must apply at the time of enrolment:

1. Patient is 18 years of age or older
2. Patient has a confirmed histological diagnosis of any gastrointestinal or lung cancer
3. Patient is newly diagnosed treatment-naïve or is previously treated with newly relapsed or progressive disease
4. Patient is being considered for, but has not commenced anticancer therapy including chemotherapy and/or radiotherapy and/or immunotherapy and/or targeted therapies, within neoadjuvant, adjuvant, curative, or palliative treatment settings.
5. Patient has expected life expectancy of at least six months, as estimated by their treating clinician
6. Patient has provided written confirmation of informed consent on participant information and consent form.

6.2 Exclusion criteria

Patients who meet **any** of the following criteria will be excluded from participation in this study:

1. Patients who have already commenced anticancer therapy
2. Patients with a clinical indication for therapeutic anticoagulation (antiplatelet agents such as clopidogrel and aspirin are permitted)
3. Patients with a contraindication to anticoagulation and/or specifically LMWH (Appendix 2)
4. Cancer diagnosis other than those specified in inclusion criteria.

6.3 Patient Registration Procedure

This is an open-label randomised study.

Eligible patients will be registered electronically using the online electronic data capture (EDC) system. Registration confirmation as well as allocation of a unique participant identification number for the will occur via the EDC.

Prior to patient registration, the investigator should ensure that all of the following requirements are met:

- The patient meets all inclusion criteria and none of the exclusion criteria apply
- The patient has signed and dated all applicable consent forms
- The eligibility checklist has been completed, signed and dated

Patients determined to be at high TE risk by baseline assessments will proceed to randomisation 1:1 for P-TP or no P-TP. Randomisation will be performed by within the EDC system with treatment allocation available to the site in real-time.

Patients upgraded from low TE risk to high TE risk at month one will be randomised at this time with 1:1 randomisation for P-TP or no P-TP. For patients randomised to P-TP, treatment should commence immediately with prescription order from the investigator, trial management approval is not required.

7. STUDY TREATMENT PLAN

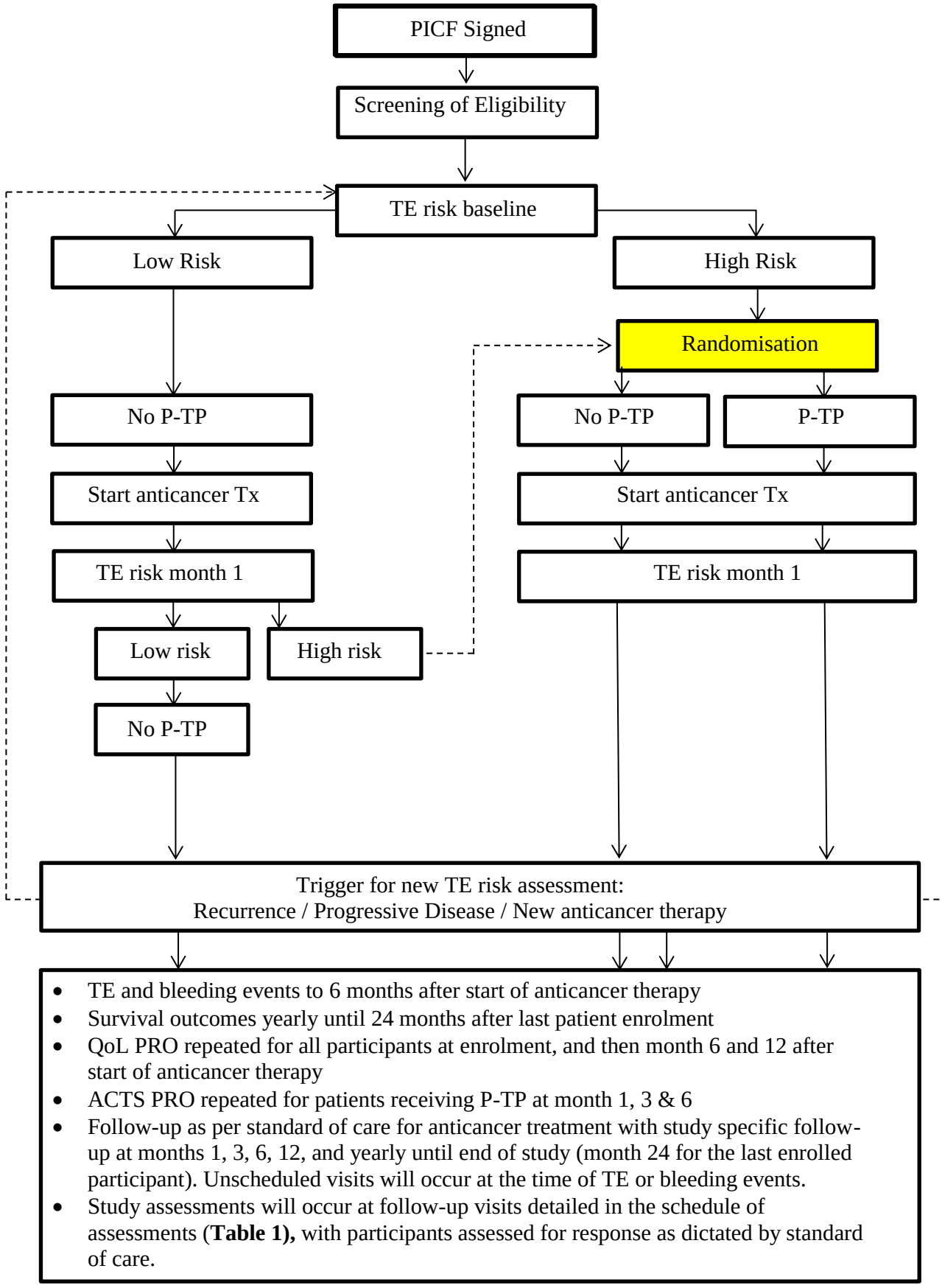

Figure 1 - Study treatment plan

7.1 Screening for eligibility criteria

Screening for the eligibility process begins when in the patient signs the IRB/IEC-approved consent form. The eligibility check-list must be signed and dated by the physician prior commencement of assessments and entered into the EDC system by the end of the next business day. Assessments, including blood tests, conducted prior to consent, as part of routine care, will be accepted so long as conforming to the schedule of assessments as detailed in **Table 1**.

The following assessments must be performed within 28 days of registration onto the study:

- Informed consent
- Demographics and identifiers
    - During screening potential trial participants will be identified by first and last initial and date of birth (DOB). For those meeting eligibility and enrolled into the study, identification will additionally include a study identification number (Study ID) which will be a chronological number automatically generated by REDCap. Enrolment site (hospital), sex, and ethnicity will also be recorded. Email addresses will be recorded for the purpose of survey distribution only, but will not otherwise be reported and will be removed from all data-sets prior to analyses or report generation.
    - The following identifiers will not be recorded on any study forms or entered into the REDCap database, but will recorded at each site as a master log of trial participants linked to allocated study IDs: first name, surname, hospital URN. It will be the responsibility of the site PI to ensure security and confidentiality of this master identification log.
- Medical history including: disease diagnosis and history, prior anticancer therapy and risk factors of thromboembolism (personal history of TE, family history of TE, COPD / COAD, smoker (current or quit within 4 weeks), atrial fibrillation, structural heart disease, long haul travel (6 or more hours within 7 days), medical hospitalisation within past 4 weeks, surgical hospitalisation within past 4 weeks, oral contraceptive pill, hormone replacement therapy, other risk factor identified by treating clinician.
    - TE risk factors will be recorded as part of medical history but will not be taken into account for TE risk categorisation. Previously completed studies in lung and GI cancer found that assessment of fibrinogen and d-dimer alone afforded greatest sensitivity for prediction of future TE.
- Review of prior/concomitant medications
- Assessment of eligibility criteria
- ECOG performance status assessment
- Height, weight, and body mass index (BMI)
- Blood exams (haematology, biochemistry, fibrinogen and d-dimer)
- Creatinine Clearance calculation

7.2 Baseline TE risk assessment

The following blood exams must be completed to perform TE risk assessment and safety of potential P-TP administration:

- Haematology

- Biochemistry
- Fibrinogen and d-dimer.

The investigator will perform real-time risk assessment as described below and as depicted in Figure 2 – Algorithm for TE Risk Assessment.

Baseline TE risk assessment:
High risk: fibrinogen ≥4g/L + d-dimer ≥0.5mg/L, or d-dimer ≥1.5mg/L
Low risk: fibrinogen <4g/L or d-dimer <0.5mg/L and d-dimer <1.5mg/L

Month 1 TE risk assessment, for low risk patients only
High risk: d-dimer ≥1.5mg/L
Low risk: d-dimer <1.5mg/L

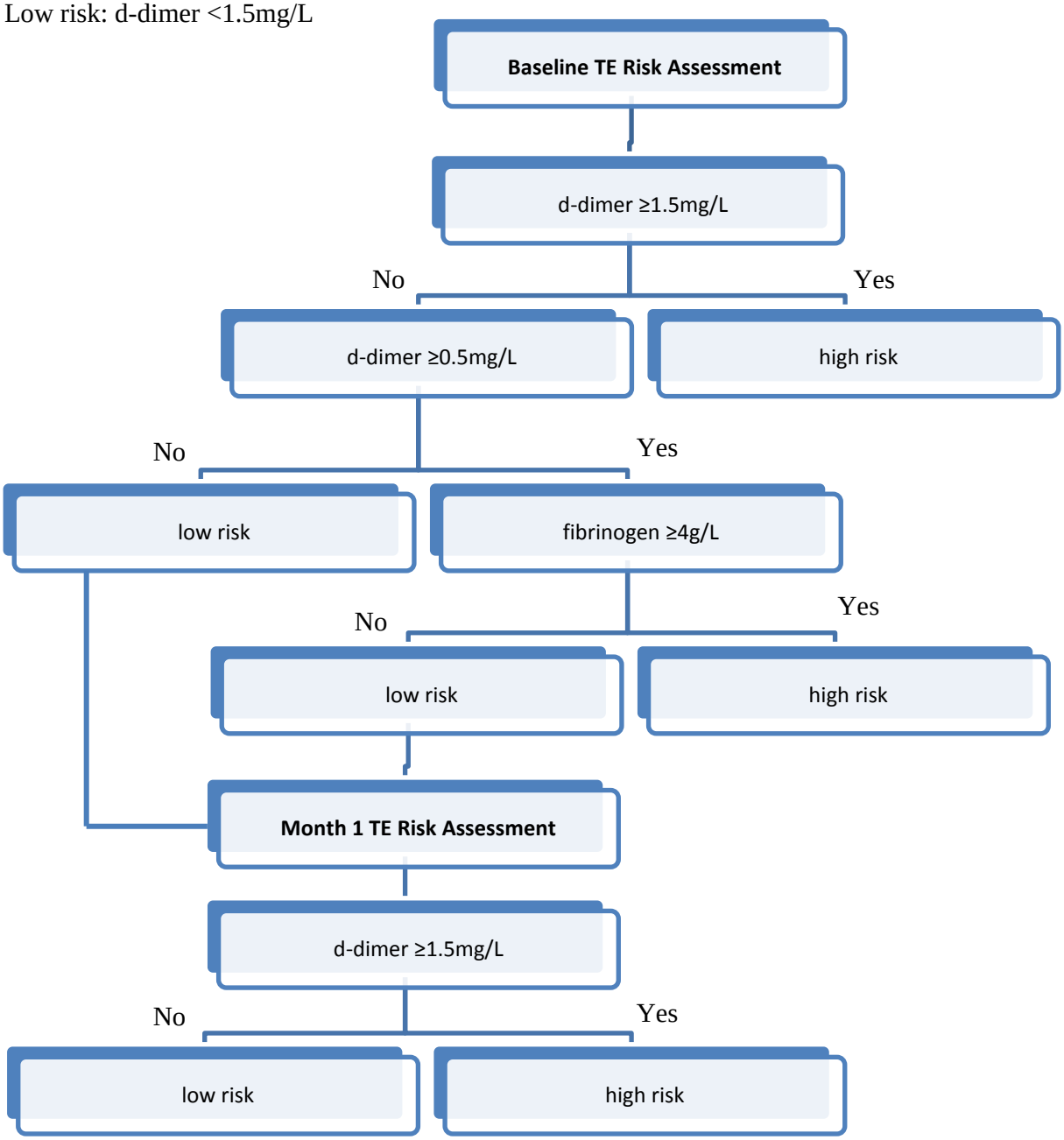

Figure 2 - Algorithm for TE risk assessment.

7.3 Randomisation and P-TP commencement

High TE risk patients will be randomised 1:1 to receive P-TP or no P-TP. Randomisation will be performed by a member of the study team using the randomisation module built into the EDC system. The randomisation module (and randomisation schedule) will be created in advance of patient recruitment by an independent statistician. Neither the trial manager nor study team member using the EDC randomisation module will be aware of the next treatment allocation. Patients will be randomised in blocks according to site of enrolment, treatment intent (curative or palliative) and cancer diagnosis (lung or gastrointestinal cancer).

P-TP should commence as soon as possible (within three days) after randomisation and continue to at least three months, or at until cancer therapy cessation, to a maximum of six months.

7.4 Sequential TE risk assessment (fibrinogen and d-dimer)

The investigator will perform real-time risk assessment according to the prescribed algorithm.

All patients will be assessed for TE risk at baseline and month one after commencement of cancer therapy. The timing of assessments should be adjusted to coincide with routine blood monitoring for cancer therapy (see visit window in schedule of assessments, **Table 1**).

Low risk patients may be upgraded to high TE risk by on-treatment assessment at month one. At this time, patients with randomised to enoxaparin P-TP or no P-TP (1:1). P-TP should commence as soon as feasible with prescription order from the investigator, trial management approval is not required.

High risk patients cannot be down-graded based on subsequent TE risk assessments.

Fibrinogen and d-dimer will be assessed at month 6 for research purposes, however results will not be used to inform risk assessment or guide treatment.

The following blood exams must be completed to perform sequential safety and TE risk assessments:

- Haematology
- Biochemistry
- Fibrinogen and d-dimer

7.5 Trigger for new TE risk assessment

This study includes a trigger for TE re-assessment to account for participants in the observation arm (low TE risk) who then receive subsequent lines of anticancer therapy during the study period. This would allow re-assessment of TE risk (new baseline and month 1 assessments) and then if high risk the participant would enter randomisation as shown in Figure 1.

Eligibility for reassessment: Participants classified at low risk that, as part of standard care cancer management, are identified to have recurrence/progression of their cancer during the trial observation period and are planned to commence a new line of anticancer therapy.

7.6 Research Samples –

This test is optional and will only be collected for patients at Peter MacCallum Cancer Centre that have provided additional consent to collection of research samples.

Correlative biomarkers will be taken longitudinally over the course of the trial (per **Table 1**). These tests will provide additional information clotting potential and the interplay between the cancer and the coagulation system. Tests will include: overall haemostasis potential, global coagulation assays and thromboelastography.

7.7 TE assessment

At each study visit, and unscheduled visits triggered by patient reported symptoms of TE, participants will be assessed for clinical symptoms of TE. If TE is suspected by the treating clinician appropriate diagnostic investigations shall be performed (see section 4.2 for accepted objective assessments). Patients will be assessed for clinically overt (new onset or acute progression) signs and symptoms suggestive of TE including: limb swelling, limb bruising/discolouration, limp pain/tenderness, shortness of breath, chest pain, or any other symptoms identified by the treating clinician. Routine imaging for detection of TE will NOT be performed in the absence of clinical symptoms.

7.8 Anticancer treatment

Anticancer treatment and response assessment is directed by the treating clinician.

7.9 Patient reported outcomes

Surveys will be administered via secure email through the EDC system or on paper if the participant prefers.

Quality of life: Patient response to SF12v2 quality of life survey, among all patients, at enrolment, month 6 and month 12 after commencement of anticancer therapy. This survey is being conducted to support economic analyses (quality adjusted life years - QALY), not to evaluate or describe lung / gastrointestinal cancer symptoms.

Anti-clot treatment: Patient response to Anti-Clot Treatment Scale (ACTS), among patients randomised to P-TP, at months one and three, and if applicable at month six after commencement of anticancer therapy.

Table 1: Schedule of study assessments

Protocol activity	**Screening**		**Treatment**						**Follow-up**	
	Eligibility criteria and enrolment	TE risk assessment and randomisation	P-TP start *intervention cohort only	Cancer therapy start	Anticancer therapy +/- P-TP				Unscheduled visit (TE, bleeding or other reportable AE)	Survival follow-up after study completion
Activity	**Day**		**Day**		**Month**				**Month**	**Year**
	-28 to -1	-28 to -1	Within 3 days randomisation and prior to start cancer therapy	0	1 ±10d	3 ±14d	6 ±30d	12 ±30d	Any time to month 6	Yearly [k]
Informed consent	X									
Demographics, medical, TE, & disease history	X									
Height and Weight	X									
ECOG performance status	X									
Haematology [a]		X			X		X			
Biochemistry [a, b]		X			X		X			
Fibrinogen & D-dimer [a]		X			X		X			
Research sample [a, c]		X			X		X			
Randomisation [d]		X			X[e]					
Start / Stop P-TP [f]			X			X	X			
CT Scan	As clinically indicated									
Response assessment [g]	At time of CT									
Anticancer and antithrombotic concomitant medications [h]	X				X	X	X	X	X	
TE symptoms	X				X	X	X	X	X	
Events (TE, bleeding, non-bleeding event related to anticoagulation)	X				X	X	X	X	X	
Survival / disease status	X				X	X	X	X		X
Patient reported outcomes, quality of life (SF-12.v2.0)	X						X	X		
Patient reported outcomes, anti-clot treatment (ACTS) [j]					X	X	X			

a) See table 2 for blood test parameters

b) Creatinine clearance to be derived using the Cockcroft-Gault formula or may be measured by 24 hour urine collection or nuclear medicine assessment as clinically indicated
c) Optional sample for consenting patients at Peter MacCallum Cancer Centre only
d) Randomisation of high risk patients to P-TP or no P-TP.
e) Randomisation of patients upgraded from low TE risk to high TE risk based on month one TE risk assessment
f) P-TP to continue to at least 3 months, or at until anticancer therapy cessation, to a maximum of 6 months.
g) RECIST 1.1
h) Only anticancer therapies, anticoagulants and/or antiplatelet, any agent used for the management of TE
i) Bleeding adverse events monitored to 7 days post cessation of P-TP
j) Anti-Clot Treatment Scale for patients receiving P-TP only, to complete month 6 survey only if received enoxaparin within the last 4 weeks.
k) Yearly survival and disease status follow-up until 24 months after the last patient is enrolled; may be completed by phone by a member of the research team.

Table 2: Blood test parameters

Test Category	Tube	Volume	Tests requested
Haematology	EDTA (pink)	3mL	White cell count, neutrophil count, lymphocyte count, haemoglobin, and platelets
Biochemistry	Serum gel tube (gold)	5mL	Sodium, potassium, chloride, creatinine, bicarbonate, urea, calcium, magnesium, phosphate, total protein, albumin, bilirubin, GGT, ALP, AST, ALT
Coagulation	Citrate (blue)	3mL	Fibrinogen and D-dimer
Research Sample (optional test for Peter Mac site only)	Citrate large (green) Citrate (blue)	10mL 4mL	5 x 2mL samples aliquoted for testing of overall haemostasis potential, global coagulation assays For thromboelastograph, **tube not to be spun.**

8. RESPONSE ASSESSMENT

Tumour response will be assessed on computed tomography (CT) conducted as part of routine care. Specific study response assessments will not be performed.

Disease response will be recorded as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) determined using the local investigator's assessment based on RECIST 1.1 criteria,[13] but without formal requirement for target lesion assessment.

Date of first response (PR or CR) and date of progression (PD) will be recorded to determine duration of response, and progression free survival.

Response will be captured until documentation of disease progression or initiation of additional anticancer treatment.

9. POTENTIAL RISKS AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS

There are potential risks associated with the delivery of preventative doses of anticoagulation as part of the interventional P-TP regimen, and to a greater extent, associated with therapeutic dose anticoagulation given for the treatment of thromboembolism. These are discussed and guidelines for management are provided below.

All thrombohaemorrhagic events will be recorded as part of study outcomes (with record made of diagnosis, treatment, worst grade experienced and relatedness to either study related procedures or TE).

Anticancer therapy related events will not be reported.

9.1 Thromboembolism

Any clinically suspected TE event should be confirmed objectively as defined in protocol section 4.2 (study endpoints). Management will be according to clinician discretion and hospital guidelines. Patients will remain on study after a TE and their anticoagulant medication documented. The PICF will advise specifically about possible symptoms/signs of TE.

9.2 Major bleeding and clinically relevant non-major (CRNM) bleeding

Bleeding events should be classified as major or CRNM as defined in protocol section 4.2 (study endpoints). Management will be according to clinician discretion and hospital guidelines. The PICF will advise specifically about the risk of bleeding adverse events and management in the event of bleeding events.

9.3 Adverse event other than bleeding associated with study drug

Participants may experience adverse events other than bleeding associated with the study drug. Such events are not limited to but may include pain at injection site, mild and reversible reduction in platelet count, short term elevation of liver enzymes, damage or death to cells at the injection site (skin necrosis), or allergic reactions such as rash or anaphylaxis. Management of adverse events will be according to clinician discretion and hospital guidelines. Withdrawal of study drug

should be considered for events grade two or above, as outlined in protocol section 5.5 (criteria for cessation of study drug).

9.4 Anticancer therapy related adverse events

Anticancer therapy is given according to clinician direction and is not part of this study. Management of anticancer treatment related adverse events will be at the discretion of the treating clinician and events do not need to be reported as a safety event for this study.

10. ADVERSE EVENTS

10.1 Event Definitions

10.1.1. Adverse Event (AE)

Adverse Event (AE) has the meaning given in the Therapeutic Goods Administration document Access to unapproved therapeutic goods Clinical trials in Australia (October 2004), or replacement, and shall mean any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.2. Related Adverse Event

Related Adverse Event i.e. Adverse Drug Reaction (ADR) means there is a reasonable possibility according to the Sponsor that the product may have caused the event.

10.1.3. Serious Adverse Event (SAE)

Serious adverse event ("SAE") means any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

10.1.4. Unexpected Adverse Event (AE) / Unexpected Adverse Drug Reaction (ADR)

Unexpected Adverse Event (AE) / Unexpected Adverse Drug Reaction (ADR) means an adverse event or adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product or Product Information/Data Sheet for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

10.2 Attribution

Attribution of cause requires at least a reasonable possibility of a causal relationship between the event and the use of the investigational drug or any other protocol-specified intervention.

All protocol-specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
UNRELATED	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
RELATED	Possible	The AE *may be related* to the intervention
	Probable	The AE is *likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

10.3 Severity Criteria

An assessment of severity grade will be made using the CTCAE (version 5.0). Where parameters are not addressed within the criteria, severity of AEs should be graded as:

Mild	Aware of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activities
Severe	Incapacitating with inability to work or perform usual activities
Life-threatening	Patient is at *immediate risk of death*
Fatal	Death

10.4 Adverse Event Reporting

All reportable adverse events, which occur whilst the patient is enrolled on the trial, must be reported in the patients' medical records and recorded on the relevant EDC.

For this study the following events should be reported:

- Thromboembolism and sequelae
- Bleeding and sequelae
- Any adverse event associated with anticoagulant therapy

For this study the following events should **NOT** be reported:

- Adverse events, including SAE, associated with cancer or anticancer treatment

10.4.1. Serious Adverse Event Reporting

10.4.1.1. Trial Sites/Investigators

All reportable SAEs that occur from the time a patient has signed consent for the trial to 30 days after the final protocol-specified treatment, intervention or procedure are required to be reported within 24 hours of being first made aware of the event to the Sponsor whether or not considered related to the treatment under investigation.

The investigator must:

- Determine whether an AE is 'Serious' (refer to Serious Adverse Event Definition)
- For SAEs, the investigator must then ascertain the suspected cause
- The attribution to the SAE must be recorded in the patients' medical records and reported on the SAE form.
- Both expected and unexpected serious adverse events and serious adverse drug reactions must be recorded in the patients' medical records.
- SAEs must be reported by completing the trial SAE form and emailing the completed form and any relevant safety information to the sponsor:

Send to	Contact Method
Drug Safety Associate	Email: safetyreporting@petermac.org Tel: 03 8559 7364

SAE forms are required at following points:

Initial Report	Within one working day/24 hours of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided in the comments section of the SAE form.
Incomplete Reports	If all details are not available at the time of the initial report a completed report must be sent within the next 10 days.
Updated Report	If the event is not resolved (or 'on-going') at the time of the initial report, the SAE Form must be submitted every 30 days until the event is resolved, death has occurred or the condition has stabilised. If a change occurs in a stable condition (i.e. either worsens or improves), then a new SAE Form should be submitted.

The Investigator is ultimately responsible for reporting the SAE and must sign the final SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24-hour period, a comment to this effect must be written on the form and the form signed by the clinician attending to the patient at the time and emailed to the Sponsor. The investigator must sign the SAE form as soon as possible and email the Sponsor.

The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and or Research Governance Office (RGO) subsequently notifying the HREC/RGO of SAEs as required.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

10.4.1.2. Severity Assessment

If required on the AE case report Forms, the investigator will use the following definitions of severity in accordance with the NCI CTCAE version 5.0 to describe the maximum intensity of the AE.

- GRADE Clinical Description of Severity
- No change from normal or reference range
- Mild Adverse Event
- Moderate Adverse Event
- Severe Adverse Event
- Life-threatening or Disabling Adverse Event
- Death related to Adverse Event

Note that a severe event is not necessarily the same as a serious adverse event.

10.4.1.3. Causality Assessment

All protocol specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Unrelated
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

10.4.1.4. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events reported by the trial patient. In addition, each trial participant will be questioned about adverse events.

10.4.1.5. Sponsor Reporting Requirements

1. The Sponsor warrants the trial will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

2. The Sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.

3. The Sponsor shall be responsible for ensuring submission of required expedited and periodic reports to the appropriate Regulatory Authority (RA), the Sponsor's Ethics Committee and Investigators.

11.DATA ANALYSIS AND STATISTICAL METHODS

11.1 Sample size and precision of estimates

Sample size calculations are based on TE event rates observed in supporting local studies and international published data. This study will be powered to show a significant difference in TE event rates for patients randomised to P-TP versus no TP. With a two sided significance level of 0.05 and 80% power, 20% TE rate with no TP, and 5% TE rate with P-TP, we must enrol 176 high TE risk patients, with 88 patients in each the intervention and control arms (1:1 randomisation). To achieve this, based on an expected 60-70% 'high risk' classification rate we would enrol a total 252-294 patients. To allow for patient drop-out we aim to randomise 100 patients to P-TP.

Table 3 - Sample size requirements to demonstrate a statistically significant difference in TE event rates between randomisation cohorts.

TE rate, high TE risk no TP	TE rate, high TE risk e-TP	Sample size, high TE risk *randomisation cohort*	Total patients enrolled, if 70% high TE risk	Total patients enrolled, if 60% high TE risk
25%	10%	226	323	377
25%	5%	118	169	197
20%	5%	176	251	293
15%	5%	320	457	533
20%	10%	438	626	730

*sample sizes calculated using www.openepi.com based on formula from Kelsey et al., Methods in Observational Epidemiology 2nd Edition

Published data for TE rates without P-TP – 25% TE rate among 'high risk' lung cancer in Peter Mac BIOTEL prospective biomarker study (n=117);[in press] 14% TE rate all ambulatory lung cancer patients (not stratified by risk) USA cohort study (n=6732);[14] 19% TE rate all ambulatory pancreatic cancer patients (not stratified by risk) USA cohort study (n=1336);[14] 16% TE rate all ambulatory upper gastrointestinal cancer patients (not stratified by risk) USA cohort study (n=787);[14] 11% TE rate all ambulatory lower gastrointestinal cancer patients (not stratified by risk) USA cohort study (n=4548).[14]

Published data for TE rates with P-TP – 5% TE rate among ambulatory lung cancer patients receiving P-TP in FRAGMATIC RCT (n>2000);[15] 4.5% TE rate among ambulatory lung cancer patients receiving P-TP in TOPIC-2 RCT (n=268);[16] 1.2% TE rate among ambulatory cancer patients receiving P-TP in SAVE-ONCO RCT (n=1608);[17] 2% TE rate among ambulatory cancer patients receiving P-TP in PROTECHT RCT (n=1608).[18]

11.2 Timing of analyses

11.2.1 *Reports for the Data Safety Monitoring Board (DSMB)*

There will be safety reviews prepared by the trial manager for the DSMB yearly during accrual, summarising thrombohaemorrhagic events. The first safety review will occur six months after enrolment of the first patient on study.

11.2.2 Analysis of six *month outcomes*

Analysis will occur once all patients have had six months follow up (or withdrawn from study follow up). This analysis will report all patient baseline characteristics, treatment details and primary and secondary endpoint data collected up to that time point.

11.2.3 Analysis of 12 month outcomes

Analysis will occur once all patients have had 12 months follow up (or withdrawn from study follow up). This analysis will report all patient baseline characteristics, treatment details and primary and secondary endpoint data collected up to that time point.

11.2.4 Final Analysis

The final analysis will occur once all patients have had 24 months follow up (or withdrawn from study follow up). This analysis will update any analyses reported in the main analysis where additional data has been reported. The report will include analyses relating to the exploratory objectives.

11.3 Statistical methods

Prior to analysis of TE and bleeding events an independent medical review panel - the Clinical Event Committee (CEC) - will be formed and tasked with evaluating and adjudicating on reported TE and bleeding events. During this process the committee will be blinded to the participant and the treatment assignment. The CEC may include study investigators but only where blinding can be maintained (i.e. clinician may evaluate events from patients outside of their trial centre).

For the main trial outcomes related to TE and bleeding events (10.4.1-10.4.3), exploratory analysis of the cumulative incidence of TE and bleeding according to cancer type, stage, and anticancer therapy, will be undertaken by inclusion of these factors in multivariable cause specific Cox proportional hazards models. All endpoints related to TE and bleeding will be independently analysed by a second statistician.

11.3.1 Analysis of TE incidence (primary objective)

TE incidence rates will be presented as absolute number of events divided by person-time (years). Participant follow-up (person-years at risk) will be counted from date of study enrolment until the date of the first occurring event: TE, death, loss to follow-up, or study end (24 months after the enrolment of the last patient). For cause-specific time to event analyses, participants who do not experience the event of interest will be treated as censored at the end of follow-up. Cox proportional hazards models will be used for cause-specific analyses and will include an indicator variable for whether participants were randomised to enoxaparin P-TP vs. no P-TP. The cumulative incidence functions (CIF) for TE will be used to estimate TE incidence at 6 months for randomised study arms, noting that the CIF depends on the cause-specific hazards of both TE and the competing event, death.

11.3.2 Analysis of bleeding events (secondary objective 1)

As for TE, the risk of bleeding, according to definitions in section 4.2 and in separate analyses for major, CRNM, and major or CRNM bleeding, for high TE risk patients randomised to enoxaparin P-TP vs. no P-TP will be assessed using univariable case-specific Cox proportional hazards regression models with the randomisation arm comparison reported as a hazard ratio (HR). Corresponding cumulative incidence functions (death as competing risk) will be used to describe risk.

11.3.3 Analysis of adverse events other than bleeding (secondary objective 2)

Adverse events other than bleeding, probably or definitely related to the study drug, will be reported. Events will be categorised and graded according to CTCAEv5.0.

11.3.4 Performance of TE risk assessment model (secondary objective 3)

Among patients not receiving P-TP, sensitivity and specificity of the TE risk-assessment model will be assessed by cause-specific analyses. Sensitivity is defined as the number of TE-positive patients classified as high risk, as a proportion of all TE-positive patients. Specificity is defined as the number of TE-negative patients classified as low risk, as a proportion of all TE-negative patients. For analyses, risk status will be based on classification at month one, at which time final risk status is known for all patients. Analysis will occur after month 6, the specified time period for primary assessment of TE events.

11.3.5 Analysis of response to anticancer therapies, overall survival and progression free survival (secondary objective 4)

Duration of best overall response (OR), progression free survival (PFS), and overall survival (OS) will be assessed by Kaplan-Meier methods, with a close-out date applied. The close out date will generally be taken to be the earliest of the dates of last contact, at which the assessments relevant to the identification of the events were made, of the patients who are still alive and being followed up. Thus, with the exception of any patients who have been lost to follow-up, the status of all patients in the trial, regarding the events of interest, should be known at this date. OR, PFS, and OS will be assessed for all participants, according to treatment allocation, and according to TE incidence.

OR, PFS and OS will be analysed using previously described methods for Cox proportional hazards regression. Multivariable analysis will include the following variables TE, bleeding, cancer type, stage, and anticancer therapy.

11.3.6 Analysis of patient reported outcomes data (secondary objective 5)

Patient reported outcomes will be described using appropriate statistical summaries including frequency / percentage counts and median and range of scores / rating scales.

11.3.7 Analysis of health resource utilisation costs (secondary objective 6)

Taking a health system perspective, we will measure and value costs associated with health-care resource utilisation for all study patients. A modelled cost analysis comparing resource utilisation for patients with TE-related events against those without TE-related events will be conducted using hospital administrative data. The following cost parameters have been identified for measurement:

- Component costs (medical, nursing, pharmacy, imaging, pathology, hotel, allied health and non-clinical salaries, operating rooms and specialist procedure suites) associated with diagnosis-related group (DRG) and length of hospital stay, including hospital-in-the-home. Drug costs include preventative dose anticoagulation for the prevention of TE and therapeutic dose anticoagulation for the treatment of TE.
- Intensive Care Unit (ICU) stay valued by critical care component cost by DRG and length of ICU stay.
- Use of mechanical ventilation
- Readmission(s) associated with TE-related complication
- Outpatient clinic visits valued by Australian Medicare Benefits Schedule (MBS)
- Complications of the TE
- Additional radiology necessitated (CTs, Doppler) as valued by MBS.
- Additional pathology tests e.g. FBE, coagulation screen as valued by MBS cost.
- Medical treatment (with enoxaparin according to standard hospital protocol), [36] with pharmaceutical costs valued according to Health Purchasing Victoria (HPV) Contract.
- Costs associated with complications arising from iatrogenic causes of TE-management including bleeding and concomitant medication to minimise bleeding risk.

The costs captured in this study are likely to be skewed and so in analysing this data, non-parametric methods will be used. All costs will be expressed in real terms and future costs discounted at 5% in line with standard Australian economic evaluation guidelines. Robustness of the costing data will be tested through sensitivity analyses, with the main variables being cost of hospitalisation, incidence of TE-events and complications post-study, and other drivers of cost as determined through the study.

12. QUALITY CONTRAL AND QUALITY ASSURANCE

During this trial, the Sponsor may conduct periodic monitoring visits as per Peter Mac policy, to ensure that the protocol and GCP are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigators will permit monitors and appropriate regulatory agents direct access to source documents to perform this verification. The

site may also be subject to review by the HREC committee and/or to inspection by appropriate regulatory authorities.

13. DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

All trial data required for the monitoring and analysis of the study will be recorded electronically on the electronic data capture platform. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. Site investigators will be asked to confirm the accuracy of completed eCRFs by signing key eCRFs as indicated.

13.2 Record Retention

To enable monitoring, audits and inspections from regulatory authorities, the investigator and study team will keep records, including:

- The identity of all participating patients
- All original signed consent forms
- Copies of all CRFs
- Safety reporting forms
- Source documents
- Records of treatment
- Correspondence

All records should be retained by the Investigator as per GCP requirements.

14. ETHICS

14.1 Human Research Ethics Committee (HREC)

It is the responsibility of the Investigator to ensure HREC approval is in place for the trial protocol, protocol amendments, informed consent documents and any other relevant study documents. All correspondence with the HREC must be maintained in the site file. The only circumstance in which an amendment can be implemented prior to HREC approval is to eliminate any immediate safety concerns to the patient. In this situation, the investigator must notify the HREC in writing immediately after the event.

14.2 Ethical Conduct of the Trial

The study will be conducted in accordance with legal and regulatory requirements, as well as the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

14.3 Patient Information and Consent

The investigator and study team will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports or publications except where required by law. The informed consent documents must be in compliance with GCP, local regulatory requirements and legal requirements. All informed consent documents must be approved by the HREC before use.

Information and consent forms may be issued by a member of the study team on the directive of the study investigator. Participants will be given appropriate time to consider participation and discuss participation with a study investigator. In most instances participants will be given several days to consider participation. In some rare instances, where delays to initiating anticancer treatment (corresponding with start of trial), are considered detrimental to the patient and the primary treating clinician prescribes immediate (same or next day) initiation, the time period for review of trial information may be lessened. In these rare scenarios, the patient would be given at least two hours to independently consider participation.

The investigator will ensure that each study patient or their legally acceptable representative is fully informed about the study and its objectives and risks. The investigator or their designee will obtain written informed consent from each patient or their legally acceptable representative before any protocol-specific activity it performed. The original signed consent form will be retained by the investigator.

At any stage during the study participants have the opportunity to review and confirm (or withdraw) their consent for this study.

15. DATA SAFETY MONITORING BOARD

The statistician / data manager will prepare reports for the DSMB, as stated in section 11.3.1. The DSMB will operate as specified by the Sponsor (Peter MacCallum Cancer Centre) safety and monitoring guidelines.

The DSMB will include members from (or affiliated with) the same institution as the sponsor or investigator, but who are not part of the trial team.

16. DEFINITION OF END OF TRIAL

End of trial is defined as the time at which sufficient patients have been recruited and completed the trial as specified in the protocol and the study statistical report has been completed.

17. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of regulatory authority decision, change in the opinion of the HREC, medication safety problems or at the discretion of the Sponsor and/or Investigator and/or DSMB.

If the trial is prematurely terminated or discontinued, the Investigator will promptly contact all patients and will be responsible for ensuring ongoing clinical care.

18. PUBLICATION OF TRIAL RESULTS

This trial will be published in accordance with the Peter MacCallum Cancer Centre Policies and Procedures Manual, Volume 3, Research Management: Authorship and Publication (February 2002).

19. APPENDIX 1 – RECIST 1.1 CRITERIA – RESPONE EVALUATION CRITERIA IN SOLID TUMOURS

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
- Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases 'unequivocal progression' of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases'.

RECIST 1.1 Response Criteria	Target lesions	Non-target lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as *reference the baseline sum diameters*	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as *reference the smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

	absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.	
Stable Disease (SD)		Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as *reference the smallest sum diameters while on study.*

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should ideally be confirmed later on by the review panel (or Study Chair).

20. APPENDIX 2 – CONTRAINDICATIONS TO ANTICOAGULANT THERAPY

Patients with **any** of the following contraindications to anticoagulation and/or specifically LMWH will be excluded from participation in this study:

- Allergy to enoxaparin, heparin or its derivatives including other LMWH
- Past history of heparin induced thrombocytopenia (HIT)
- Thrombocytopenia, defend as baseline platelet count $<30 \times 10^9/L$
- Severe hepatic impairment or disease, including oesophageal varices
- Active bleeding
- Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis)
- Acute bacterial endocarditis

21. APPENDIX 3 – ANTI-CLOT TREATMENT SCALE

We are interested in your experiences of anti-clot treatment. We would be grateful if you could help us by filling out this questionnaire. The questions below ask about your experiences of anti-clot treatment during the past 4 weeks. All of the information you provide is COMPLETELY CONFIDENTIAL. Please be sure to answer all questions.

INSTRUCTIONS: We are interested in your experiences of anti-clot treatment during the past 4 weeks. Please circle the number in the box that best describes your views.

During the past 4 weeks...	**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in vigorous physical activities (e.g. exercise, sports, dancing, etc.)?	1	2	3	4	5
2. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in your usual activities (e.g. work, shopping, housework etc.)?	1	2	3	4	5
3. How bothered are you by the possibility of bruising as a result of your anti-clot treatment?	1	2	3	4	5
4. How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of your anti-clot treatment?	1	2	3	4	5
5. How much does your anti-clot treatment limit what you eat and drink (including alcohol)?	1	2	3	4	5
6. How much of a hassle (inconvenience) are the daily aspects of your anti-clot treatment (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, limiting what you eat and drink (including alcohol), etc.)?	1	2	3	4	5
7. How much of a hassle (inconvenience) are the occasional aspects of your anti-clot treatment (e.g. the need for blood tests, going to or contacting the hospital/doctor, making arrangements for treatment while travelling etc.)?	1	2	3	4	5

Now I want to ask you about daily and occasional aspects of your anti-clot treatment during the past 4 weeks…

	Not at all	A little	Moderately	Quite a bit	Extremely
8. How difficult is it to follow your anti-clot treatment?	1	2	3	4	5
9. How time-consuming is your anti-clot treatment?	1	2	3	4	5
10. How much do you worry about your anti-clot treatment?	1	2	3	4	5
11. How frustrating is your anti-clot treatment?	1	2	3	4	5
12. How much of a burden is your anti-clot treatment?	1	2	3	4	5
13. **Overall**, how much of a negative impact has your anti-clot treatment had on your life?	1	2	3	4	5
14. How confident are you that your anti-clot treatment will protect your health (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)?	1	2	3	4	5
15. How reassured do you feel because of your anti-clot treatment?	1	2	3	4	5
16. How satisfied are you with your anti-clot treatment?	1	2	3	4	5
17. **Overall**, how much of a positive impact has your anti-clot treatment had on your life?	1	2	3	4	5

THANK YOU FOR YOUR HELP

22. APPENDIX 4 – QUALITY OF LIFE SURVEY

SF-12v2.0 Health Survey This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer**. If you are unsure how to answer a question, please give the best answer you can.

1. **In general, would you say your health is**:

☐1 Excellent ☐2 Very good ☐3 Good ☐4 Fair ☐5 Poor

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	YES, limited a lot	**YES, limited a little**	**NO, not limited at all**
2. **Moderate activities** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐1	☐2	☐3
3. Climbing **several** flights of stairs.	☐1	☐2	☐3

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	YES	**NO**
4. **Accomplished less** than you would like.	☐1	☐2
5. Were limited in the **kind** of work or other activities.	☐1	☐2

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	YES	**NO**
6. **Accomplished less** than you would like.	☐1	☐2
7. Did work or activities **less carefully than usual**.	☐1	☐2

8. **During the <u>past 4 weeks</u>, how much <u>did pain interfere</u> with your normal work (including work outside the home and housework)?**

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

These questions are about how you have been feeling during the <u>past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
10. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
11. Have you felt down-hearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6

12. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

☐1 All of the time ☐2 Most of the time ☐3 Some of the time ☐4 A little of the time ☐5 None of the time

Patient name:	Date:		
Visit type (circle one)	Enrollment	6 Month	12 month

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Targeted thromboprophylaxis in ambulatory patients receiving anticancer therapies for lung or gastrointestinal cancers: an investigator-initiated, open-label, multicentre, randomised, phase 3 trial (TARGET-TP)

Short Title: Target-TP

Protocol Number: TargetTP-3.0

Version 3.0 dated 02 July 2019

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Abbreviations

AE	Adverse event
ATE	Arterial thromboembolism
CEC	Clinical Events Committee – panel of independent experts that conducts central review of trial endpoints in a blinded and unbiased manner, ascertaining whether they meet protocol definitions.
CI	Confidence interval
CT	Computed tomography
DSMB	Data and Safety Monitoring Board – multidisciplinary group established to review accumulating trial data in order to monitor progress of the trial and comprising of members who may be from (or affiliated with) the same institution as the sponsor or investigator but are not part of the trial team.
DVT	Deep vein thrombosis
ECOG	Eastern cooperative oncology group
EOS	End of Study
GI	Gastrointestinal
HIT	heparin induced thrombocytopenia
HR	Hazard Ratio
LMWH	Low molecular weight heparin
LNL	Lower normal limit
NCI CTCAE v4.03	US National Cancer Institute Common Terminology Criteria for adverse events, version 4.03
NNT	Number needed to treat
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PE	Pulmonary embolism
PICF	Patient Information and Consent Form
PFS	Progression free survival
PRO	Patient reported outcomes
P-TP	Pharmacologic thromboprophylaxis
QoL	Quality of Life
RECIST v1.1	Response evaluation criteria in solid tumours version 1.1
SCLC	Small cell lung cancer
TE	Thromboembolism
TP	Thromboprophylaxis
UNL	Upper normal limit
VTE	Venous thromboembolism

Document History

Document	Version Date	Summary of changes and rationale
Amendment 3	02 July 2019	Synopsis: update number of sits, increase from 5 to 6 with participating sites including: Peter MacCallum Cancer Centre Bendigo Health, Border Medical Oncology, Goulburn Valley Health, Ballarat Health Care Group and Kerang District Health. 5.2 treatment commencement and duration: Greater detail to guide commencement of P-TP for high-risk patients in the intervention cohort. Clarified preference for commencement as soon as feasible post randomisation but with flexibility for discretion so long as commences prior to or on day 1 of cancer therapy where additive insult of treatment associated TE risk begins. 5.2 treatment commencement and duration: Clarification of PTP duration for patients receiving systemic therapy for greater than 3 months duration. For systemic regimens of 3-6 months (i.e. 4 months curative chemoradiotherapy), it is recommended P-TP continue to end of treatment. This is based on rationale that while the highest TE risk period is within the first 3 months, for patients on curative protocols with defined end dates shorter than 6 months, it is recommended to continue to end of treatment for full risk mitigation. The most common scenario is this cohort will be curative intent chemoradiotherapy lung cancer protocols (i.e. 6 cycles carboplatin/paclitaxel plus RT = 18 weeks) For systemic regimens of six months or longer (i.e. planned continuation until disease progression), P-TP may be ceased after three months if the patient is considered to have stable or responding disease, will continue the same regimen, has no newly identified TE risk factors. This is based on rationale that the highest risk period is in the first 3 months, and given stability of disease and new other new risk factors, TE risk will be largely mitigated and PTP can be stopped. The most common scenario in this cohort will be adjuvant GI protocols and palliative GI/lung protocols. Section 7.1 Trial visits: updated detail around ability for trial visits to occur via telehealth under tele-trial model. Update to detailed listing of sites involved now including: Peter MacCallum Cancer Centre Bendigo Health, Border Medical Oncology, Goulburn Valley Health, Ballarat Health and Kerang District Health. Section 7.4 randomisation: previously title ‘randomised and commencement of PTP’, updated to remove duplicates protocol

Document	Version Date	Summary of changes and rationale
		information relating to PTP commencement detailed in section 5.2. The previous requirement to start PTP within 3 days of randomisation has been updated in section 5.2 Section 7 study treatment plan: Table 1 has been updated to clarify that the 12-month visit also represents secondary follow-up (same as yearly visits) and may be conducted by phone given no requirement for on-site investigations. Appendix 4 quality of life survey: updated formatting to licenced PDF version (no change to content). Appendix 5 clot awareness survey: updated formatting to REDCap PDF version which includes version date (no change to content)

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1. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the NHMRC's *National Statement on Ethical Conduct of Research in Humans*, the TGA's *Clinical Trial Handbook*, Good Clinical Practice, the Sponsor's SOPs, and other regulatory requirements as amended.

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

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

For and on behalf of the Study Sponsor:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Principal Investigator 1:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Principal Investigator 2:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Principal Investigator 3:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

Study Statistician:

Signature: ..... Date: ...../...../.....

Name (please print): .....

Position: .....

2. PROTOCOL SYNOPSIS

Title	Targeted thromboprophylaxis in ambulatory patients receiving anticancer therapies for lung or gastrointestinal cancers: an investigator-initiated, open-label, multicentre, randomised, phase 3 trial (TARGET-TP)
Short Title	TARGET-TP
Sponsor	Peter MacCallum Cancer Centre
Indication	Ambulatory patients aged 18 years and over, receiving anticancer therapy (chemotherapy or immunotherapy +/- targeted therapy +/- radiotherapy) for the treatment of gastrointestinal or lung cancer, for whom there is no contraindication for pharmacologic thromboprophylaxis (P-TP), and who fulfil all of the other protocol-defined eligibility criteria.
No of sites	6
Study design	Open-label, multicentre, randomised, phase 3 trial to assess the efficacy and safety of enoxaparin P-TP among ambulatory patients with cancer at high risk of TE, receiving anticancer therapy. Approximately 300 patients with gastrointestinal or lung cancer will be assessed for TE risk, based on an established algorithm. According to the algorithm, TE risk will be assessed at baseline (prior to anticancer treatment) and one month after commencing anticancer treatment. Patients classified as high TE risk at baseline (target n=200) will be randomised to enoxaparin P-TP or no P-TP (1:1), in addition to their clinician-directed anticancer therapy. Patients classified as low risk at baseline (expected n=100) will commence anticancer treatment with no P-TP but will be re-assessed one month after commencing anticancer therapy with patients meeting defined risk thresholds upgraded to high TE risk and randomised (1:1) to enoxaparin P-TP for immediate initiation (estimated 10% of low risk cohort). Patients who remain low risk will continue with no P-TP and be monitored for the duration of the study period. The study will commence recruitment at a single site (Peter MacCallum Cancer Centre) in an initial phase, with additional sites planned to open in an expansion phase. It is expected that approximately 100 patients will be recruited in the initial phase, with 200 patients in the expansion phase. **Risk assessment**: High risk if receiving chemotherapy/immunotherapy and: (i) or (i) or (iii) (i) fibrinogen ≥4g/L + d-dimer ≥0.5mg/L at baseline, or (ii) d-dimer ≥1.5mg/L at baseline, or (iii) d-dimer ≥1.5mg/L at month one. Patients receiving single modality radiotherapy are eligible for enrolment but will be classified as low risk and enter the observation arm regardless of blood test results.

Background and study rationale	Appropriate P-TP can reduce TE rates in up to 80% of at-risk patients, but must be balanced against potential bleeding complications. Targeting patients and time points in their journey, that are high TE risk, while avoiding intervention in those at lowest risk, will optimise the risk-to-benefit ratio and result in greater TE risk reduction with demonstrable survival benefits. The TE risk assessment algorithm has been derived from prospective thrombogenic biomarker studies conducted at Peter MacCallum Cancer Centre. These studies sequentially assessed thromboembolic risk among patients with cancer (multiple myeloma, lung-, and gastrointestinal- cancer) using clinical parameters and thrombogenic biomarkers. The model demonstrated greater potency and specificity in terms of risk stratification, than published models, predicting with regards to TE, NNT 4-6 vs. 15-25 in published risk assessment models and 30-60 in studies for non-targeted interventions. The model has predicted TE with 80-100% sensitivity in gastrointestinal and lung cancer cohorts, compared to sensitivty of 20-25% with application of existing risk models.
Aims and objectives	**Aim:** To assess the efficacy and safety of enoxaparin P-TP among high TE risk ambulatory patients with lung or gastrointestinal cancer, receiving anticancer therapy. **Primary Objectives** 1. To compare incidence of objectively confirmed TE at 6 months after randomisation, among high TE risk patients receiving enoxaparin P-TP versus no P-TP. **Secondary Objectives** 1. To compare incidence of major bleeding or clinically relevant non-major (CRNM) bleeding at 6 months after randomisation, among high TE risk patients receiving enoxaparin P-TP versus no P-TP. 2. To report incidence of adverse events other than bleeding, probably or definitely related to enoxaparin P-TP, from randomisation to two days after last dose of study drug. 3. To compare incidence of objectively confirmed TE at 6 months after enrolment, among high TE risk patients receiving no P-TP versus low TE risk patients receiving no P-TP (risk model sensitivity and specificity) 4. Overall response (OR) to anticancer therapies, Overall Survival (OS) and Progression Free Survival (PFS). 5. Patient reported outcomes related to QoL and P-TP 6. Healthcare resource utilisation costs related to P-TP and TE
Investigational product	7. The investigational product used in the study is enoxaparin (Clexane®), a low molecular weight heparin (LMWH) licenced for use in the prevention of venous TE in surgical patients and medical patients bedridden due to acute illness; not in at-risk ambulatory medical (or cancer) patients. Enoxaparin is the LMWH of choice at Peter MacCallum Cancer Centre.

Cohorts	Low TE risk, no P-TP (approximately 100 patients) High TE risk, randomised to enoxaparin P-TP in 1:1 (approximately 200 patients)
Duration of follow-up	Patients will be enrolled in the initiation phase (one site), with continued enrolled in the expansion phase (additional sites) until recruitment target reached. Patients will be followed for minimum 12 months for TE and thrombohaemorrhagic complications, and followed for minimum 24 months for survival outcomes. **Follow-up:** As per standard of care for anticancer treatment with study specific follow-up at months 1, 3, 6, 12, and then yearly until end of study (month 24 for the last enrolled patient). Unscheduled visits will occur at the time of TE or bleeding events.

3. BACKGROUND AND RATIONALE

3.1 Thromboembolism and Cancer

Despite availability of safe and efficacious antithrombotic agents, as well as our vast clinical experience justifying their use, cancer associated TE remains a frequent preventable complication with substantial adverse health and economic consequences.[1-3] It is a negative predictor of survival and leading cause of death, associated with extensive clot burden, post-thrombotic syndrome, higher (2-3 fold) clot recurrence rates, higher (2-6 fold) bleeding complications on anticoagulant therapy, catheter-related complications, increased hospitalisation and impaired quality of life.[4-6] An incident TE event, once a cancer has been diagnosed and treatment started, often denotes a significant clinical hurdle, not only related to the morbidity and mortality associated, but the potential detrimental effect of an interruption or modification in therapy attributable to the event and/or delivery of therapeutic anticoagulation. As such, risk-adapted primary P-TP can have a substantial impact not only on TE reduction, but also disease response, survival, quality of life and healthcare resources.

3.2 Thromboembolism Prevention

Risk stratification and predictive modeling tools are important enablers to facilitate targeted strategies and improve patient outcomes. Appropriate P-TP can reduce TE rates in up to 80% of at-risk patients,[7] but must be balanced against potential bleeding complications. Risk stratification can facilitate this by identifying patients at risk and duration of risk, allowing a personalised risk-directed approach, rather than the broad application in patients with cancer. Targeting patients and time points in their journey that are high TE risk, while avoiding intervention in those at lowest risk, will optimise the risk-to-benefit ratio and result in greater TE risk reduction with demonstrable survival benefits.

Despite continued efforts over more than a decade, current TE risk models [8, 9] lack the necessary precision (19-64% sensitivity) to adequately stratify patients. Moreover, there has been no definitive study to date, that has investigated the use of a relevant and potent risk prediction model, with directed management algorithms, to assess whether this approach can safely and effectively reduce rates of TE, the attributable morbidity and mortality, and improve overall outcomes of patients with cancer.

3.3 Risk assessment model development

At this institution, we have undertaken four studies in three disease groups (multiple myeloma, lung-, and gastrointestinal- cancer), to prospectively and sequentially assess TE risk profile of ambulatory cancer patients using clinical, therapeutic, and thrombogenic biomarkers. From these studies we have derived and cross-validated a TE risk assessment and P-TP guidance algorithm, which will be used for this study. Risk stratification considers cancer treatment and thrombogenic biomarker profile reflecting clot formation potential (fibrinogen and d-dimer). When applied to the gastrointestinal and lung cancer cohorts, the model had more potency, in terms of TE risk stratification, than those previously proposed, predicting NNT 4-6 vs. 15-25 in published studies using risk assessment models, and 30-45 in studies of non-targeted interventions.[10] Our model has predicted TE with 90-100% sensitivity in gastrointestinal and lung cancer cohorts, compared to sensitivty of 20-25% with application of the Khorana TE risk score.[9] Data for patients

treated with single modality radiotherapy is lacking, and while important to obtain prospective longitudinal thrombogenic biomarker profiles and correlative thrombohaemorrhagic clinical outcomes, there is currently insufficient data to support risk-directed therapy using the current model.

3.4 Safety Considerations

The risk of non-major but clinically relevant bleeding events is higher with LMWH P-TP compared to no P-TP (HR 3.40, 95%CI 1.20-9.63). In a 2016 Cochrane meta-analysis, 102 events were observed among 1543 patients receiving LMWH P-TP, compared to 37 events among 1562 patients receiving no P-TP.[7]

The risk of a major bleeding event for patients receiving LMWH P-TP is low. From the same 2016 Cochrane meta-analysis, a non-significant increased risk of major bleeding was observed for LMWH P-TP versus no P-TP (HR 1.44, 95%CI 0.98-2.11). This analysis included 3378 patients with LMWH P-TP (69 major bleeding events) and 2978 patients with no P-TP (44 major bleeding events).[7]

Differing from the application of P-TP in studies included in this meta-analysis, we will be targeting interventions only to patents at high TE risk, and therefore avoiding intervention and potential bleeding risks in patients at low risk of TE.

Among high TE risk patients, the significant risk of morbidity and mortality associated with TE that occurs in up to 25% of high risk patients, outweighs the small but real increased risk of bleeding complications. Furthermore, intervention will be limited to a short duration where TE risk is highest, minimising long term effects and potential bleeding complications.

3.5 Study Rationale

The described application of P-TP provides a highly targeted and promising prophylactic approach to address a clinically important unmet need, and provide a supportive care tool to improve outcomes for patients with gastrointestinal and lung cancers.

4. TRIAL AIM, OBJECTIVES AND ENDPOINTS

4.1 Aim

To assess the efficacy and safety of P-TP among high TE risk patients with gastrointestinal or lung cancer, receiving anticancer therapy.

4.2 Objectives and Endpoints

Primary Objective	**Endpoint**
Assess the efficacy of enoxaparin primary P-TP	• Objectively confirmed symptomatic or asymptomatic TE (DVT, PE, ATE) at 6 months after randomisation. DVT must be confirmed by ultrasonography, venography or magnetic resonance angiography (cerebral events). PE must be confirmed by spiral CT, CT pulmonary angiography (CTPA) or lung ventilation/perfusion scan. ATE must be

	confirmed by relevant radiologic imaging, or specifically for myocardial infarct (MI) must meet criteria outlined in the universal definition of MI considering biomarker changes, ischemic symptoms, ECG changes, cardiac imaging abnormalities, and cardiac death.[11] Superficial Vein Thrombosis (SVT) will not be considered a TE event, but will be documented if they occur. All TE events will be adjudicated by a committee unaware of randomisation (Clinical Event Committee – CEC).

Secondary Objectives	**Endpoints**
Assess the safety of enoxaparin primary P-TP	• Major bleeding, clinically relevant non-major (CRNM) bleeding, any bleeding (major or CRNM) at 6 months after randomisation, excluding patients on therapeutic anticoagulation. Major bleeding: *clinically* overt bleeding meeting at least one of the following criteria: fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.[12] Clinically overt was defined as new onset visible bleeding or signs and symptoms suggestive of bleeding which in the absence of visible bleeding were confirmed by relevant imaging techniques.[11] *CRNM bleeding:* bleeding not meeting criteria for major bleeding but that would be considered relevant and not trivial by a patient and physician.[11] All bleeding events will be adjudicated by a committee unaware of randomisation (Clinical Event Committee – CEC).
Assess the safety of enoxaparin primary P-TP	• Adverse event other than bleeding, probably or definitely related to the study drug, from randomisation to two days after the last dose of study drug.
Assess sensitivity and specificity of TE risk assessment tool	Among patients <u>not</u> receiving enoxaparin P-TP: • TE-positive patients classified as high risk, as a proportion of all TE-positive patients • TE-negative patients classified as low risk, as a proportion of all TE-negative patients Analysis will occur after month 6, the specified time period for primary assessment of TE events, using risk classification assigned at month 1.

Assess the overall response to anticancer therapies, overall survival, and progression free survival.	• Overall response (OR), defined as clinician reported best response to therapy [Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)]. • Duration of response, defined as the time from the date of first response of PR or better until the date of disease progression, for those patients who experience a PR or better (death is a censoring event), for those patients who experience a PR or better. • Progression free survival, defined as the time from registration on study to the earliest of date of disease progression or death. • Overall survival, defined as the time from registration on study to date of death.
Assess patient reported outcomes – quality of life and anti-clot treatment	• Patient quality of life survey (SF12 v2.0) for all patients at enrolment and six and twelve months after commencement of anticancer therapy. • Patient response to Anti-Clot Treatment Scale (ACTS), among patients randomised to P-TP at one and three months, and six if applicable, after commencement of anticancer therapy.
Assess healthcare resource utilisation costs directly associated with P-TP and TE	• Cost of P-TP, defined as unit cost of drug for duration of therapy, plus costs associated with P-TP related AE. • Cost of anticoagulation for treatment of TE, defined as unit cost of drug for duration of therapy, plus costs associated with TE event.

5. TRIAL DESIGN

This is a prospective, open-label, randomised controlled study designed to investigate the safety and efficacy of enoxaparin primary P-TP in adult ambulatory care patients with gastrointestinal or lung cancers, at high risk of TE.

Consenting patients presenting for the treatment of gastrointestinal or lung cancer (any line of therapy and including chemotherapy, radiotherapy, immunotherapy, and/or targeted therapy) will be screened for eligibility and, if found to fulfil the eligibility criteria, will be registered in the study.

All patients will undergo TE risk assessment and observational follow-up including sequential assessments of fibrinogen and d-dimer. Patients receiving chemotherapy and/or immunotherapy identified to be at high TE risk will proceed to randomisation for treatment with or without P-TP. Patients identified to be at low TE risk will be observed and then re-assessed one month after commencement of cancer therapy, and if fulfilling requirements for high TE risk, will be randomised to receive P-TP (1:1).

Patients receiving single modality radiotherapy are eligible for enrolment but will be classified as low risk and enter the observation arm regardless of blood test results.

The study will commence recruitment at a single site (Peter MacCallum Cancer Centre) in an initial phase, with up to two additional sites planned to open in an expansion phase. It is expected that approximately 100 patients will be recruited in the initial phase, with 200 patients in the expansion phase.

5.1 Treatment dosing

All high TE risk patients will be randomised to receive P-TP (1:1), as enoxaparin 40mg daily by subcutaneous injection unless meeting any of the below dose modification criteria:

- Creatinine Clearance <30mL/minute: enoxaparin 20mg daily
- Weight <50kg: enoxaparin 20mg daily
- Weight >120kg: enoxaparin 60mg daily
- Platelet count <30 $x10^9$/L: withhold

5.2 Treatment Commencement and Duration

For high TE risk patients randomised to the intervention cohort, P-TP will commence as soon as practical after completion of risk assessment and prior to commencing cancer therapy, and continue to at least three months, or at until cancer therapy cessation to a maximum of six months. For systemic regimens of 3-6 months (i.e. 4 months curative chemoradiotherapy), it is recommended P-TP continue to end of treatment. For systemic regimens of six months or longer or without end date (i.e. planned continuation until disease progression), P-TP may be ceased after three months if the patient is considered to have stable or responding disease, will continue the same regimen, has no newly identified TE risk factors.

For low TE risk patients escalated to high TE risk after on-treatment re-assessment at month one, P-TP will commence as soon as feasible and continue until cancer therapy cessation, to a maximum of six months.

Investigators may prescribe up to three months' supply of study drug (90 x enoxaparin single dose pre-filled syringes) as a single dispensing at the commencement of P-TP, with secondary supply quantity tailored to expected duration of anticancer therapy, not exceeding maximum six months of P-TP.

5.3 Study Duration

Patients will be enrolled over an anticipated period of 12 months and followed from the later date of enrolment or randomisation, for minimum 12 months for thrombohaemorrhagic outcomes and minimum 24 months for survival outcomes. End of study (EOS) is defined as 24 months after commencement of anticancer therapy for the last enrolled patient.

5.4 Patient Withdrawal from Study

Every effort within the bounds of safety and patient choice will be made to have each patient continue within the trial. However, patients may withdraw from the trial at any time and for any reason, without affecting their right for further standard treatment and without their care being affected in any way. The investigator has the right to withdraw a patient for any reason that is in the best interests of the patient, including concurrent illness.

A patient may be discontinued from the study for any of the following reasons:

- Patient withdrawal of consent
- Study termination by investigator
- Study termination by sponsor
- Death

5.5 Criteria for Cessation of Study Drug

P-TP will be permanently stopped for any of the following reasons:

- Development of a radiologically confirmed TE requiring full dose anticoagulation
- Any adverse event following which the responsible physician determines that P-TP should be stopped, including any haemorrhage (grade two or above) and haematoma (grade two or above), other adverse event attributable to drug (grade two or above) or if the physician feels that is in the best interest of the participant to stop
- The P-TP interval ended
- If the participant chose to stop

5.6 Criteria for Temporary Suspension of the study

Should a fatal bleeding event occur in a patient receiving P-TP at any time, or a major bleeding event that is solely attributed to P-TP, the study will be temporarily suspended to determine whether causality is attributed to P-TP and whether drug can safely be continued in other patients.

5.7 Criteria for Termination of the Study

The study can be terminated at any time by the Sponsor, the DSMB, TGA or the Ethics Committee (EC) for any reason. The Investigator may be informed of additional procedures to be followed in order to ensure adequate protection of patients.

6. PATIENT SELECTION

The study will enrol consecutive patients presenting for the treatment of gastrointestinal or lung cancer (any line of therapy) at participating trial centres, that meet all the following inclusion criteria and none of the exclusion criteria.

6.1 Inclusion criteria

All of the following must apply at the time of enrolment:

1. Patient is 18 years of age or older
2. Patient has a confirmed histological diagnosis of any gastrointestinal or lung cancer
3. Patient is newly diagnosed treatment-naïve or is previously treated with newly relapsed or progressive disease
4. Patient is being considered for, but has not commenced anticancer therapy including chemotherapy and/or radiotherapy and/or immunotherapy and/or targeted therapies, within neoadjuvant, adjuvant, curative, or palliative treatment settings.

5. Patient has expected life expectancy of at least six months, as estimated by their treating clinician
6. Patient has provided written confirmation of informed consent on participant information and consent form.

6.2 Exclusion criteria

Patients who meet **any** of the following criteria will be excluded from participation in this study:

1. Patients who have already commenced anticancer therapy
2. Patients with a clinical indication for therapeutic anticoagulation (antiplatelet agents such as clopidogrel and aspirin are permitted)
3. Patients with a contraindication to anticoagulation and/or specifically LMWH (Appendix 2)
4. Cancer diagnosis other than those specified in inclusion criteria.

6.3 Patient Registration Procedure

This is an open-label randomised study.

Eligible patients will be registered electronically using the online electronic data capture (EDC) system. Registration confirmation as well as allocation of a unique participant identification number for the will occur via the EDC.

Prior to patient registration, the investigator should ensure that all of the following requirements are met:

- The patient meets all inclusion criteria and none of the exclusion criteria apply
- The patient has signed and dated all applicable consent forms
- The eligibility checklist has been completed, signed and dated

Patients determined to be at high TE risk by baseline assessments will proceed to randomisation 1:1 for P-TP or no P-TP. Randomisation will be performed by within the EDC system with treatment allocation available to the site in real-time.

Patients upgraded from low TE risk to high TE risk at month one will be randomised at this time with 1:1 randomisation for P-TP or no P-TP. For patients randomised to P-TP, treatment should commence immediately with prescription order from the investigator, trial management approval is not required.

7. STUDY TREATMENT PLAN

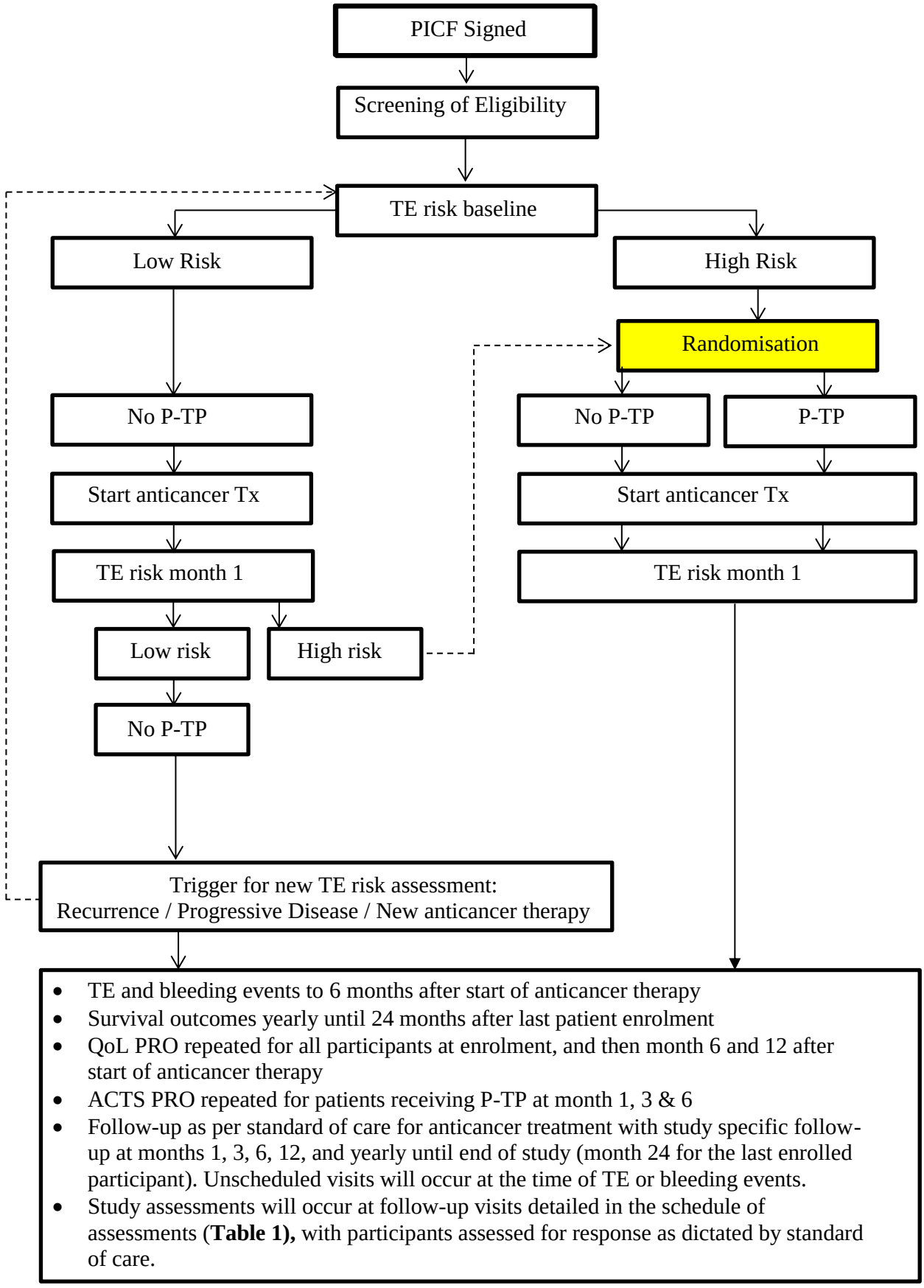

Figure 1 - Study treatment plan

7.1 Trial Visits

All trial visits must occur at an approved trial site. Sites may be approved as independent sites or as satellite sites under Peter Mac as part of the Tele-Trials model. Follow-up visit schedule is calculated based on time zero representing commencement of anticancer treatment (Table 1. Schedule of Study Assessments).

Patients enrolled at satellite sites under the Tele-Trials model may have some trial visits with trial doctors and coordinators at their enrolment site, but also via teleconference to trial doctors and coordinators at the primary site (Peter Mac). Where a trial visit is conducted by teleconference to Peter Mac, patient information will be recorded in a Peter Mac medical record as well as the patient's local hospital medical record. Patients will not be required to attend Peter Mac in person unless Peter Mac is their enrolment site.

The Tele-Trials model (patient care and delegation of responsibilities) will be conducted according to site specific Supervision Plan. The Supervision Plan and any amendments will be approved by the trial sponsor.

Primary site:
Peter MacCallum Cancer Centre

Satellite sites:
Border Medical Oncology
Bendigo Health Care Group
Goulburn Valley Health
Ballarat Health Services
Kerang District Health / Bendigo Health Care Group (joint satellite site)

7.2 Screening for eligibility criteria

Screening for the eligibility process begins when in the patient signs the IRB/IEC-approved consent form. The eligibility check-list must be signed and dated by the physician prior commencement of assessments and entered into the EDC system by the end of the next business day. Assessments, including blood tests, conducted prior to consent, as part of routine care, will be accepted so long as conforming to the schedule of assessments as detailed in **Table 1**.

The following assessments must be performed within 28 days of registration onto the study:

- Informed consent
- Demographics and identifiers
    - During screening potential trial participants will be identified by first and last initial and date of birth (DOB). For those meeting eligibility and enrolled into the study, identification will additionally include a study identification number (Study ID) which will be a chronological number automatically generated by REDCap. Enrolment site (hospital), sex, and ethnicity will also be recorded. Email addresses will be recorded for the purpose of survey distribution only, but will not

otherwise be reported and will be removed from all data-sets prior to analyses or report generation.
    - The following identifiers will not be recorded on any study forms or entered into the REDCap database, but will recorded at each site as a master log of trial participants linked to allocated study IDs: first name, surname, hospital URN. It will be the responsibility of the site PI to ensure security and confidentiality of this master identification log.

- Medical history including: disease diagnosis and history, prior anticancer therapy and risk factors of thromboembolism (personal history of TE, family history of TE, COPD / COAD, smoker (current or quit within 4 weeks), atrial fibrillation, structural heart disease, long haul travel (6 or more hours within 7 days), medical hospitalisation within past 4 weeks, surgical hospitalisation within past 4 weeks, oral contraceptive pill, hormone replacement therapy, other risk factor identified by treating clinician.
    - TE risk factors will be recorded as part of medical history but will not be taken into account for TE risk categorisation. Previously completed studies in lung and GI cancer found that assessment of fibrinogen and d-dimer alone afforded greatest sensitivity for prediction of future TE.
- Review of prior/concomitant medications
- Assessment of eligibility criteria
- ECOG performance status assessment
- Height, weight, and body mass index (BMI)
- Blood exams (haematology, biochemistry, fibrinogen and d-dimer)
- Creatinine Clearance calculation
- Clot awareness survey (Appendix 5)

7.3 Baseline TE risk assessment

The following blood exams must be completed to perform TE risk assessment and safety of potential P-TP administration:

- Haematology
- Biochemistry
- Fibrinogen and d-dimer.

The investigator will perform real-time risk assessment as described below and as depicted in Figure 2 – Algorithm for TE Risk Assessment.

Baseline TE risk assessment for patients receiving chemotherapy and/or immunotherapy:
High risk: fibrinogen ≥4g/L + d-dimer ≥0.5mg/L, or d-dimer ≥1.5mg/L
Low risk: fibrinogen <4g/L or d-dimer <0.5mg/L and d-dimer <1.5mg/L

Month 1 TE risk assessment, for low risk patients only
High risk: d-dimer ≥1.5mg/L
Low risk: d-dimer <1.5mg/L

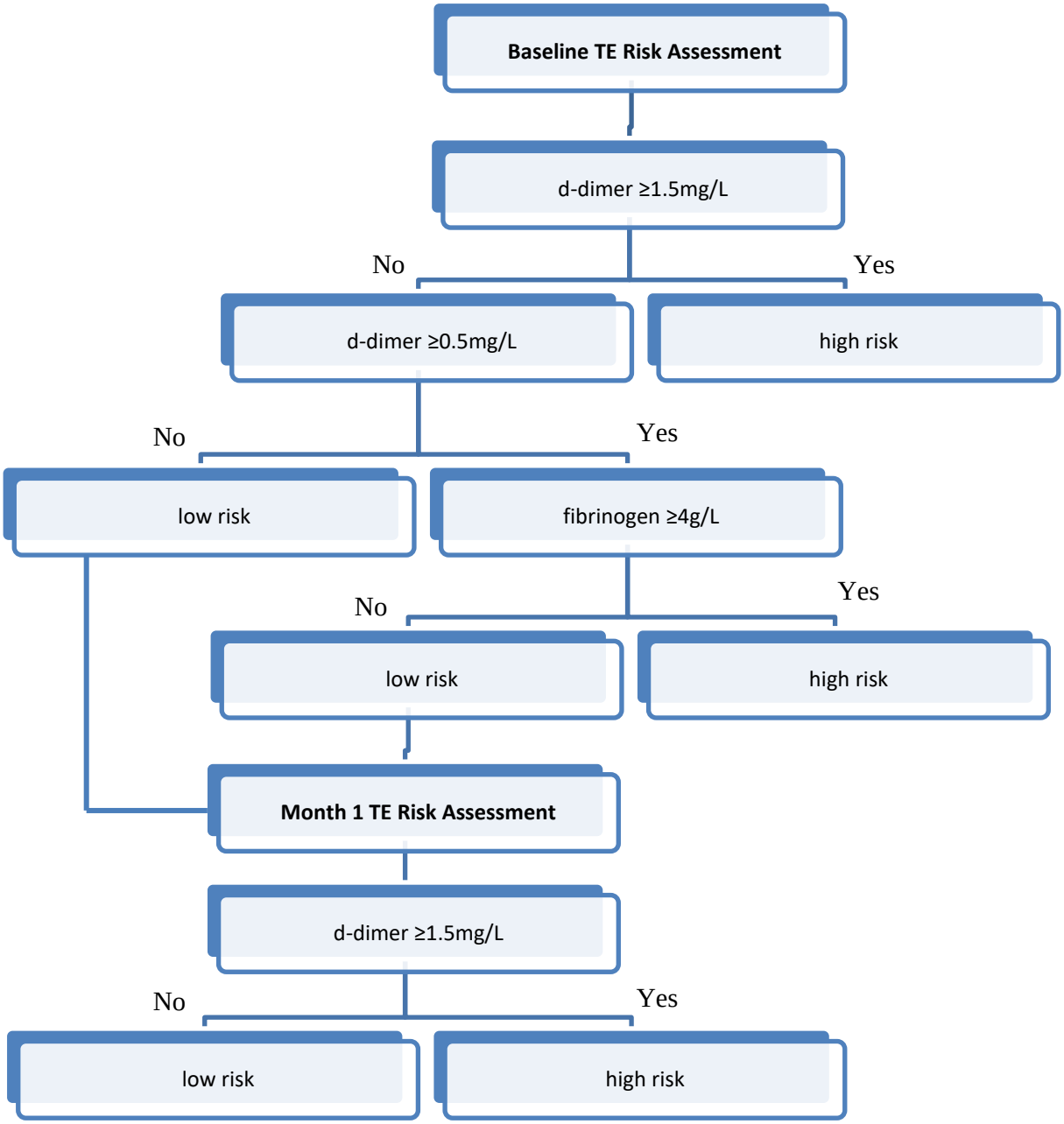

Figure 2 - Algorithm for TE risk assessment.

7.4 Randomisation

High TE risk patients will be randomised 1:1 to receive P-TP or no P-TP. Randomisation will be performed by a member of the study team using the randomisation module built into the EDC system. The randomisation module (and randomisation schedule) will be created in advance of patient recruitment by an independent statistician. Neither the trial manager nor study team member using the EDC randomisation module will be aware of the next treatment allocation. Patients will be randomised in blocks according to site of enrolment, treatment intent (curative or palliative) and cancer diagnosis (lung or gastrointestinal cancer).

7.5 Sequential TE risk assessment (fibrinogen and d-dimer)

The investigator will perform real-time risk assessment according to the prescribed algorithm.

All patients will be assessed for TE risk at baseline and month one after commencement of cancer therapy. The timing of assessments should be adjusted to coincide with routine blood monitoring for cancer therapy (see visit window in schedule of assessments, **Table 1**).

Low risk patients may be upgraded to high TE risk by on-treatment assessment at month one. At this time, patients with randomised to enoxaparin P-TP or no P-TP (1:1). P-TP should commence as soon as feasible with prescription order from the investigator, trial management approval is not required.

High risk patients cannot be down-graded based on subsequent TE risk assessments.

Fibrinogen and d-dimer will be assessed at month 6 for research purposes, however results will not be used to inform risk assessment or guide treatment.

Patients receiving single modality radiotherapy will undergo risk assessment as above, however results will not be utilised to direct therapy and all patients will enter the observation arm.

The following blood exams must be completed to perform sequential safety and TE risk assessments:

- Haematology
- Biochemistry
- Fibrinogen and d-dimer

7.6 Trigger for new TE risk assessment

This study includes a trigger for TE re-assessment to account for participants in the observation arm (low TE risk) who then receive subsequent lines of anticancer therapy during the study period. This would allow re-assessment of TE risk (new baseline and month 1 assessments) and then if high risk the participant would enter randomisation as shown in Figure 1.

Eligibility for reassessment: Participants classified at low risk that, as part of standard care cancer management, are identified to have recurrence/progression of their cancer during the trial observation period and are planned to commence a new line of anticancer therapy.

7.7 Research Samples –

This test is optional and will only be collected for patients at Peter MacCallum Cancer Centre that have provided additional consent to collection of research samples.

Correlative biomarkers will be taken longitudinally over the course of the trial (per **Table 1**). These tests will provide additional information clotting potential and the interplay between the cancer and the coagulation system. Tests will include: overall haemostasis potential, global coagulation assays and thromboelastography.

7.8 TE assessment

At each study visit, and unscheduled visits triggered by patient reported symptoms of TE, participants will be assessed for clinical symptoms of TE. If TE is suspected by the treating clinician appropriate diagnostic investigations shall be performed (see section 4.2 for accepted objective assessments). Patients will be assessed for clinically overt (new onset or acute progression) signs and symptoms suggestive of TE including: limb swelling, limb bruising/discolouration, limp pain/tenderness, shortness of breath, chest pain, or any other symptoms identified by the treating clinician. Routine imaging for detection of TE will NOT be performed in the absence of clinical symptoms.

7.9 Anticancer treatment

Anticancer treatment and response assessment is directed by the treating clinician.

7.10 Patient reported outcomes

Surveys will be administered via secure email through the EDC system or on paper if the participant prefers.

Quality of life: Patient response to SF12v2 quality of life survey, among all patients, at enrolment, month 6 and month 12 after commencement of anticancer therapy. This survey is being conducted to support economic analyses (quality adjusted life years - QALY), not to evaluate or describe lung / gastrointestinal cancer symptoms.

Anti-clot treatment: Patient response to Anti-Clot Treatment Scale (ACTS), among patients randomised to P-TP, at months one and three, and if applicable at month six after commencement of anticancer therapy.

Blood clot awareness survey: Patient response to Clot Awareness Survey, among patients potentially eligibility for inclusion in the Target-TP study, assessed during the screening visit.

Table 1: Schedule of study assessments

Protocol activity	**Screening**		**Treatment**						**Follow-up**	
	Eligibility criteria and enrolment	TE risk assessment and randomisation	P-TP start *intervention cohort only	Cancer therapy start	Anticancer therapy +/- P-TP				Unscheduled visit (TE, bleeding or other reportable AE)	Survival follow-up after study completion
Activity	**Day**		**Day**		**Month**				**Month**	**Year**
	-28 to -1	-28 to -1	Within 3 days randomisation and prior to start cancer therapy	0	1 ±10d	3 ±14d	6 ±30d	12[k] ±30d	Any time to month 6	Yearly [k]
Informed consent	X									
Demographics, medical, TE, & disease history	X									
Height and Weight	X									
ECOG performance status	X									
Haematology [a]		X			X		X			
Biochemistry [a, b]		X			X		X			
Fibrinogen & D-dimer [a]		X			X		X			
Research sample [a, c]		X			X		X			
Randomisation [d]		X			X[e]					
Start / Stop P-TP [f]			X			X	X			
CT Scan	As clinically indicated									
Response assessment [g]	At time of CT									
Anticancer concomitant medications [h]	X				X	X	X	X	X	X
Antithrombotic concomitant medications [h]					X	X	X	X	X	
TE symptoms	X				X	X	X	X	X	
Events (TE, bleeding, non-bleeding event related to anticoagulation)	X				X	X	X	X	X	
Survival / disease status	X				X	X	X	X		X
Patient reported outcomes, quality of life (SF-12.v2.0)	X						X	X		
Patient reported outcomes, anti-clot treatment (ACTS) [j]					X	X	X			

Protocol activity	**Screening**		**Treatment**						**Follow-up**	
	Eligibility criteria and enrolment	TE risk assessment and randomisation	P-TP start *intervention cohort only	Cancer therapy start	Anticancer therapy +/- P-TP				Unscheduled visit (TE, bleeding or other reportable AE)	Survival follow-up after study completion
Activity	**Day**		**Day**		**Month**				**Month**	**Year**
	-28 to -1	-28 to -1	Within 3 days randomisation and prior to start cancer therapy	0	1 ±10d	3 ±14d	6 ±30d	12[k] ±30d	Any time to month 6	Yearly [k]
Patient reported outcomes, clot awareness survey v1.0	X									

a) See table 2 for blood test parameters
b) Creatinine clearance to be derived using the Cockcroft-Gault formula or may be measured by 24 hour urine collection or nuclear medicine assessment as clinically indicated
c) Optional sample for consenting patients at Peter MacCallum Cancer Centre only
d) Randomisation of high risk patients to P-TP or no P-TP.
e) Randomisation of patients upgraded from low TE risk to high TE risk based on month one TE risk assessment
f) P-TP to continue to at least 3 months, or at until anticancer therapy cessation, to a maximum of 6 months.
g) RECIST 1.1
h) Only anticancer therapies, anticoagulants and/or antiplatelet, any agent used for the management of TE
i) Bleeding adverse events monitored to 7 days post cessation of P-TP
j) Anti-Clot Treatment Scale for patients receiving P-TP only, to complete month 6 survey only if received enoxaparin within the last 4 weeks.
k) Month 12 and yearly survival and disease status follow-up until 24 months after the last patient is enrolled; may be completed by phone by a member of the research team.

Table 2: Blood test parameters

Test Category	Tube	Volume	Tests requested
Haematology	EDTA (pink)	3mL	White cell count, neutrophil count, lymphocyte count, haemoglobin, and platelets
Biochemistry	Serum gel tube (gold)	5mL	Sodium, potassium, chloride, creatinine, bicarbonate, urea, calcium, magnesium, phosphate, total protein, albumin, bilirubin, GGT, ALP, AST, ALT
Coagulation	Citrate (blue)	3mL	Fibrinogen and D-dimer
Research Sample (optional test for Peter Mac site only)	Citrate (blue) Citrate (blue)	3mL 3mL	Overall haemostasis potential, global coagulation assays Thromboelastograph, **tube not to be spun.**

8. RESPONSE ASSESSMENT

Tumour response will be assessed on computed tomography (CT) conducted as part of routine care. Specific study response assessments will not be performed.

Disease response will be recorded as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) determined using the local investigator's assessment based on RECIST 1.1 criteria,[13] but without formal requirement for target lesion assessment.

Date of first response (PR or CR) and date of progression (PD) will be recorded to determine duration of response, and progression free survival.

Response will be captured until documentation of disease progression or initiation of additional anticancer treatment.

9. POTENTIAL RISKS AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS

There are potential risks associated with the delivery of preventative doses of anticoagulation as part of the interventional P-TP regimen, and to a greater extent, associated with therapeutic dose anticoagulation given for the treatment of thromboembolism. These are discussed and guidelines for management are provided below.

All thrombohaemorrhagic events will be recorded as part of study outcomes (with record made of diagnosis, treatment, worst grade experienced and relatedness to either study related procedures or TE).

Anticancer therapy related events will not be reported.

9.1 Thromboembolism

Any clinically suspected TE event should be confirmed objectively as defined in protocol section 4.2 (study endpoints). Management will be according to clinician discretion and hospital guidelines. Patients will remain on study after a TE and their anticoagulant medication documented. The PICF will advise specifically about possible symptoms/signs of TE.

9.2 Major bleeding and clinically relevant non-major (CRNM) bleeding

Bleeding events should be classified as major or CRNM as defined in protocol section 4.2 (study endpoints). Management will be according to clinician discretion and hospital guidelines. The PICF will advise specifically about the risk of bleeding adverse events and management in the event of bleeding events.

9.3 Adverse event other than bleeding associated with study drug

Participants may experience adverse events other than bleeding associated with the study drug. Such events are not limited to but may include pain at injection site, mild and reversible reduction in platelet count, short term elevation of liver enzymes, damage or death to cells at the injection site (skin necrosis), or allergic reactions such as rash or anaphylaxis. Management of adverse events will be according to clinician discretion and hospital guidelines. Withdrawal of study drug

should be considered for events grade two or above, as outlined in protocol section 5.5 (criteria for cessation of study drug).

9.4 Anticancer therapy related adverse events

Anticancer therapy is given according to clinician direction and is not part of this study. Management of anticancer treatment related adverse events will be at the discretion of the treating clinician and events do not need to be reported as a safety event for this study.

10. ADVERSE EVENTS

10.1 Event Definitions

10.1.1. Adverse Event (AE)

Adverse Event (AE) has the meaning given in the Therapeutic Goods Administration document Access to unapproved therapeutic goods Clinical trials in Australia (October 2004), or replacement, and shall mean any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

10.1.2. Related Adverse Event

Related Adverse Event i.e. Adverse Drug Reaction (ADR) means there is a reasonable possibility according to the Sponsor that the product may have caused the event.

10.1.3. Serious Adverse Event (SAE)

Serious adverse event ("SAE") means any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

10.1.4. Unexpected Adverse Event (AE) / Unexpected Adverse Drug Reaction (ADR)

Unexpected Adverse Event (AE) / Unexpected Adverse Drug Reaction (ADR) means an adverse event or adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product or Product Information/Data Sheet for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

10.2 Attribution

Attribution of cause requires at least a reasonable possibility of a causal relationship between the event and the use of the investigational drug or any other protocol-specified intervention.

All protocol-specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
UNRELATED	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
RELATED	Possible	The AE *may be related* to the intervention
	Probable	The AE is *likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

10.3 Severity Criteria

An assessment of severity grade will be made using the CTCAE (version 5.0). Where parameters are not addressed within the criteria, severity of AEs should be graded as:

Mild	Aware of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activities
Severe	Incapacitating with inability to work or perform usual activities
Life-threatening	Patient is at *immediate risk of death*
Fatal	Death

10.4 Adverse Event Reporting

All reportable adverse events, which occur whilst the patient is enrolled on the trial, must be reported in the patients' medical records and recorded on the relevant EDC.

For this study the following events should be reported:

- Thromboembolism and sequelae
- Bleeding and sequelae
- Any adverse event associated with anticoagulant therapy

For this study the following events should **NOT** be reported:

- Adverse events, including SAE, associated with cancer or anticancer treatment

10.4.1. Serious Adverse Event Reporting

10.4.1.1. Trial Sites/Investigators

All reportable SAEs that occur from the time a patient has signed consent for the trial to 30 days after the final protocol-specified treatment, intervention or procedure are required to be reported within 24 hours of being first made aware of the event to the Sponsor whether or not considered related to the treatment under investigation.

The investigator must:

- Determine whether an AE is 'Serious' (refer to Serious Adverse Event Definition)
- For SAEs, the investigator must then ascertain the suspected cause
- The attribution to the SAE must be recorded in the patients' medical records and reported on the SAE form.
- Both expected and unexpected serious adverse events and serious adverse drug reactions must be recorded in the patients' medical records.
- SAEs must be reported by completing the trial SAE form and emailing the completed form and any relevant safety information to the sponsor:

Send to	Contact Method
Drug Safety Associate	Email: safetyreporting@petermac.org Tel: 03 8559 7364

SAE forms are required at following points:

Initial Report	Within one working day/24 hours of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided in the comments section of the SAE form.
Incomplete Reports	If all details are not available at the time of the initial report a completed report must be sent within the next 10 days.
Updated Report	If the event is not resolved (or 'on-going') at the time of the initial report, the SAE Form must be submitted every 30 days until the event is resolved, death has occurred or the condition has stabilised. If a change occurs in a stable condition (i.e. either worsens or improves), then a new SAE Form should be submitted.

The Investigator is ultimately responsible for reporting the SAE and must sign the final SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24-hour period, a comment to this effect must be written on the form and the form signed by the clinician attending to the patient at the time and emailed to the Sponsor. The investigator must sign the SAE form as soon as possible and email the Sponsor.

The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and or Research Governance Office (RGO) subsequently notifying the HREC/RGO of SAEs as required.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

10.4.1.2. Severity Assessment

If required on the AE case report Forms, the investigator will use the following definitions of severity in accordance with the NCI CTCAE version 5.0 to describe the maximum intensity of the AE.

- GRADE Clinical Description of Severity
- No change from normal or reference range
- Mild Adverse Event
- Moderate Adverse Event
- Severe Adverse Event
- Life-threatening or Disabling Adverse Event
- Death related to Adverse Event

Note that a severe event is not necessarily the same as a serious adverse event.

10.4.1.3. Causality Assessment

All protocol specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Unrelated
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

10.4.1.4. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events reported by the trial patient. In addition, each trial participant will be questioned about adverse events.

10.4.1.5. Sponsor Reporting Requirements

1. The Sponsor warrants the trial will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

2. The Sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.

3. The Sponsor shall be responsible for ensuring submission of required expedited and periodic reports to the appropriate Regulatory Authority (RA), the Sponsor's Ethics Committee and Investigators.

11.DATA ANALYSIS AND STATISTICAL METHODS

11.1 Sample size and precision of estimates

Sample size calculations are based on TE event rates observed in supporting local studies and international published data. This study will be powered to show a significant difference in TE event rates for patients randomised to P-TP versus no TP. With a two sided significance level of 0.05 and 80% power, 20% TE rate with no TP, and 5% TE rate with P-TP, we must enrol 176 high TE risk patients, with 88 patients in each the intervention and control arms (1:1 randomisation). To achieve this, based on an expected 60-70% 'high risk' classification rate we would enrol a total 252-294 patients. To allow for patient drop-out we aim to randomise 100 patients to P-TP.

Table 3 - Sample size requirements to demonstrate a statistically significant difference in TE event rates between randomisation cohorts.

TE rate, high TE risk no TP	TE rate, high TE risk e-TP	Sample size, high TE risk *randomisation cohort*	Total patients enrolled, if 70% high TE risk	Total patients enrolled, if 60% high TE risk
25%	10%	226	323	377
25%	5%	118	169	197
20%	5%	176	251	293
15%	5%	320	457	533
20%	10%	438	626	730

*sample sizes calculated using www.openepi.com based on formula from Kelsey et al., Methods in Observational Epidemiology 2nd Edition

Published data for TE rates without P-TP – 25% TE rate among 'high risk' lung cancer in Peter Mac BIOTEL prospective biomarker study (n=117);[in press] 14% TE rate all ambulatory lung cancer patients (not stratified by risk) USA cohort study (n=6732);[14] 19% TE rate all ambulatory pancreatic cancer patients (not stratified by risk) USA cohort study (n=1336);[14] 16% TE rate all ambulatory upper gastrointestinal cancer patients (not stratified by risk) USA cohort study (n=787);[14] 11% TE rate all ambulatory lower gastrointestinal cancer patients (not stratified by risk) USA cohort study (n=4548).[14]

Published data for TE rates with P-TP – 5% TE rate among ambulatory lung cancer patients receiving P-TP in FRAGMATIC RCT (n>2000);[15] 4.5% TE rate among ambulatory lung cancer patients receiving P-TP in TOPIC-2 RCT (n=268);[16] 1.2% TE rate among ambulatory cancer patients receiving P-TP in SAVE-ONCO RCT (n=1608);[17] 2% TE rate among ambulatory cancer patients receiving P-TP in PROTECHT RCT (n=1608).[18]

11.2 Timing of analyses

11.2.1 *Reports for the Data Safety Monitoring Board (DSMB)*

There will be safety reviews prepared by the trial manager for the DSMB yearly during accrual, summarising thrombohaemorrhagic events. The first safety review will occur six months after enrolment of the first patient on study.

11.2.2 Analysis of six *month outcomes*

Analysis will occur once all patients have had six months follow up (or withdrawn from study follow up). This analysis will report all patient baseline characteristics, treatment details and primary and secondary endpoint data collected up to that time point.

11.2.3 Analysis of 12 month outcomes

Analysis will occur once all patients have had 12 months follow up (or withdrawn from study follow up). This analysis will report all patient baseline characteristics, treatment details and primary and secondary endpoint data collected up to that time point.

11.2.4 Final Analysis

The final analysis will occur once all patients have had 24 months follow up (or withdrawn from study follow up). This analysis will update any analyses reported in the main analysis where additional data has been reported. The report will include analyses relating to the exploratory objectives.

11.3 Statistical methods

Prior to analysis of TE and bleeding events an independent medical review panel - the Clinical Event Committee (CEC) - will be formed and tasked with evaluating and adjudicating on reported TE and bleeding events. During this process the committee will be blinded to the participant and the treatment assignment. The CEC may include study investigators but only where blinding can be maintained (i.e. clinician may evaluate events from patients outside of their trial centre).

For the main trial outcomes related to TE and bleeding events (10.4.1-10.4.3), exploratory analysis of the cumulative incidence of TE and bleeding according to cancer type, stage, anticancer therapy and trial recruitment site (individual site and tele-trial vs. traditional site), and anticancer therapy, will be undertaken by inclusion of these factors in multivariable cause specific Cox proportional hazards models. All endpoints related to TE and bleeding will be independently analysed by a second statistician.

11.3.1 Analysis of TE incidence (primary objective)

TE incidence rates will be presented as absolute number of events divided by person-time (years). Participant follow-up (person-years at risk) will be counted from date of study enrolment until the date of the first occurring event: TE, death, loss to follow-up, or study end (24 months after the enrolment of the last patient). For cause-specific time to event analyses, participants who do not experience the event of interest will be treated as censored at the end of follow-up. Cox proportional hazards models will be used for cause-specific analyses and will include an indicator variable for whether participants were randomised to enoxaparin P-TP vs. no P-TP. The cumulative incidence functions (CIF) for TE will be used to estimate TE incidence at 6 months for randomised study arms, noting that the CIF depends on the cause-specific hazards of both TE and the competing event, death.

11.3.2 Analysis of bleeding events (secondary objective 1)

As for TE, the risk of bleeding, according to definitions in section 4.2 and in separate analyses for major, CRNM, and major or CRNM bleeding, for high TE risk patients randomised to enoxaparin P-TP vs. no P-TP will be assessed using univariable case-specific Cox proportional hazards regression models with the randomisation arm comparison reported as a hazard ratio (HR). Corresponding cumulative incidence functions (death as competing risk) will be used to describe risk.

11.3.3 Analysis of adverse events other than bleeding (secondary objective 2)

Adverse events other than bleeding, probably or definitely related to the study drug, will be reported. Events will be categorised and graded according to CTCAEv5.0.

11.3.4 Performance of TE risk assessment model (secondary objective 3)

Among patients not receiving P-TP, sensitivity and specificity of the TE risk-assessment model will be assessed by cause-specific analyses. Sensitivity is defined as the number of TE-positive patients classified as high risk, as a proportion of all TE-positive patients. Specificity is defined as the number of TE-negative patients classified as low risk, as a proportion of all TE-negative patients. For analyses, risk status will be based on classification at month one, at which time final risk status is known for all patients. Analysis will occur after month 6, the specified time period for primary assessment of TE events.

11.3.5 Analysis of response to anticancer therapies, overall survival and progression free survival (secondary objective 4)

Duration of best overall response (OR), progression free survival (PFS), and overall survival (OS) will be assessed by Kaplan-Meier methods, with a close-out date applied. The close out date will generally be taken to be the earliest of the dates of last contact, at which the assessments relevant to the identification of the events were made, of the patients who are still alive and being followed up. Thus, with the exception of any patients who have been lost to follow-up, the status of all patients in the trial, regarding the events of interest, should be known at this date. OR, PFS, and OS will be assessed for all participants, according to treatment allocation, and according to TE incidence.

OR, PFS and OS will be analysed using previously described methods for Cox proportional hazards regression. Multivariable analysis will include the following variables TE, bleeding, cancer type, stage, and anticancer therapy.

11.3.6 Analysis of patient reported outcomes data (secondary objective 5)

Patient reported outcomes will be described using appropriate statistical summaries including frequency / percentage counts and median and range of scores / rating scales.

11.3.7 Analysis of health resource utilisation costs (secondary objective 6)

Taking a health system perspective, we will measure and value costs associated with health-care resource utilisation for all study patients. A modelled cost analysis comparing resource utilisation for patients with TE-related events against those without TE-related events will be conducted using hospital administrative data. The following cost parameters have been identified for measurement:

- Component costs (medical, nursing, pharmacy, imaging, pathology, hotel, allied health and non-clinical salaries, operating rooms and specialist procedure suites) associated with diagnosis-related group (DRG) and length of hospital stay, including hospital-in-the-home. Drug costs include preventative dose anticoagulation for the prevention of TE and therapeutic dose anticoagulation for the treatment of TE.
- Intensive Care Unit (ICU) stay valued by critical care component cost by DRG and length of ICU stay.
- Use of mechanical ventilation
- Readmission(s) associated with TE-related complication
- Outpatient clinic visits valued by Australian Medicare Benefits Schedule (MBS)
- Complications of the TE
- Additional radiology necessitated (CTs, Doppler) as valued by MBS.
- Additional pathology tests e.g. FBE, coagulation screen as valued by MBS cost.
- Medical treatment (with enoxaparin according to standard hospital protocol), [36] with pharmaceutical costs valued according to Health Purchasing Victoria (HPV) Contract.
- Costs associated with complications arising from iatrogenic causes of TE-management including bleeding and concomitant medication to minimise bleeding risk.

The costs captured in this study are likely to be skewed and so in analysing this data, non-parametric methods will be used. All costs will be expressed in real terms and future costs discounted at 5% in line with standard Australian economic evaluation guidelines. Robustness of the costing data will be tested through sensitivity analyses, with the main variables being cost of hospitalisation, incidence of TE-events and complications post-study, and other drivers of cost as determined through the study.

12. QUALITY CONTRAL AND QUALITY ASSURANCE

During this trial, the Sponsor may conduct periodic monitoring visits as per Peter Mac policy, to ensure that the protocol and GCP are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigators will permit monitors and appropriate regulatory agents direct access to source documents to perform this verification. The

site may also be subject to review by the HREC committee and/or to inspection by appropriate regulatory authorities.

13. DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

All trial data required for the monitoring and analysis of the study will be recorded electronically on the electronic data capture platform. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. Site investigators will be asked to confirm the accuracy of completed eCRFs by signing key eCRFs as indicated.

13.2 Record Retention

To enable monitoring, audits and inspections from regulatory authorities, the investigator and study team will keep records, including:

- The identity of all participating patients
- All original signed consent forms
- Copies of all CRFs
- Safety reporting forms
- Source documents
- Records of treatment
- Correspondence

All records should be retained by the Investigator as per GCP requirements.

14. ETHICS

14.1 Human Research Ethics Committee (HREC)

It is the responsibility of the Investigator to ensure HREC approval is in place for the trial protocol, protocol amendments, informed consent documents and any other relevant study documents. All correspondence with the HREC must be maintained in the site file. The only circumstance in which an amendment can be implemented prior to HREC approval is to eliminate any immediate safety concerns to the patient. In this situation, the investigator must notify the HREC in writing immediately after the event.

14.2 Ethical Conduct of the Trial

The study will be conducted in accordance with legal and regulatory requirements, as well as the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

14.3 Patient Information and Consent

The investigator and study team will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports or publications except where required by law. The informed consent documents must be in compliance with GCP, local regulatory requirements and legal requirements. All informed consent documents must be approved by the HREC before use.

Information and consent forms may be issued by a member of the study team on the directive of the study investigator. Participants will be given appropriate time to consider participation and discuss participation with a study investigator. In most instances participants will be given several days to consider participation. In some rare instances, where delays to initiating anticancer treatment (corresponding with start of trial), are considered detrimental to the patient and the primary treating clinician prescribes immediate (same or next day) initiation, the time period for review of trial information may be lessened. In these rare scenarios, the patient would be given at least two hours to independently consider participation.

The investigator will ensure that each study patient or their legally acceptable representative is fully informed about the study and its objectives and risks. The investigator or their designee will obtain written informed consent from each patient or their legally acceptable representative before any protocol-specific activity it performed. The original signed consent form will be retained by the investigator.

At any stage during the study participants have the opportunity to review and confirm (or withdraw) their consent for this study.

15. DATA SAFETY MONITORING BOARD

The statistician / data manager will prepare reports for the DSMB, as stated in section 11.3.1. The DSMB will operate as specified by the Sponsor (Peter MacCallum Cancer Centre) safety and monitoring guidelines.

The DSMB will include members from (or affiliated with) the same institution as the sponsor or investigator, but who are not part of the trial team.

16. DEFINITION OF END OF TRIAL

End of trial is defined as the time at which sufficient patients have been recruited and completed the trial as specified in the protocol and the study statistical report has been completed.

17. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of regulatory authority decision, change in the opinion of the HREC, medication safety problems or at the discretion of the Sponsor and/or Investigator and/or DSMB.

If the trial is prematurely terminated or discontinued, the Investigator will promptly contact all patients and will be responsible for ensuring ongoing clinical care.

18. PUBLICATION OF TRIAL RESULTS

This trial will be published in accordance with the Peter MacCallum Cancer Centre Policies and Procedures Manual, Volume 3, Research Management: Authorship and Publication (February 2002).

19. APPENDIX 1 – RECIST 1.1 CRITERIA – RESPONE EVALUATION CRITERIA IN SOLID TUMOURS

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.
- Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases 'unequivocal progression' of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases'.

RECIST 1.1 Response Criteria	Target lesions	Non-target lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as *reference the baseline sum diameters*	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as *reference the smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

	absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.	
Stable Disease (SD)		Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as *reference the smallest sum diameters while on study.*

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should ideally be confirmed later on by the review panel (or Study Chair).

20. APPENDIX 2 – CONTRAINDICATIONS TO ANTICOAGULANT THERAPY

Patients with **any** of the following contraindications to anticoagulation and/or specifically LMWH will be excluded from participation in this study:

- Allergy to enoxaparin, heparin or its derivatives including other LMWH
- Past history of heparin induced thrombocytopenia (HIT)
- Thrombocytopenia, defend as baseline platelet count $<30 \times 10^9/L$
- Severe hepatic impairment or disease, including oesophageal varices
- Active bleeding
- Conditions with a high risk of uncontrolled haemorrhage including major bleeding disorders, focal lesions, haemorrhagic stroke, active ulcerative conditions showing a tendency to haemorrhage (e.g. peptic ulcer, ulcerative colitis)
- Acute bacterial endocarditis

21. APPENDIX 3 – ANTI-CLOT TREATMENT SCALE

We are interested in your experiences of anti-clot treatment. We would be grateful if you could help us by filling out this questionnaire. The questions below ask about your experiences of anti-clot treatment during the past 4 weeks. All of the information you provide is COMPLETELY CONFIDENTIAL. Please be sure to answer all questions.

INSTRUCTIONS: We are interested in your experiences of anti-clot treatment during the past 4 weeks. Please circle the number in the box that best describes your views.

During the past 4 weeks...	Not at all	A little	Moderately	Quite a bit	Extremely
1. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in vigorous physical activities (e.g. exercise, sports, dancing, etc.)?	1	2	3	4	5
2. How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in your usual activities (e.g. work, shopping, housework etc.)?	1	2	3	4	5
3. How bothered are you by the possibility of bruising as a result of your anti-clot treatment?	1	2	3	4	5
4. How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of your anti-clot treatment?	1	2	3	4	5
5. How much does your anti-clot treatment limit what you eat and drink (including alcohol)?	1	2	3	4	5
6. How much of a hassle (inconvenience) are the daily aspects of your anti-clot treatment (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, limiting what you eat and drink (including alcohol), etc.)?	1	2	3	4	5
7. How much of a hassle (inconvenience) are the occasional aspects of your anti-clot treatment (e.g. the need for blood tests, going to or contacting the hospital/doctor, making arrangements for treatment while travelling etc.)?	1	2	3	4	5

Now I want to ask you about daily and occasional aspects of your anti-clot treatment during the past 4 weeks…

	Not at all	A little	Moderately	Quite a bit	Extremely
8. How difficult is it to follow your anti-clot treatment?	1	2	3	4	5
9. How time-consuming is your anti-clot treatment?	1	2	3	4	5
10. How much do you worry about your anti-clot treatment?	1	2	3	4	5
11. How frustrating is your anti-clot treatment?	1	2	3	4	5
12. How much of a burden is your anti-clot treatment?	1	2	3	4	5
13. **Overall**, how much of a negative impact has your anti-clot treatment had on your life?	1	2	3	4	5
14. How confident are you that your anti-clot treatment will protect your health (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)?	1	2	3	4	5
15. How reassured do you feel because of your anti-clot treatment?	1	2	3	4	5
16. How satisfied are you with your anti-clot treatment?	1	2	3	4	5
17. **Overall**, how much of a positive impact has your anti-clot treatment had on your life?	1	2	3	4	5

THANK YOU FOR YOUR HELP

22. APPENDIX 4 – QUALITY OF LIFE SURVEY

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

23. APPENDIX 5 – CLOT AWARENESS SURVEY

Confidential

Blood Clot Awareness Survey

Study ID _____

Please answer the following questions based on your knowledge / understanding BEFORE talking to staff about the TargetTP clinical trial

Q1. Do you know what a blood clot is? ○ Yes ○ No

Q2. Are you aware whether you might be at risk of developing a clot? ○ Yes ○ No

Please answer the following questions based on how you feel now, including knowledge / understanding gained by talking to staff about the TargetTP clinical trial

Q3. If you were made aware that you were at risk of developing a blood clot, would you want to be proactive to prevent clots? ○ Yes ○ No

Q4. Would you be willing to use clot prevention medication? ○ Yes ○ No

Q5. Would you be willing to use oral or injected clot prevention medications?

	Yes	No
Daily tablet or capsule	○	○
Daily injection under the skin that you could administer at home yourself	○	○

Q6. Please select your level of agreement with the following responses to the statement "I would consider using an injected medication instead of an oral medication to prevent blood clots if the injection was.... "

	Definitely	Probably	Maybe	No	Not sure
Less likely to cause bleeding	○	○	○	○	○
More likely to prevent clots	○	○	○	○	○
Less likely to interact with my cancer medications / treatment	○	○	○	○	○

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