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Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056431
Article Type:	Protocol
Date Submitted by the Author:	13-Aug-2021
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Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, ONCOLOGY, Pancreatic disease < GASTROENTEROLOGY, Thromboembolism < CARDIOLOGY

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Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

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Article type: Protocol

Word count: 297 (abstract) – 3732(main text)

KEYWORDS: Venous thrombosis; pancreatic neoplasm; gastric neoplasm; oesophageal neoplasm; risk prediction model.

ABSTRACT

Introduction

Venous thromboembolism (VTE) is a common complication of cancer. Pancreatic and gastro-oesophageal cancers are among malignancies that have the highest rates of VTE occurrence. VTE can increase cancer-related morbidity and mortality and disrupt cancer treatment. The risk of VTE can be managed with measures such as using anticoagulant drugs, although the risk of bleeding may be an impeding factor. Therefore, a VTE risk assessment should be performed before the start of anticoagulation in individual patients. Several prediction models have been published, but most of them have low sensitivity and unknown clinical applicability in pancreatic or gastro-oesophageal cancers. We intend to do this systematic review to identify all applicable published predictive models and compare their performance in those types of cancer.

Methods and analysis

All studies in which a prediction model for VTE have been developed, validated, or compared using adult ambulatory patients with pancreatic or gastro-oesophageal cancers will be identified and the reported predictive performance indicators will be extracted. Full text peer-reviewed journal articles of observational or experimental studies published in English will be included. Five databases (Medline, EMBASE, Web of Science, CINAHL and Cochrane) will be searched. Two reviewers will independently undertake each of the phases of screening, data extraction, and risk of bias assessment. The quality of the selected studies will be assessed using Prediction model Risk Of Bias Assessment Tool (PROBAST). The results from the review will be used for a narrative information synthesis, and if the same models have been validated in multiple studies, meta-analyses will be done to pool the predictive performance measures.

Ethics and dissemination

There is no need for ethics approval because the review will use previously peer-reviewed articles. The results will be published.

PROSPERO registration number: CRD42021253887

Article summary:

Strengths and limitations of this study

- This review will seek to stratify risk models according to their predictive performance for VTE risk.
- The methodological issues identified by this review may help design more robust predictive models.
- High levels of heterogeneity across the studies may affect the feasibility of a meta-analysis.

- Exclusion of journal articles published in languages other than English is a limitation of this study.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs as a serious complication of cancer.¹ The relationship between malignancy and a hypercoagulable state was first described by Armand Trousseau in early 19th century.² VTE is the second most common cause of death in cancer patients.³ Compared to the general population, patients with upper gastrointestinal cancer including gastro-esophageal and pancreas have a 60-fold increased risk of developing a VTE⁴ with approximately 13% diagnosed with a VTE prior to any intervention (e.g., surgery or chemotherapy)⁵ and approximately 21% diagnosed with a VTE within 12 months from cancer diagnosis.^{6,7} In addition to cancer itself, other factors such as treatment modalities (chemotherapy and surgery), and venous access devices may contribute to the risk of VTE in these patients.⁸ Studies have suggested that development of VTE in pancreatic or upper gastrointestinal cancer patients is associated with a poor prognosis.^{8,9}

Several studies have demonstrated that thromboprophylaxis can significantly decrease the rate of VTE events in patients with pancreatic and gastric cancer, especially in outpatients¹⁰⁻¹⁴. However, the management of VTE risk in cancer patients represents a major challenge for clinicians, as the use of anticoagulants can increase the risk of potentially dangerous haemorrhage¹⁵. This risk is even higher in outpatients because they are beyond the observation of medical staff most of the time. Furthermore, although patients with pancreatic cancer have a higher risk for VTE compared to other types of cancer¹⁶, generally, they have twice the risk of major bleeds⁷. This highlights a need for the assessment of the risk of VTE in ambulatory cancer patients before starting anticoagulation. This can be attained through using sensitive and reliable VTE risk prediction models.

Predictive models in health care are statistical tools that use individual patient data (e.g., demographics, patient history, and biomarkers) to help estimate the likelihood of occurring an event, such as VTE, in a defined time^{17,18}. An appropriately built and validated model can improve clinical decision-making and improve patient management. Examples of clinical prediction models include the updated Vienna prediction model for the recurrence of VTE¹⁹; the Wells rule to predict DVT and PE in hospitalised patients^{20,21}; and a well-known risk stratification tool called the Khorana score (KS)²², designed to stratify cancer outpatients prior to the start of chemotherapy according to their risks of developing VTE.

A reliable predictive model for VTE in ambulatory patients with cancer may help reduce the number of patients needed to be treated for VTE by guiding clinicians towards taking a prophylactic approach in high-risk patients. As noted above, a widely used clinical VTE risk assessment tool is the KS which was derived and validated based on a split-sample method.²² The KS was developed in 2008, using the data from a cohort of 2,701 ambulatory patients with different types of cancer and it was further validated in another cohort of

1,365 patients²². In the development of this score, a logistic regression model was used with five clinical and laboratory variables including the type of cancer, the patient's Body Mass Index (BMI), the pre-treatment platelet count, leukocyte count and hemoglobin levels as well as the administration of erythropoietin stimulating agents.²² Notably, for pancreatic and gastric cancers they assigned a score of 2 points, which means that these types of cancer are associated with very high risk of VTE. In the derivation as well as validation cohorts, rates of VTE were 0.8% and 0.3% in the low-risk category (score=1), 1.8% and 2% in the intermediate category (score 1-2), and 7.1 and 6.7% in the high-risk category (score ≥ 3) for a median follow up period of 2.5 months. The two biggest advantages of KS are that firstly it uses patient data which are routinely available during the diagnosis or at the start of chemotherapy; and secondly, it has a high specificity of 93%²³. However, the disadvantages include the model's low sensitivity (23%)²⁴ and its failure in differentiating cancer patients with a low from those with a high risk of VTE.

Several independent investigators have validated the Khorana score²⁵⁻²⁷, but its generalisability to all types of tumors remains controversial as different cancer types have produced mixed results. Studies in pancreatic cancer patients have shown that the KS failed to discriminate high risk from those at intermediate risk for VTE²⁸⁻³⁰. A possible explanation for the poor performance of this score in pancreatic cancer patients may be that only <2% of patients who were included in the development and validation cohorts were patients with pancreatic cancer²². Furthermore, recent studies have reported no significant association between VTE risk and KS³⁰⁻³³. For instance, in a randomized control trial enrolling 312 pancreatic cancer patients showed that none of the Khorana score parameters was associated with risk of VTE.²⁹ Similarly, a study including 112 participants found that risk stratification using Khorana score was not predictive of VTE in the cohort of gastric cancer patients.³³

For outpatients with cancer, initially, a KS cutoff ≥ 3 was suggested to identify patients who are at high risk of VTE³⁴. However, as mentioned above, it was realised that the KS has low sensitivity for certain types of cancer such as pancreatic cancer³⁰ and gastric cancer³³. This issue is also applied to lung cancer^{31,35}. A key reported disadvantage of KS was that more than 50% of patients fell into the intermediate risk group, making it difficult for the physicians to decide whether to use anticoagulation. To alleviate those shortcomings, in two independent trials,^{36,37} undertaken to evaluate the effects of direct oral anticoagulation (DOAC) in ambulatory patients with cancer, a modified KS cutoff value of ≥ 2 was used. CASSINI³⁷ (Clinical Trials.gov identifier: NCT2555878) assessed the use of rivaroxaban in patients with solid tumours (over 50% of the study participants had diagnosis with very high-risk cancer types i.e, pancreatic or gastro-oesophageal) starting systemic anti-neoplastic therapy. The results not only showed significantly reduced VTE and VTE-related death during the treatment period, but also showed that the revised cut off was able to identify cancer patients who were at high risk of VTE both at baseline (4.53%) and during study 8.79% (HR:0.66;95% CI,0.40 to 1.09). The practicability of this revised cutoff value was recently confirmed by Mulder et al in a meta-analysis, using the KS cutoff value of two points or more reported a marked increase in proportion of patients from 17% to 47% in high-risk group with a decreased absolute risk of VTE from 11% (95% CI: 8.8-13.8) to 9% (95% CI: 7.3-10.8) in this group.³⁸

To improve the predictive performance of KS, several modifications have been proposed, such as the addition of D-dimer and P-selectin by the Vienna group of Cancer And

Thrombosis Study investigators (CATS score)²⁵, the inclusion of chemotherapeutic agents such as platinum-based regimens and gemcitabine as in the PROphylaxis of ThromboEmbolism during CHemoTherapy (PROTECHT) score³⁹, or replacing BMI with the performance status (used to quantify general wellbeing and daily life activities in cancer patients) as in the Charité-ONKOlogie (CONKO) score²⁹. The clinical usefulness of these risk assessment models remains a matter of debate because most of these models performed well in the initial derivation studies but when externally validated, showed conflicting results^{28,40}. A multinational prospective cohort study evaluated and compared the performances of all the above-mentioned risk scores for VTE in patients with solid cancer and found a poor discriminatory performance of all the scores. However, Vienna CATS and PROTECHT scores were found to distinguish better in low-risk and high-risk patients⁴¹.

Several clinical trials have also demonstrated that the risk of VTE can be reduced in pancreatic cancer patients on anticoagulant prophylaxis^{10,12-14,42}. Based on the results of these studies, the National Comprehensive Cancer Network recommended prophylactic treatment for patients with locally advanced or metastatic pancreatic cancer who are receiving chemotherapy⁴³. The American Society of Clinical Oncology's (ASCO) practice guidelines does not recommend routine thromboprophylaxis in all ambulatory cancer patients; however, they do recommend thromboprophylaxis for patients with Khorana score of ≥ 2 ⁴⁴ if there are no contraindications. On the other hand, the National Institute for Health and Care Excellence (NICE) recommended thromboprophylaxis only for patients with myeloma or pancreatic cancer⁴⁵.

Because of the above-mentioned controversies, a better understanding of the strengths and limitations of the available published VTE risk prediction models applicable to the ambulatory patients with pancreatic or gastro-oesophageal cancer will be highly useful. To date, no systematic review has been conducted to assess the predictive performance of risk assessment models of VTE in those groups of cancer patients. Therefore, this systematic review will seek to analyse and synthesise information regarding the predictive performance measures of the available models in assessing the risk of VTE in ambulate patients with pancreatic or gastro-oesophageal cancer.

Research question

In adult ambulatory patients with pancreatic or gastro-oesophageal cancer, which VTE risk prediction model has the best predictive performance (discrimination and calibration) during the first year following cancer diagnosis?

The research question has been outlined according to the PICOTS system⁴⁶ in Table 1 below.

TABLE 1. PICOTS system for predictive models

Population	Adult ambulatory patients with pancreatic, gastric or oesophageal cancer
Intervention	Use of internally/externally validated predictive models for VTE
Comparator	No predefined comparator. However, models will be compared to each other.

Outcome to be predicted	Venous thromboembolism within 12 months from the cancer diagnosis
Follow up period	12 months from diagnosis of cancer
Setting	Models used in ambulatory settings.

Objectives of the systematic review

The objectives are as follows.

1. Identify all internally and/or externally validated prediction models in the published literature, which can be used to predict the risk of VTE in ambulatory patients with pancreatic or gastro-oesophageal cancer.
2. Summarise the characteristics of these prediction models according to valid guidelines such as “Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist”⁴⁷.
3. Appraise the predictive accuracy (calibration, discrimination, and classification measures) for the identified models.
4. If possible, compare the model performance measures of available risk prediction models by meta-analysing the reported performance statistics for the same time points across the studies.
5. Identify the predictors/risk factors for the occurrence of VTE in patients with ambulatory pancreatic, gastric or oesophageal cancers.

METHODS AND ANALYSIS

This study protocol is prepared in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol (PRISMA-P)⁴⁸ and the outcomes of the review will follow Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement 2020⁴⁹. The methodology for data extraction and evaluation will be guided by the CHARMS checklist⁴⁷ and the recommendations reported by Debray and colleagues⁴⁶.

Eligibility criteria

Inclusion criteria

Study design

This review will include cohort studies (prospective or retrospective), case-control studies and clinical trials with at least one prediction model developed and/or validated. For randomised trials evaluating thromboprophylaxis, only control arms will be included for analysis. Also, reference list of systematic reviews and included articles will be searched to

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3 identify additional original studies which were not found through the standard database
4 searching.
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6 *Patient group*

7 We will include studies undertaken on patients ≥ 18 years of age with pancreatic, gastric, or
8 oesophageal cancers diagnosed by histopathology, which have developed or validated a
9 prediction model for VTE prediction. For a study to be included, the diagnosis of VTE should
10 be confirmed by appropriate reference methods (e.g., ultrasonography or computerised
11 tomography). There is no restriction on the stage or grade of cancer. Studies with mixed
12 population/cancer types will also be included provided that they report the relevant
13 information for pancreatic, gastric, or oesophageal cancer subgroups.
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18 *Intervention*

19 Studies must report a prognostic model using multiple prognostic factors to predict the risk
20 of VTE in ambulatory patients with pancreatic or gastro-oesophageal cancer.
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23 *Outcome*

24 Primary outcome to be predicted: Composite of VTE events (which includes symptomatic or
25 incidentally detected VTE and PE, splanchnic venous thrombosis or catheter-related
26 thrombosis)
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30 *Settings*

31 Studies developing models to be used in adult ambulatory patients with cancer.
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35 **Exclusion Criteria**

36 The review will exclude the following:

- 37 1. Studies enrolling patients under 18 years of age only.
- 38 2. All other cancers other than pancreatic, gastric, and oesophageal cancers.
- 39 3. Animal models, and *in vitro* studies.
- 40 4. Studies of VTE diagnosed 6 months prior to or more than 12 months after the
41 diagnosis of cancer.
- 42 5. Studies enrolling patients on long-term (>2 months) anticoagulants, anti-thrombotic
43 or thrombolytic treatment within 3 months prior to recruitment or within the follow-
44 up period.
- 45 6. Studies on mixed types of cancer with no subgroup analysis for pancreatic, gastric or
46 oesophageal cancers.
- 47 7. Studies occasionally reporting VTE as an adverse effect of intervention rather than a
48 study outcome.
- 49 8. Studies purely focused on finding potential predictors of VTE rather than estimating
50 the predictive performance of associated models.
- 51 9. Studies based on genetic profiling only.
- 52 10. Studies published in languages other than English.
- 53 11. Full text unavailable.
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Information sources

We will search all records in the following databases.

1. Medline via EBSCOhost
2. Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost
3. Web of science
4. EMBASE(Scopus)
5. Cochrane library

Use of multiple databases will minimize the selection bias^{50 51}.

Search strategy

We will use both electronic search and manual search strategies to identify relevant articles. The search strategy (below) has been designed with assistance from a liaison librarian at the Faculty of Health, University of Canberra, and was approved by the co-authors AZ, NN, KT, TN, NB, and RM.

One reviewer (AZ) will search the above-mentioned databases using a combination of subject terms with free-text terms and search filters suggested by Geersing et al⁵². The following search words are adopted for each data base : ("Venous Thromboembolism" OR VTE OR Thromboemboli* OR "cancer associated thrombosis" OR CAT OR thrombosis OR "Pulmonary embolism" OR PE OR "deep vein thrombosis" OR DVT) AND ("pancreatic cancer*" OR "pancreatic carcinoma*" OR "carcinoma of pancreas" OR "pancreatic tumor*" OR "pancreatic tumour*" OR "upper gastrointestinal cancer*" OR "upper gastrointestinal carcinoma*" OR "upper gastrointestinal neoplasm*" OR "Pancreatic Neoplasm*" OR "stomach cancer*" OR "gastric cancer*" OR "oesophageal cancer*" OR "esophageal cancer*" OR "cancer of the pancreas") AND ("risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR "nomogram" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*" OR "stratification" OR "ROC curve" OR "discriminate" OR "c-statistics" OR " c statistic" OR " area under the curve" OR "AUC" OR "calibration" OR "indices" OR "algorithm" OR "Multivariable").

Boolean and proximity operators, parentheses, truncation commands will be used in line with the interfaces used for searching the databases. The search will cover from the start of indexing up to the date of publication submission. We will read the reference lists of included studies and relevant review articles to identify additional studies. If required, forward or backward citation will be used in the searching. Furthermore, relevant 'grey literature' will be searched via Google or MedNar. Each of the stages of systematic review including title and abstract screening, full text screening, risk-of-bias assessment, and data extraction will be undertaken by two of the reviewers and the conflicts at each stage will be referred to a third reviewer for resolution.

An example of Medline search strategy is provided in the online supplementary additional file 1. The outcomes of the review will be reported using 'Preferred Reporting Items for systematic Review and Meta-analysis'(PRISMA) checklist 2020⁴⁹ and PRISMA flow diagram will be used to show the selection process.

Study Records

Data management

All study records will be processed through an electronic reference tool, EndNote 20 (Clarivate Analytics), which will facilitate removing the duplicate results. Covidence (Veritas Health Innovation, Melbourne, Australia) will be used for streaming, extracting and recording included and excluded studies.

Study selection and data collection process

Title, abstract, and full text screening will be performed by two researchers independently (AZ & RM) according to predefined criteria for inclusion and exclusion. Any disagreement will be resolved by a third researcher (KT). Data extraction will be conducted by two researchers (AZ) and (RM). The extracted data will be checked by TN and NN.

Data Items

Data extraction from selected studies will be guided primarily by CHARMS checklist⁴⁷. The data extraction, where available, will include author, year of publication, study design, sample size, source of participants (e.g., country, facility type, setting), eligibility criteria of selected participants, treatment and description, study outcome(s), missing data and methods of handling missing data, follow-up period, lost to follow-up, type of VTE risk model(s) and candidate predictors, number of events/sample size, incidence of VTE as well as odds ratios or risk ratios for the predictors, the modeling method and evaluation, model validated internally or externally (yes/no), model presentation (e.g., full presentation of model is given including all variables and their beta weights), model performance such as discrimination (assessed using area under the receiver operating characteristic (ROC) curve or C-statistics (Harrell's C-index)⁵³, calibration measures (e.g., calibration plot and Hosmer-Lemeshow test), and classification measures (i.e., sensitivity, specificity, positive predictive value and negative predictive values). Where an essential piece of information has not been reported for a study, the corresponding author will be contacted via an e-mail for enquiries. Data from all included studies will be extracted using a Microsoft Excel spread sheet (version 2016, Microsoft Office).

Risk of bias assessment

Two researchers AZ and RM will independently assess the risk of bias and applicability of each included study using the Prediction model Risk of Bias ASsessment Tool (PROBAST).⁵⁴ Difficulties encountered, and the conflicts will be discussed and resolved by TN or NB. The PROBAST tool consists of signaling questions divided to four different domains: participants, predictors, outcome, and statistical analysis. Risk of bias in each of the domains will be considered low if signaling questions can be answered with ('probably') 'yes'. Applicability assessment examines whether the model development/validation study matches our systematic review question in terms of the target population, predictors, or outcome of

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3 interest. An overall rating for each domain will be assigned as low, high, or unclear risk of
4 bias.
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6 7 **Data Synthesis**

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9 For each individual study, we will provide a qualitative overview of the model used. Study
10 characteristics and results extracted using CHARMS⁴⁷ checklist, as guidance will be
11 tabulated. This will include: (1) source of data; (2) participant population; (3) number of
12 events /sample size; (4) type of model; (5) outcome type; (6) follow-up time; (7) number of
13 predictors; (8) discrimination; (9) calibration; (10) internal/external validation (yes/no); and
14 (11) presentation of the risk model.
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18 We will use qualitative information synthesis to evaluate the performance characteristics of
19 the models both individually and in comparison, to each other. The odds ratio (OR) or
20 hazard ratios (HR) of risk factors/predictors (derived from published articles) will also be
21 reported.
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24 Clinical and methodological heterogeneity across studies will be assessed by considering
25 variability in the participant's characteristics (e.g., age and sex distribution, setting),
26 definition and measurement methods of outcome assessments and risk of bias. Statistical
27 heterogeneity will be identified using Cochran's Q statistic, which indicates the presence (p
28 < 0.05) or absence ($p > 0.05$) of heterogeneity. To quantify statistical heterogeneity, I^2
29 statistic test will be done. I^2 values between 0–30%, 31–50% and $>50\%$ will indicate mild,
30 moderate, and marked heterogeneity, respectively. A high amount of clinical or statistical
31 heterogeneity may affect our choice of meta-analysis.
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34 Meta-analysis will be undertaken to combine the reported performance measures of the
35 individual models and estimate the overall performance index. If there is clinical
36 homogeneity among the included studies (or sub-sets of them), the random effects model
37 approach will be used instead of the fixed effect approach.
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43 **Meta-Biases**

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45 If more than 10 studies are included in the review, reporting bias will be explored
46 graphically using funnel plot, and statistically by Egger's test. As suggested, $p < 0.05$ will be
47 considered to indicate publication bias.
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50 **DISCUSSION**

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53 Studies have shown that VTE incidence is highest among pancreatic and gastro-oesophageal
54 cancer. Several risk assessments models have been developed to help assess the risk of VTE
55 in ambulatory patients with these types of cancer, but their predictive performance is less
56 known. To the best of our knowledge, no systematic review or VTE prediction models in
57 pancreatic or gastro-oesophageal patients has been published. Thus, we plan to conduct a
58 systematic review and meta-analysis on this subject topic. This review will identify various
59 risk models currently in existence/use, identify their methodological strengths and
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3 limitations, and compare their performance measures. The results of this review will provide
4 the clinicians and researchers with clearer evidence about the usefulness of the current VTE
5 prediction models which can be used in ambulatory patients with pancreatic or gastro-
6 oesophageal cancers. This protocol provides a detailed and complete description of the
7 methodology of our intended systematic review.
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10 This systematic review will have some limitations. First, only studies published in English will
11 be included, which could make us lose data published in other languages. Second, we expect
12 to find some heterogeneity across the included studies in the study population study design,
13 or other elements which may affect the feasibility of a meta-analysis. This could limit the
14 generalisability of our systematic review's findings.
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17 **Ethics and Dissemination**

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20 The proposed systematic review and meta-analyses will collect and analyse data from the
21 published literature; therefore, ethical approval is not required. The results will be
22 submitted for publication in a peer-reviewed journal and presented in a relevant
23 conference. Data generated during the research will be available from the corresponding
24 author upon reasonable request.
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26

27 **Acknowledgements**

28
29 The authors would like to acknowledge the contribution of Mr Murray Turner, the liaison
30 librarian for the faculty of health, University of Canberra, for his support and guidance in
31 designing the search methodology.
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37 **Author Contributions**

38
39 AZ and RM conceived the research idea and planned the entire method of undertaking the
40 study. AZ wrote the draft protocol. AZ, RM, KT, NN, TN and NB designed and finalized the
41 search strategy and planned the data extraction. All authors made contributions to the
42 critical analysis of the manuscript as well as its conceptual development. All authors revised
43 and approved the final version of the manuscript.
44
45
46

47 **Funding**

48
49 The research receives no specific grant from any funding agency in the public, commercial or
50 non-profit sectors.
51
52

53 **Declaration of competing interests**

54
55 The authors have no competing interests to declare.
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58 **Patient and public involvement**

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60 Patients and/or public were not involved in the design, or conduct, or reporting, or

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3 dissemination plans of this research.
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6 **Patient consent for publication**
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8 Not required.
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10 **Data availability statement**
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12 No data were generated in writing this protocol.
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REFERENCES:

1. Martin LK, Bekaii-Saab T. Management of venous thromboembolism in patients with advanced gastrointestinal cancers: what is the role of novel oral anticoagulants? *Thrombosis* 2012;2012
2. Trousseau A. Lectures on clinical medicine at the Hotel-Dieu, Paris, translated from the 1868 edition by Cormack JR, London. *The New Sydenham Society* 1872;5:287.
3. Al-Samkari H, Connors JM. The role of direct oral anticoagulants in treatment of cancer-associated thrombosis. *Cancers* 2018;10(8):271.
4. Blom J, Osanto S, Rosendaal F. High risk of venous thrombosis in patients with pancreatic cancer: a cohort study of 202 patients. *Eur J Cancer* 2006;42(3):410-14.
5. Rollins K, Peters C, Safranek P, et al. Venous thromboembolism in oesophago-gastric carcinoma: incidence of symptomatic and asymptomatic events following chemotherapy and surgery. *Eur J Surg Oncol* 2011;37(12):1072-77.
6. Lyman GH. Venous Thromboembolism in the Patient With Cancer Focus on Burden of Disease and Benefits of Thromboprophylaxis. *CANCER* 2011;117(7):1334-49. doi: 10.1002/cncr.2571
7. Lyman GH, Eckert L, Wang Y, et al. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist* 2013;18(12):1321.
8. Larsen AC, Brøndum Frøkjær J, Wishwanath Iyer V, et al. Venous thrombosis in pancreaticobiliary tract cancer: outcome and prognostic factors. *J Thromb Haemost* 2015;13(4):555-62.
9. Maraveyas A, Muazzam I, Noble S, et al. Advances in managing and preventing thromboembolic disease in cancer patients. *Curr Opin Support Palliat Care* 2017;11(4):347-54.
10. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J cancer* 2012;48(9):1283-92.
11. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol* 2015;33(18):2028-34.
12. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009;10(10):943-49.
13. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012;366(7):601-09.
14. van Doormaal FF, Di Nisio M, Otten H-M, et al. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *J Clin Oncol* 2011;29(15):2071-76.
15. Fuentes H, Oramas D, Paz L, et al. Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. *Thromb Res* 2017;154:28-34.
16. Dallos MC, Eisenberger AB, Bates SE. Prevention of venous thromboembolism in pancreatic cancer: breaking down a complex clinical dilemma. *The oncologist* 2020;25(2):132.
17. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10(2):e1001381.

18. Hendriksen JM, Geersing G-J, Moons KG, et al. Diagnostic and prognostic prediction models. *J Thromb Haemost* 2013;11:129-41.
19. Tritschler T, Méan M, Limacher A, et al. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model. *Blood* 2015;126(16):1949-51.
20. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350(9094):1795-98.
21. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(03):416-20.
22. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111(10):4902-07. doi: 10.1182/blood-2007-10-116327
23. Haltout J, Awada A, Paesmans M, et al. Predictive factors for cancer-associated thrombosis in a large retrospective single-center study. *Support Care Cancer* 2019;27(4):1163-70.
24. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica* 2019;104(6):1277-87. doi: 10.3324/haematol.2018.209114
25. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010;116(24):5377-82. doi: 10.1182/blood-2010-02-270116
26. Posch F, Riedl J, Reitter E-M, et al. Hypercoagulability, venous thromboembolism, and death in patients with cancer. A Multi-State Model. *Thromb Haemost* 2016;115(4):817-26.
27. Lustig DB, Rodriguez R, Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. *Thromb Res* 2015;136(6):1099-102.
28. Muñoz Martín AJ, García Alfonso P, Rupérez Blanco AB, et al. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana's predictive model. *Clin Transl Oncol* 2014;16(10):927-30. doi: 10.1007/s12094-014-1165-y
29. Pelzer U, Sinn M, Stieler J, et al. Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy? *Dtsch Med Wochenschr* 2013;138(41):2084-88.
30. Van Es N, Franke V, Middeldorp S, et al. The Khorana score for the prediction of venous thromboembolism in patients with pancreatic cancer. *Thromb Res* 2017;150:30-32.
31. Mansfield A, Tafur AJ, Wang CE, et al. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016;14(9):1773-78.
32. Rupa-Matysek J, Lembicz M, Rogowska EK, et al. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. *Med Oncol* 2018;35(5):1-10.
33. Fuentes HE, Paz L, Wang Y, et al. Performance of current thromboembolism risk assessment tools in patients with gastric cancer and validity after first treatment. *Clin Appl Thromb Hemost* 2018;24(5):790-96.

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- 2
- 3
- 4 34. Khorana A, Otten H, Zwicker J, et al. Prevention of venous thromboembolism in cancer
- 5 outpatients: guidance from the SSC of the ISTH. *J Thromb Haemost*
- 6 2014;12(11):1928-31.
- 7 35. Noble S, Alikhan R, Robbins A, et al. Predictors of active cancer thromboembolic
- 8 outcomes: validation of the Khorana score among patients with lung cancer:
- 9 comment. *J Thromb Haemost* 2017;15(3):590-91.
- 10 36. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous
- 11 thromboembolism in patients with cancer. *N Engl J Med* 2019;380(8):711-19.
- 12 37. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban thromboprophylaxis in high-risk
- 13 ambulatory cancer patients receiving systemic therapy: results of a randomized
- 14 clinical trial (CASSINI). *Blood* 2018;132(Supplement 1):LBA-1-LBA-1.
- 15 38. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of
- 16 venous thromboembolism in cancer patients: a systematic review and meta-analysis.
- 17 *Haematologica* 2019;104(6):1277-87.
- 18 39. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous
- 19 thromboembolism in cancer patients receiving chemotherapy: the Protecht score.
- 20 *Intern Emerg Med* 2012;7(3):291.
- 21 40. Simanek R, Vormittag R, Ay C, et al. High platelet count associated with venous
- 22 thromboembolism in cancer patients: results from the Vienna Cancer and
- 23 Thrombosis Study (CATS). *J Thromb Haemost* 2010;8(1):114-20.
- 24 41. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous
- 25 thromboembolism in cancer patients: a prospective cohort study. *Haematologica*
- 26 2017;102(9):1494-501.
- 27 42. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of Prophylactic Low-Molecular Weight
- 28 Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From
- 29 the CONKO-004 Trial. *J Clin Oncol* 2015;33(18):2028-34. doi:
- 30 10.1200/JCO.2014.55.1481
- 31 43. Streiff MB, Holmstrom B, Angelini D, et al. NCCN guidelines insights: cancer-associated
- 32 venous thromboembolic disease, version 2.2018. *J Natl Compr Canc Netw*
- 33 2018;16(11):1289-303.
- 34 44. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and
- 35 treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin*
- 36 *Oncol* 2020;38(5):496-520.
- 37 45. National Institute of Health and Care Excellence. Venous Thromboembolism over 16s:
- 38 Reducing the Risk of Hospital-acquired Deep Vein Thrombosis or Pulmonary
- 39 Embolism. NICE Guideline (NG89). 2018 [Available from:
- 40 [https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer)
- 41 [for-people-with-cancer](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer) accessed 11 August 2021.
- 42 46. Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-
- 43 analysis of prediction model performance. *BMJ* 2017;356:i6460. doi:
- 44 10.1136/bmj.i6460
- 45 47. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for
- 46 systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med*
- 47 2014;11(10):e1001744.
- 48 48. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review
- 49 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4(1):1-9.
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49. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021;10(1):89. doi: 10.1186/s13643-021-01626-4
50. Zhao J-G. Combination of multiple databases is necessary for a valid systematic review. *Int Orthop* 2014;38(12):2639-39. doi: 10.1007/s00264-014-2556-y
51. Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol* 2011;64(11):1168-77.
52. Geersing G-J, Bouwmeester W, Zuithoff P, et al. Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. *PloS one* 2012;7(2):e32844.
53. Harrell FE, Califf RM, Pryor DB, et al. Evaluating the yield of medical tests. *JAMA* 1982;247(18):2543-46.
54. Wolff RF, Moons KG, Riley RD, et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. *Ann Intern Med* 2019;170(1)

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For peer review only

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Appendix 1: Medline search via EBSCOhost

S1: (MH "Venous Thromboembolism" OR VTE OR Thromboembolism OR "cancer associated thrombosis" OR CAT OR thrombosis OR MH "Pulmonary Embolism" OR PE OR MH "Venous Thrombosis" OR "deep vein thrombosis" OR DVT)

S2: (MH "Pancreatic Neoplasms" OR "pancreatic cancer*" OR "pancreatic carcinoma*" OR "carcinoma of pancreas" OR "pancreatic tumor*" OR "pancreatic tumour*" OR "cancer of the pancreas" OR MH "Stomach Neoplasms" OR "stomach cancer*" OR "gastric cancer*" OR MH "Esophageal Neoplasms" OR "oesophageal cancer*" OR "esophageal cancer*" OR "upper gastrointestinal cancer" OR "upper gastrointestinal carcinoma*" OR "upper gastrointestinal neoplasm*")

S3: ("risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR MH "Risk Factors" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR MH "nomogram" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*" OR MH "Clinical Decision Rules" OR "stratification" OR MH "ROC curve" OR "discriminate" OR "c-statistics" OR "c statistic" OR "area under the curve" OR "AUC" OR "calibration" OR "indices" OR "algorithm" OR "Multivariable")

S4: S1 AND S2 AND S3

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

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

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

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

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11

Amendments

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4	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
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Support

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11	Sources	#5a Indicate sources of financial or other support for the review	11
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13	Sponsor	#5b Provide name for the review funder and / or sponsor	n/a
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15	Role of sponsor or funder	#5c Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
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Introduction

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22	Rationale	#6 Describe the rationale for the review in the context of what is already known	3-5
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25	Objectives	#7 Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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Methods

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33	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
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40	Information sources	#9 Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
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45	Search strategy	#10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
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49	Study records - data management	#11a Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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53	Study records - selection process	#11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
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58	Study records - data	#11c Describe planned method of extracting data from reports (such as	9
59		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	
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1	collection process		piloting forms, done independently, in duplicate), any processes for	
2			obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought (such as	9
5			PICO items, funding sources), any pre-planned data assumptions and	
6			simplifications	
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9	Outcomes and	#13	List and define all outcomes for which data will be sought, including	7
10	prioritization		prioritization of main and additional outcomes, with rationale	
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13	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	9
14	individual studies		studies, including whether this will be done at the outcome or study	
15			level, or both; state how this information will be used in data synthesis	
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18	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	9-10
19			synthesised	
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22	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned	10
23			summary measures, methods of handling data and methods of	
24			combining data from studies, including any planned exploration of	
25			consistency (such as I ² , Kendall's τ)	
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29	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or	10
30			subgroup analyses, meta-regression)	
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33	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of	10
34			summary planned	
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37	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication	10
38			bias across studies, selective reporting within studies)	
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41	Confidence in	#17	Describe how the strength of the body of evidence will be assessed	n/a
42	cumulative		(such as GRADE)	
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BMJ Open

Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056431.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Dec-2021
Complete List of Authors:	Zaheer, Asma; University of Canberra, Department of Health; University of Canberra Faculty of Health, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) research Group Naumovski, Nenad; University of Canberra, Faculty of Health; University of Canberra Faculty of Health Sciences, Functional Foods and Nutritional Research (FFNR) Laboratory Toohey, Kellie; University of Canberra, School of Health Sciences; University of Canberra Faculty of Health, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) Research group Niyonsenga, Theophile; University of Canberra, Faculty of Health; University of South Australia, School of Health Sciences Yip, Desmond; Canberra Hospital, Department of Medical Oncology; Australian National University, ANU Medical School Brown, Nicholas; University of Canberra Faculty of Health, Faculty of Health; Office of Executive Director of Allied Health, Canberra Health Services, Garran Mortazavi, Reza; University of Canberra Faculty of Health; University of Canberra Faculty of Health Sciences, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) Research group
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, ONCOLOGY, Pancreatic disease < GASTROENTEROLOGY, Thromboembolism < CARDIOLOGY

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Manuscripts

Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

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Article type: Protocol

Word count: 297 (abstract) – 3732(main text)

KEYWORDS: Venous thrombosis; pancreatic neoplasm; gastric neoplasm; oesophageal neoplasm; risk prediction model.

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ABSTRACT

Introduction

Venous thromboembolism (VTE) is a common complication of cancer. Pancreatic and gastro-oesophageal cancers are among malignancies that have the highest rates of VTE occurrence. VTE can increase cancer-related morbidity and mortality and disrupt cancer treatment. The risk of VTE can be managed with measures such as using anticoagulant drugs, although the risk of bleeding may be an impeding factor. Therefore, a VTE risk assessment should be performed before the start of anticoagulation in individual patients. Several prediction models have been published, but most of them have low sensitivity and unknown clinical applicability in pancreatic or gastro-oesophageal cancers. We intend to do this systematic review to identify all applicable published predictive models and compare their performance in those types of cancer.

Methods and analysis

All studies in which a prediction model for VTE have been developed, validated, or compared using adult ambulatory patients with pancreatic or gastro-oesophageal cancers will be identified and the reported predictive performance indicators will be extracted. Full text peer-reviewed journal articles of observational or experimental studies published in English will be included. Five databases (Medline, EMBASE, Web of Science, CINAHL and Cochrane) will be searched. Two reviewers will independently undertake each of the phases of screening, data extraction, and risk of bias assessment. The quality of the selected studies will be assessed using Prediction model Risk Of Bias Assessment Tool (PROBAST). The results from the review will be used for a narrative information synthesis, and if the same models have been validated in multiple studies, meta-analyses will be done to pool the predictive performance measures.

Ethics and dissemination

There is no need for ethics approval because the review will use previously peer-reviewed articles. The results will be published.

PROSPERO registration number: CRD42021253887

Article summary:

Strengths and limitations of this study

- This review will seek to stratify risk models according to their predictive performance for VTE risk.
- The methodological issues identified by this review may help design more robust predictive models.
- High levels of heterogeneity across the studies may affect the feasibility of a meta-analysis.

- Exclusion of journal articles published in languages other than English is a limitation of this study.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs as a serious complication of cancer.¹ The relationship between malignancy and a hypercoagulable state was first described by Armand Trousseau in early 19th century.² VTE is the second most common cause of death in cancer patients.³ Compared to the general population, patients with upper gastrointestinal cancer including gastro-esophageal and pancreas have a 60-fold increased risk of developing a VTE⁴ with approximately 13% diagnosed with a VTE prior to any intervention (e.g., surgery or chemotherapy)⁵ and approximately 21% diagnosed with a VTE within 12 months from cancer diagnosis.^{6,7} In addition to cancer itself, other factors such as treatment modalities (chemotherapy and surgery), and venous access devices may contribute to the risk of VTE in these patients.⁸ Studies have suggested that development of VTE in pancreatic or upper gastrointestinal cancer patients is associated with a poor prognosis.^{8,9}

Several studies have demonstrated that thromboprophylaxis can significantly decrease the rate of VTE events in patients with pancreatic and gastric cancer, especially in outpatients¹⁰⁻¹⁴. However, the management of VTE risk in cancer patients represents a major challenge for clinicians, as the use of anticoagulants can increase the risk of potentially dangerous haemorrhage¹⁵. This risk is even higher in outpatients because they are beyond the observation of medical staff most of the time. Furthermore, although patients with pancreatic cancer have a higher risk for VTE compared to other types of cancer¹⁶, generally, they have twice the risk of major bleeds⁷. This highlights a need for the assessment of the risk of VTE in ambulatory cancer patients before starting anticoagulation. This can be attained through using sensitive and reliable VTE risk prediction models.

Predictive models in health care are statistical tools that use individual patient data (e.g., demographics, patient history, and biomarkers) to help estimate the likelihood of occurring an event, such as VTE, in a defined time^{17,18}. An appropriately built and validated model can improve clinical decision-making and improve patient management. Examples of clinical prediction models include the updated Vienna prediction model for the recurrence of VTE¹⁹; the Wells rule to predict DVT and PE in hospitalised patients^{20,21}; and a well-known risk stratification tool called the Khorana score (KS)²², designed to stratify cancer outpatients prior to the start of chemotherapy according to their risks of developing VTE.

A reliable predictive model for VTE in ambulatory patients with cancer may help reduce the number of patients needed to be treated for VTE by guiding clinicians towards taking a prophylactic approach in high-risk patients. As noted above, a widely used clinical VTE risk assessment tool is the KS which was derived and validated based on a split-sample method.²² The KS was developed in 2008, using the data from a cohort of 2,701 ambulatory patients with different types of cancer and it was further validated in another cohort of

1,365 patients²². In the development of this score, a logistic regression model was used with five clinical and laboratory variables including the type of cancer, the patient's Body Mass Index (BMI), the pre-treatment platelet count, leukocyte count and hemoglobin levels as well as the administration of erythropoietin stimulating agents.²² Notably, for pancreatic and gastric cancers they assigned a score of 2 points, which means that these types of cancer are associated with very high risk of VTE. In the derivation as well as validation cohorts, rates of VTE were 0.8% and 0.3% in the low-risk category (score=1), 1.8% and 2% in the intermediate category (score 1-2), and 7.1 and 6.7% in the high-risk category (score ≥ 3) for a median follow up period of 2.5 months. The two biggest advantages of KS are that firstly it uses patient data which are routinely available during the diagnosis or at the start of chemotherapy; and secondly, it has a high specificity of 93%²³. However, the disadvantages include the model's low sensitivity (23%)²⁴ and its failure in differentiating cancer patients with a low from those with a high risk of VTE.

Several independent investigators have validated the Khorana score²⁵⁻²⁷, but its generalisability to all types of tumors remains controversial as different cancer types have produced mixed results. Studies in pancreatic cancer patients have shown that the KS failed to discriminate high risk from those at intermediate risk for VTE²⁸⁻³⁰. A possible explanation for the poor performance of this score in pancreatic cancer patients may be that only <2% of patients who were included in the development and validation cohorts were patients with pancreatic cancer²². Furthermore, recent studies have reported no significant association between VTE risk and KS³⁰⁻³³. For instance, in a randomized control trial enrolling 312 pancreatic cancer patients showed that none of the Khorana score parameters was associated with risk of VTE.²⁹ Similarly, a study including 112 participants found that risk stratification using Khorana score was not predictive of VTE in the cohort of gastric cancer patients.³³

For outpatients with cancer, initially, a KS cutoff ≥ 3 was suggested to identify patients who are at high risk of VTE³⁴. However, as mentioned above, it was realised that the KS has low sensitivity for certain types of cancer such as pancreatic cancer³⁰ and gastric cancer³³. This issue is also applied to lung cancer^{31,35}. A key reported disadvantage of KS was that more than 50% of patients fell into the intermediate risk group, making it difficult for the physicians to decide whether to use anticoagulation. To alleviate those shortcomings, in two independent trials,^{36,37} undertaken to evaluate the effects of direct oral anticoagulation (DOAC) in ambulatory patients with cancer, a modified KS cutoff value of ≥ 2 was used. CASSINI³⁷ (Clinical Trials.gov identifier: NCT2555878) assessed the use of rivaroxaban in patients with solid tumours (over 50% of the study participants had diagnosis with very high-risk cancer types i.e, pancreatic or gastro-oesophageal) starting systemic anti-neoplastic therapy. The results not only showed significantly reduced VTE and VTE-related death during the treatment period, but also showed that the revised cut off was able to identify cancer patients who were at high risk of VTE both at baseline (4.53%) and during study 8.79% (HR:0.66;95% CI,0.40 to 1.09). The practicability of this revised cutoff value was recently confirmed by Mulder et al in a meta-analysis, using the KS cutoff value of two points or more reported a marked increase in proportion of patients from 17% to 47% in high-risk group with a decreased absolute risk of VTE from 11% (95% CI: 8.8-13.8) to 9% (95% CI: 7.3-10.8) in this group.³⁸

To improve the predictive performance of KS, several modifications have been proposed, such as the addition of D-dimer and P-selectin by the Vienna group of Cancer And

179 Thrombosis Study investigators (CATS score)²⁵, the inclusion of chemotherapeutic agents
 180 such as platinum-based regimens and gemcitabine as in the PROphylaxis of
 181 ThromboEmbolism during CHemoTherapy (PROTECHT) score³⁹, or replacing BMI with the
 182 performance status (used to quantify general wellbeing and daily life activities in cancer
 183 patients) as in the Charité-ONKOlogie (CONKO) score²⁹. The clinical usefulness of these risk
 184 assessment models remains a matter of debate because most of these models performed
 185 well in the initial derivation studies but when externally validated, showed conflicting
 186 results^{28,40}. A multinational prospective cohort study evaluated and compared the
 187 performances of all the above-mentioned risk scores for VTE in patients with solid cancer
 188 and found a poor discriminatory performance of all the scores. However, Vienna CATS and
 189 PROTECHT scores were found to distinguish better in low-risk and high-risk patients⁴¹.

190 Several clinical trials have also demonstrated that the risk of VTE can be reduced in
 191 pancreatic cancer patients on anticoagulant prophylaxis^{10,12-14,42}. Based on the results of
 192 these studies, the National Comprehensive Cancer Network recommended prophylactic
 193 treatment for patients with locally advanced or metastatic pancreatic cancer who are
 194 receiving chemotherapy⁴³. The American Society of Clinical Oncology's (ASCO) practice
 195 guidelines does not recommend routine thromboprophylaxis in all ambulatory cancer
 196 patients; however, they do recommend thromboprophylaxis for patients with Khorana
 197 score of ≥ 2 ⁴⁴ if there are no contraindications. On the other hand, the National Institute for
 198 Health and Care Excellence (NICE) recommended thromboprophylaxis only for patients with
 199 myeloma or pancreatic cancer⁴⁵.

200 Because of the above-mentioned controversies, a better understanding of the strengths and
 201 limitations of the available published VTE risk prediction models applicable to the
 202 ambulatory patients with pancreatic or gastro-oesophageal cancer will be highly useful. To
 203 date, no systematic review has been conducted to assess the predictive performance of risk
 204 assessment models of VTE in those groups of cancer patients. Therefore, this systematic
 205 review will seek to analyse and synthesise information regarding the predictive performance
 206 measures of the available models in assessing the risk of VTE in ambulate patients with
 207 pancreatic or gastro-oesophageal cancer.

208

209 Research question

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211 In adult ambulatory patients with pancreatic or gastro-oesophageal cancer, which VTE risk
 212 prediction model has the best predictive performance (discrimination and calibration)
 213 during the first year following cancer diagnosis?

214 The research question has been outlined according to the PICOTS system⁴⁶ in Table 1
 215 below.

216 **TABLE 1. PICOTS system for predictive models**

Population	Adult ambulatory patients with pancreatic, gastric or oesophageal cancer receiving one or more of the treatment options including systemic chemotherapy, radiation therapy, immunotherapy, and targeted therapy.
Intervention	Use of internally/externally validated predictive models for VTE

Comparator	No predefined comparator. However, models will be compared to each other.
Outcome to be predicted	Venous thromboembolism within 12 months from the cancer diagnosis
Follow up period	12 months from diagnosis of cancer
Setting	Models used in ambulatory settings.

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219 Objectives of the systematic review

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221 The objectives are as follows.

222

- 223 1. Identify all internally and/or externally validated prediction models in the published
- 224 literature, which can be used to predict the risk of VTE in ambulatory patients with
- 225 pancreatic, gastric, or oesophageal cancer separately.
- 226 2. Summarise the characteristics of these prediction models according to valid
- 227 guidelines such as “Critical Appraisal and Data Extraction for Systematic Reviews of
- 228 Prediction Modelling Studies: The CHARMS Checklist”⁴⁷.
- 229 3. Appraise the predictive accuracy (calibration, discrimination, and classification
- 230 measures) for the identified models.
- 231 4. If possible, compare the model performance measures of available risk prediction
- 232 models by meta-analysing the reported performance statistics for the same time
- 233 points across the studies.
- 234 5. Identify the predictors/risk factors for the occurrence of VTE in patients with
- 235 ambulatory pancreatic, gastric or oesophageal cancers.

236

237 METHODS AND ANALYSIS

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239 This study protocol is prepared in compliance with the Preferred Reporting Items for
 240 Systematic Reviews and Meta-analysis Protocol (PRISMA-P)⁴⁸ and the outcomes of the
 241 review will follow Preferred Reporting Items for Systematic Reviews and Meta-analysis
 242 (PRISMA) statement 2020⁴⁹. The methodology for data extraction and evaluation will be
 243 guided by the CHARMS checklist⁴⁷ and the recommendations reported by Debray and
 244 colleagues⁴⁶. The start date for this review is 1 August, 2021, and the anticipated completion
 245 date will be the end of July 2022.

244

245 Eligibility criteria

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247 Inclusion criteria

248 *Study design*

249 This review will include cohort studies (prospective or retrospective), case-control studies
 250 and clinical trials with at least one prediction model developed and/or validated. For

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3 251 randomised trials evaluating thromboprophylaxis, only control arms will be included for
4 252 analysis. Also, reference list of systematic reviews and included articles will be searched to
5 253 identify additional original studies which were not found through the standard database
6 254 searching.
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11 256 *Patient group*

12 257 We will include studies which have developed or validated a prediction model for VTE on
13 258 patients ≥ 18 years of age with pancreatic, gastric, or oesophageal cancers diagnosed by
14 259 histopathology, who were receiving one or more of the treatment options including
15 260 systemic chemotherapy, radiation therapy, immunotherapy, and targeted therapy. For a
16 261 study to be included, the diagnosis of VTE should be confirmed by appropriate reference
17 262 methods (e.g., ultrasonography or computerised tomography). There is no restriction on the
18 263 stage or grade of cancer. Studies with mixed population/cancer types will also be included
19 264 provided that they report the relevant information for pancreatic, gastric, or oesophageal
20 265 cancer subgroups.
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26 267 *Intervention*

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29 268 Studies must report a prognostic model using multiple prognostic factors to predict the risk
30 269 of VTE in ambulatory patients with pancreatic or gastro-oesophageal cancer.
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32 270 *Outcome*

33 271 Primary outcome to be predicted: Composite of VTE events which includes symptomatic or
34 272 incidentally detected VTE (including upper and lower deep and superficial venous
35 273 thrombosis, splanchnic thrombosis and PE) and catheter-related thrombosis.
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40 275 *Settings*

41 276 Studies developing models to be used in adult ambulatory patients with cancer.
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44 279 **Exclusion Criteria**

45 280 The review will exclude the following:

- 46 281 1. Studies enrolling patients under 18 years of age only.
- 47 282 2. All other cancers other than pancreatic, gastric, and oesophageal cancers.
- 48 283 3. Animal models, and *in vitro* studies.
- 49 284 4. Studies of VTE diagnosed 6 months prior to or more than 12 months after the
50 285 diagnosis of cancer.
- 51 286 5. Studies enrolling patients on long-term (>2 months) anticoagulants, anti-thrombotic
52 287 or thrombolytic treatment within 3 months prior to recruitment or within the follow-
53 288 up period.
- 54 289 6. Studies on mixed types of cancer with no subgroup analysis for pancreatic, gastric or
55 290 oesophageal cancers.
- 56 291 7. Studies occasionally reporting VTE as an adverse effect of intervention rather than a
57 292 study outcome.
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3 292 8. Studies purely focused on finding potential predictors of VTE rather than estimating
4 293 the predictive performance of associated models.
5 294 9. Studies based on genetic profiling only.
6 295 10. Studies published in languages other than English.
7 296 11. Full text unavailable.
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12 299 **Information sources**

13 300 We will search all records in the following databases.

- 14 301 1. Medline via EBSCOhost
15 302 2. Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost
16 303 3. Web of science
17 304 4. EMBASE(Scopus)
18 305 5. Cochrane library

19 306 Use of multiple databases will minimize the selection bias^{50 51}.
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22 308 **Search strategy**

23 309 We will use both electronic search and manual search strategies to identify relevant articles.
24 310 The search strategy (below) has been designed with assistance from a liaison librarian at the
25 311 Faculty of Health, University of Canberra, and was approved by the co-authors AZ, NN, KT,
26 312 TN, NB, and RM.
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28 313

29 314 One reviewer (AZ) will search the above-mentioned databases using a combination of
30 315 subject terms with free-text terms and search filters suggested by Geersing et al⁵². The
31 316 following search words are adopted for each data base : (“Venous Thromboembolism” OR
32 317 VTE OR Thromboemboli* OR “cancer associated thrombosis” OR CAT OR thrombosis OR
33 318 “Pulmonary embolism” OR PE OR “deep vein thrombosis” OR DVT) AND (“pancreatic
34 319 cancer*” OR “pancreatic carcinoma*” OR “carcinoma of pancreas” OR “pancreatic tumor*”
35 320 OR “pancreatic tumour*” OR “upper gastrointestinal cancer*” OR “upper gastrointestinal
36 321 carcinoma*” OR “upper gastrointestinal neoplasm*” OR “Pancreatic Neoplasm*” OR
37 322 “stomach cancer*” OR “gastric cancer*” OR “oesophageal cancer*” OR “esophageal
38 323 cancer*” OR “cancer of the pancreas”) AND (“risk model*” OR “risk assessment” OR “risk
39 324 stratification” OR “risk prediction” OR “risk scor*” OR “predict* model*” OR “predictive
40 325 scor*” OR “prediction tool*” OR “nomogram” OR “scoring system*” OR “score system*” OR
41 326 “prognos* predict*” OR “multivaria* predict*” OR “stratification” OR “ROC curve” OR
42 327 “discriminate” OR “c-statistics” OR “ c statistic” OR “ area under the curve” OR “AUC” OR
43 328 “calibration” OR “indices” OR “algorithm” OR “Multivariable”).
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52 330 Boolean and proximity operators, parentheses, truncation commands will be used in line
53 331 with the interfaces used for searching the databases. The search will cover from the start of
54 332 indexing up to the date of publication submission. We will read the reference lists of
55 333 included studies and relevant review articles to identify additional studies. If required,
56 334 forward or backward citation will be used in the searching. Furthermore, relevant ‘grey
57 335 literature’ will be searched via Google or MedNar. Each of the stages of systematic review
58 336 including title and abstract screening, full text screening, risk-of-bias assessment, and data

337 extraction will be undertaken by two of the reviewers and the conflicts at each stage will be
338 referred to a third reviewer for resolution.

339
340 An example of Medline search strategy is provided in the online supplementary additional
341 file 1. The outcomes of the review will be reported using 'Preferred Reporting Items for
342 systematic Review and Meta-analysis'(PRISMA) checklist 2020⁴⁹ and PRISMA flow diagram
343 will be used to show the selection process.

344

345

346 **Study Records**

347 *Data management*

348 All study records will be processed through an electronic reference tool, EndNote 20
349 (Clarivate Analytics), which will facilitate removing the duplicate results. Covidence (Veritas
350 Health Innovation, Melbourne, Australia) will be used for streaming, extracting and
351 recording included and excluded studies.

352

353 *Study selection and data collection process*

354 Title, abstract, and full text screening will be performed by two researchers independently
355 (AZ & RM) according to predefined criteria for inclusion and exclusion. Any disagreement
356 will be resolved by a third researcher (KT). Data extraction will be conducted by two
357 researchers (AZ) and (RM). The extracted data will be checked by TN and NN.

358 **Data Items**

359 Data extraction from selected studies will be guided primarily by CHARMS checklist⁴⁷. The
360 data extraction, where available, will include author, year of publication, study design,
361 sample size, source of participants (e.g., country, facility type, setting), eligibility criteria of
362 selected participants, treatment or type of chemotherapy and description, study
363 outcome(s), patient's performance status, stage of cancer, grade of cancer, missing data and
364 methods of handling missing data, follow-up period, lost to follow-up, type of VTE risk
365 model(s) and candidate predictors, number of events/sample size, incidence of VTE as well
366 as odds ratios or risk ratios for the predictors, the modeling method and evaluation, model
367 validated internally or externally (yes/no), model presentation (e.g., full presentation of
368 model is given including all variables and their beta weights), model performance such as
369 discrimination (assessed using area under the receiver operating characteristic (ROC) curve
370 or C-statistics (Harrell's C-index)⁵³, calibration measures (e.g., calibration plot and Hosmer-
371 Lemeshow test), and classification measures (i.e., sensitivity, specificity, positive predictive
372 value and negative predictive values). Where an essential piece of information has not been
373 reported for a study, the corresponding author will be contacted via an e-mail for enquiries.
374 Data from all included studies will be extracted using a Microsoft Excel spread sheet (version
375 2016, Microsoft Office).

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377 **Risk of bias assessment**

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3 378 Two researchers AZ and RM will independently assess the risk of bias and applicability of
4 379 each included study using the Prediction model Risk of Bias ASsessment Tool (PROBAST).⁵⁴
5 380 Difficulties encountered, and the conflicts will be discussed and resolved by TN or NB. The
6 381 PROBAST tool consists of signaling questions divided to four different domains: participants,
7 382 predictors, outcome, and statistical analysis. Risk of bias in each of the domains will be
8 383 considered low if signaling questions can be answered with ('probably') 'yes'. Applicability
9 384 assessment examines whether the model development/validation study matches our
10 385 systematic review question in terms of the target population, predictors, or outcome of
11 386 interest. An overall rating for each domain will be assigned as low, high, or unclear risk of
12 387 bias.

13 388

14 389 **Data Synthesis**

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17 390 For each individual study, we will provide a qualitative overview of the model used. Study
18 391 characteristics and results extracted using CHARMS ⁴⁷checklist, as guidance will be
19 392 tabulated. This will include: (1) source of data; (2) participant population; (3) number of
20 393 events /sample size; (4) type of model; (5) outcome type; (6) follow-up time; (7) number of
21 394 predictors; (8) discrimination; (9) calibration; (10) internal/external validation (yes/no); and
22 395 (11) presentation of the risk model.

23 396

24 397 We will use qualitative information synthesis to evaluate the performance characteristics of
25 398 the models both individually and in comparison, to each other. The odds ratio (OR) or
26 399 hazard ratios (HR) of risk factors/predictors (derived from published articles) will also be
27 400 reported.

28 401

29 402 Clinical and methodological heterogeneity across studies will be assessed by considering
30 403 variability in the participant's characteristics (e.g., age and sex distribution, setting),
31 404 definition and measurement methods of outcome assessments and risk of bias. Statistical
32 405 heterogeneity will be identified using Cochran's Q statistic, which indicates the presence (p
33 406 < 0.05) or absence ($p > 0.05$) of heterogeneity. To quantify statistical heterogeneity, I^2
34 407 statistic test will be done. I^2 values between 0–30%, 31–50% and $>50\%$ will indicate mild,
35 408 moderate, and marked heterogeneity, respectively. A high amount of clinical or statistical
36 409 heterogeneity may affect our choice of meta-analysis.

37 410 Meta-analysis will be undertaken to combine the reported performance measures of the
38 411 individual models and estimate the overall performance index. If there is clinical
39 412 homogeneity among the included studies (or sub-sets of them), the random effects model
40 413 approach will be used instead of the fixed effect approach. Depending on the availability of
41 414 data, we will undertake separate meta-analyses for prospective studies compared with
42 415 retrospective studies. We may however be obliged to combine both types of studies in case
43 416 of small number of studies in each group.

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46 419 **Meta-Biases**

47 419 If more than 10 studies are included in the review, reporting bias will be explored
48 420 graphically using funnel plot, and statistically by Egger's test. As suggested, $p < 0.05$ will be

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4 421 considered to indicate publication bias.

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6 422 **DISCUSSION**

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8 423 Studies have shown that VTE incidence is highest among pancreatic and gastro-oesophageal
9 424 cancer. Several risk assessments models have been developed to help assess the risk of VTE
10 425 in ambulatory patients with these types of cancer, but their predictive performance is less
11 426 known. To the best of our knowledge, no systematic review or VTE prediction models in
12 427 pancreatic or gastro-oesophageal patients has been published. Thus, we plan to conduct a
13 428 systematic review and meta-analysis on this subject topic. This review will identify various
14 429 risk models currently in existence/use, identify their methodological strengths and
15 430 limitations, and compare their performance measures. The results of this review will provide
16 431 the clinicians and researchers with clearer evidence about the usefulness of the current VTE
17 432 prediction models which can be used in ambulatory patients with pancreatic or gastro-
18 433 oesophageal cancers. This protocol provides a detailed and complete description of the
19 434 methodology of our intended systematic review.

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24 435 This systematic review will have some limitations. First, only studies published in English will
25 436 be included, which could make us lose data published in other languages. Second, we expect
26 437 to find some heterogeneity across the included studies in the study population study design,
27 438 or other elements which may affect the feasibility of a meta-analysis. This could limit the
28 439 generalisability of our systematic review's findings. The assessment of bleeding risk and
29 440 identification of its predictors and risk factors will not be reviewed as it was
30 441 considered to be out of scope of this review.

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41 444 **Ethics and Dissemination**

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43 445 The proposed systematic review and meta-analyses will collect and analyse data from the
44 446 published literature; therefore, ethical approval is not required. The results will be
45 447 submitted for publication in a peer-reviewed journal and presented in a relevant
46 448 conference. Data generated during the research will be available from the corresponding
47 449 author upon reasonable request.

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50
51 450 **Acknowledgements**

52
53 451 The authors would like to acknowledge the contribution of Mr Murray Turner, the liaison
54 452 librarian for the faculty of health, University of Canberra, for his support and guidance in
55 453 designing the search methodology.

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3 455 **Author Contributions**
4

5 456 AZ and RM conceived the research idea and planned the entire method of undertaking the
6 457 study. AZ wrote the draft protocol. AZ, RM, KT, NN, TN and NB designed and finalized the
7 458 search strategy and planned the data extraction. All authors made contributions to the
8 459 critical analysis of the manuscript as well as its conceptual development. All authors revised
9
10 460 and approved the final version of the manuscript.
11
12

13 461 **Funding**
14

15 462 The research receives no specific grant from any funding agency in the public, commercial or
16 463 non-profit sectors.
17

18
19 464 **Declaration of competing interests**
20

21 465 The authors have no competing interests to declare.
22

23
24 466 **Patient and public involvement**
25

26 467 Patients and/or public were not involved in the design, or conduct, or reporting, or
27 468 dissemination plans of this research.
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30 469 **Patient consent for publication**
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32 470 Not required.
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34 471 **Data availability statement**
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36 472 No data were generated in writing this protocol.
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REFERENCES:

1. Martin LK, Bekaii-Saab T. Management of venous thromboembolism in patients with advanced gastrointestinal cancers: what is the role of novel oral anticoagulants? *Thrombosis* 2012;2012
2. Trousseau A. Lectures on clinical medicine at the Hotel-Dieu, Paris, translated from the 1868 edition by Cormack JR, London. *The New Sydenham Society* 1872;5:287.
3. Al-Samkari H, Connors JM. The role of direct oral anticoagulants in treatment of cancer-associated thrombosis. *Cancers* 2018;10(8):271.
4. Blom J, Osanto S, Rosendaal F. High risk of venous thrombosis in patients with pancreatic cancer: a cohort study of 202 patients. *Eur J Cancer* 2006;42(3):410-14.
5. Rollins K, Peters C, Safranek P, et al. Venous thromboembolism in oesophago-gastric carcinoma: incidence of symptomatic and asymptomatic events following chemotherapy and surgery. *Eur J Surg Oncol* 2011;37(12):1072-77.
6. Lyman GH. Venous Thromboembolism in the Patient With Cancer Focus on Burden of Disease and Benefits of Thromboprophylaxis. *CANCER* 2011;117(7):1334-49. doi: 10.1002/cncr.2571
7. Lyman GH, Eckert L, Wang Y, et al. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist* 2013;18(12):1321.
8. Larsen AC, Brøndum Frøkjær J, Wishwanath Iyer V, et al. Venous thrombosis in pancreaticobiliary tract cancer: outcome and prognostic factors. *J Thromb Haemost* 2015;13(4):555-62.
9. Maraveyas A, Muazzam I, Noble S, et al. Advances in managing and preventing thromboembolic disease in cancer patients. *Curr Opin Support Palliat Care* 2017;11(4):347-54.
10. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J cancer* 2012;48(9):1283-92.
11. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol* 2015;33(18):2028-34.
12. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009;10(10):943-49.
13. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012;366(7):601-09.
14. van Doormaal FF, Di Nisio M, Otten H-M, et al. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *J Clin Oncol* 2011;29(15):2071-76.
15. Fuentes H, Oramas D, Paz L, et al. Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. *Thromb Res* 2017;154:28-34.
16. Dallos MC, Eisenberger AB, Bates SE. Prevention of venous thromboembolism in pancreatic cancer: breaking down a complex clinical dilemma. *The oncologist* 2020;25(2):132.
17. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10(2):e1001381.

18. Hendriksen JM, Geersing G-J, Moons KG, et al. Diagnostic and prognostic prediction models. *J Thromb Haemost* 2013;11:129-41.
19. Tritschler T, Méan M, Limacher A, et al. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model. *Blood* 2015;126(16):1949-51.
20. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350(9094):1795-98.
21. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(03):416-20.
22. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111(10):4902-07. doi: 10.1182/blood-2007-10-116327
23. Haltout J, Awada A, Paesmans M, et al. Predictive factors for cancer-associated thrombosis in a large retrospective single-center study. *Support Care Cancer* 2019;27(4):1163-70.
24. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica* 2019;104(6):1277-87. doi: 10.3324/haematol.2018.209114
25. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010;116(24):5377-82. doi: 10.1182/blood-2010-02-270116
26. Posch F, Riedl J, Reitter E-M, et al. Hypercoagulability, venous thromboembolism, and death in patients with cancer. A Multi-State Model. *Thromb Haemost* 2016;115(4):817-26.
27. Lustig DB, Rodriguez R, Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. *Thromb Res* 2015;136(6):1099-102.
28. Muñoz Martín AJ, García Alfonso P, Rupérez Blanco AB, et al. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana's predictive model. *Clin Transl Oncol* 2014;16(10):927-30. doi: 10.1007/s12094-014-1165-y
29. Pelzer U, Sinn M, Stieler J, et al. Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy? *Dtsch Med Wochenschr* 2013;138(41):2084-88.
30. Van Es N, Franke V, Middeldorp S, et al. The Khorana score for the prediction of venous thromboembolism in patients with pancreatic cancer. *Thromb Res* 2017;150:30-32.
31. Mansfield A, Tafur AJ, Wang CE, et al. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016;14(9):1773-78.
32. Rupa-Matysek J, Lembicz M, Rogowska EK, et al. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. *Med Oncol* 2018;35(5):1-10.
33. Fuentes HE, Paz L, Wang Y, et al. Performance of current thromboembolism risk assessment tools in patients with gastric cancer and validity after first treatment. *Clin Appl Thromb Hemost* 2018;24(5):790-96.

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2
3 566 34. Khorana A, Otten H, Zwicker J, et al. Prevention of venous thromboembolism in cancer
4 567 outpatients: guidance from the SSC of the ISTH. *J Thromb Haemost*
5 568 2014;12(11):1928-31.
- 7 569 35. Noble S, Alikhan R, Robbins A, et al. Predictors of active cancer thromboembolic
8 570 outcomes: validation of the Khorana score among patients with lung cancer:
9 571 comment. *J Thromb Haemost* 2017;15(3):590-91.
- 11 572 36. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous
12 573 thromboembolism in patients with cancer. *N Engl J Med* 2019;380(8):711-19.
- 13 574 37. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban thromboprophylaxis in high-risk
14 575 ambulatory cancer patients receiving systemic therapy: results of a randomized
15 576 clinical trial (CASSINI). *Blood* 2018;132(Supplement 1):LBA-1-LBA-1.
- 17 577 38. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of
18 578 venous thromboembolism in cancer patients: a systematic review and meta-analysis.
19 579 *Haematologica* 2019;104(6):1277-87.
- 21 580 39. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous
22 581 thromboembolism in cancer patients receiving chemotherapy: the Protecht score.
23 582 *Intern Emerg Med* 2012;7(3):291.
- 24 583 40. Simanek R, Vormittag R, Ay C, et al. High platelet count associated with venous
25 584 thromboembolism in cancer patients: results from the Vienna Cancer and
26 585 Thrombosis Study (CATS). *J Thromb Haemost* 2010;8(1):114-20.
- 28 586 41. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous
29 587 thromboembolism in cancer patients: a prospective cohort study. *Haematologica*
30 588 2017;102(9):1494-501.
- 31 589 42. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of Prophylactic Low-Molecular Weight
32 590 Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From
33 591 the CONKO-004 Trial. *J Clin Oncol* 2015;33(18):2028-34. doi:
34 592 10.1200/JCO.2014.55.1481
- 36 593 43. Streiff MB, Holmstrom B, Angelini D, et al. NCCN guidelines insights: cancer-associated
37 594 venous thromboembolic disease, version 2.2018. *J Natl Compr Canc Netw*
38 595 2018;16(11):1289-303.
- 40 596 44. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and
41 597 treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin*
42 598 *Oncol* 2020;38(5):496-520.
- 43 599 45. National Institute of Health and Care Excellence. Venous Thromboembolism over 16s:
44 600 Reducing the Risk of Hospital-acquired Deep Vein Thrombosis or Pulmonary
45 601 Embolism. NICE Guideline (NG89). 2018 [Available from:
46 602 [https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer)
47 603 [for-people-with-cancer](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer) accessed 11 August 2021.
- 50 604 46. Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-
51 605 analysis of prediction model performance. *BMJ* 2017;356:i6460. doi:
52 606 10.1136/bmj.i6460
- 53 607 47. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for
54 608 systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med*
55 609 2014;11(10):e1001744.
- 57 610 48. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review
58 611 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4(1):1-9.

- 1
2
3 612 49. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated
4 613 guideline for reporting systematic reviews. *Syst Rev* 2021;10(1):89. doi:
5 614 10.1186/s13643-021-01626-4
6
7 615 50. Zhao J-G. Combination of multiple databases is necessary for a valid systematic review.
8 616 *Int Orthop* 2014;38(12):2639-39. doi: 10.1007/s00264-014-2556-y
9
10 617 51. Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and
11 618 the Effective Health Care Program. *J Clin Epidemiol* 2011;64(11):1168-77.
12 619 52. Geersing G-J, Bouwmeester W, Zuithoff P, et al. Search filters for finding prognostic and
13 620 diagnostic prediction studies in Medline to enhance systematic reviews. *PloS one*
14 621 2012;7(2):e32844.
15 622 53. Harrell FE, Califf RM, Pryor DB, et al. Evaluating the yield of medical tests. *JAMA*
16 623 1982;247(18):2543-46.
17
18 624 54. Wolff RF, Moons KG, Riley RD, et al. PROBAST: a tool to assess the risk of bias and
19 625 applicability of prediction model studies. *Ann Intern Med* 2019;170(1)

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For peer review only

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Appendix 1: Medline search via EBSCOhost

S1: (MH "Venous Thromboembolism" OR VTE OR Thromboembolism OR "cancer associated thrombosis" OR CAT OR thrombosis OR MH "Pulmonary Embolism" OR PE OR MH "Venous Thrombosis" OR "deep vein thrombosis" OR DVT)

S2: (MH "Pancreatic Neoplasms" OR "pancreatic cancer*" OR "pancreatic carcinoma*" OR "carcinoma of pancreas" OR "pancreatic tumor*" OR "pancreatic tumour*" OR "cancer of the pancreas" OR MH "Stomach Neoplasms" OR "stomach cancer*" OR "gastric cancer*" OR MH "Esophageal Neoplasms" OR "oesophageal cancer*" OR "esophageal cancer*" OR "upper gastrointestinal cancer" OR "upper gastrointestinal carcinoma*" OR "upper gastrointestinal neoplasm*")

S3: ("risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR MH "Risk Factors" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR MH "nomogram" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*" OR MH "Clinical Decision Rules" OR "stratification" OR MH "ROC curve" OR "discriminate" OR "c-statistics" OR "c statistic" OR "area under the curve" OR "AUC" OR "calibration" OR "indices" OR "algorithm" OR "Multivariable")

S4: S1 AND S2 AND S3

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

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

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

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

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11

Amendments

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4	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
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Support

10	Sources	#5a	Indicate sources of financial or other support for the review	11
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13	Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
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15	Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
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Introduction

21	Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
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25	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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Methods

33	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
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40	Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
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45	Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
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49	Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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53	Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
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58	Study records - data	#11c	Describe planned method of extracting data from reports (such as	9
59			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	
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1	collection process		piloting forms, done independently, in duplicate), any processes for	
2			obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought (such as	9
5			PICO items, funding sources), any pre-planned data assumptions and	
6			simplifications	
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9	Outcomes and	#13	List and define all outcomes for which data will be sought, including	7
10	prioritization		prioritization of main and additional outcomes, with rationale	
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13	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	9
14	individual studies		studies, including whether this will be done at the outcome or study	
15			level, or both; state how this information will be used in data synthesis	
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18	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	9-10
19			synthesised	
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22	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned	10
23			summary measures, methods of handling data and methods of	
24			combining data from studies, including any planned exploration of	
25			consistency (such as I ² , Kendall's τ)	
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29	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or	10
30			subgroup analyses, meta-regression)	
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33	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of	10
34			summary planned	
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37	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication	10
38			bias across studies, selective reporting within studies)	
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41	Confidence in	#17	Describe how the strength of the body of evidence will be assessed	n/a
42	cumulative		(such as GRADE)	
43	evidence			
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BMJ Open

Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056431.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2022
Complete List of Authors:	Zaheer, Asma; University of Canberra, Department of Health; University of Canberra Faculty of Health, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) research Group Naumovski, Nenad; University of Canberra, Faculty of Health; University of Canberra Faculty of Health Sciences, Functional Foods and Nutritional Research (FFNR) Laboratory Toohey, Kellie; University of Canberra, School of Health Sciences; University of Canberra Faculty of Health, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) Research group Niyonsenga, Theophile; University of Canberra, Faculty of Health; University of South Australia, School of Health Sciences Yip, Desmond; Canberra Hospital, Department of Medical Oncology; Australian National University, ANU Medical School Brown, Nicholas; University of Canberra Faculty of Health, Faculty of Health; Office of Executive Director of Allied Health, Canberra Health Services, Garran Mortazavi, Reza; University of Canberra Faculty of Health; University of Canberra Faculty of Health Sciences, Prehab, Activity, Cancer, Exercise and Survivorship (PACES) Research group
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	Gastrointestinal tumours < GASTROENTEROLOGY, ONCOLOGY, Pancreatic disease < GASTROENTEROLOGY, Thromboembolism < CARDIOLOGY

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Manuscripts

Prediction models for venous thromboembolism in ambulatory adults with pancreatic and gastro-oesophageal cancer: protocol for systematic review and meta-analysis

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Article type: Protocol

Word count: 297 (abstract) – 3732(main text)

KEYWORDS: Venous thrombosis; pancreatic neoplasm; gastric neoplasm; oesophageal neoplasm; risk prediction model.

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ABSTRACT

Introduction

Venous thromboembolism (VTE) is a common complication of cancer. Pancreatic and gastro-oesophageal cancers are among malignancies that have the highest rates of VTE occurrence. VTE can increase cancer-related morbidity and mortality and disrupt cancer treatment. The risk of VTE can be managed with measures such as using anticoagulant drugs, although the risk of bleeding may be an impeding factor. Therefore, a VTE risk assessment should be performed before the start of anticoagulation in individual patients. Several prediction models have been published, but most of them have low sensitivity and unknown clinical applicability in pancreatic or gastro-oesophageal cancers. We intend to do this systematic review to identify all applicable published predictive models and compare their performance in those types of cancer.

Methods and analysis

All studies in which a prediction model for VTE have been developed, validated, or compared using adult ambulatory patients with pancreatic or gastro-oesophageal cancers will be identified and the reported predictive performance indicators will be extracted. Full text peer-reviewed journal articles of observational or experimental studies published in English will be included. Five databases (Medline, EMBASE, Web of Science, CINAHL and Cochrane) will be searched. Two reviewers will independently undertake each of the phases of screening, data extraction, and risk of bias assessment. The quality of the selected studies will be assessed using Prediction model Risk Of Bias Assessment Tool (PROBAST). The results from the review will be used for a narrative information synthesis, and if the same models have been validated in multiple studies, meta-analyses will be done to pool the predictive performance measures.

Ethics and dissemination

There is no need for ethics approval because the review will use previously peer-reviewed articles. The results will be published.

PROSPERO registration number: CRD42021253887

Article summary:

Strengths and limitations of this study

- This review will seek to stratify risk models according to their predictive performance for VTE risk.
- The methodological issues identified by this review may help design more robust predictive models.
- High levels of heterogeneity across the studies may affect the feasibility of a meta-analysis.

- Exclusion of journal articles published in languages other than English is a limitation of this study.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs as a serious complication of cancer.¹ The relationship between malignancy and a hypercoagulable state was first described by Armand Trousseau in early 19th century.² VTE is the second most common cause of death in cancer patients.³ Compared to the general population, patients with upper gastrointestinal cancer including gastro-esophageal and pancreas have a 60-fold increased risk of developing a VTE⁴ with approximately 13% diagnosed with a VTE prior to any intervention (e.g., surgery or chemotherapy)⁵ and approximately 21% diagnosed with a VTE within 12 months from cancer diagnosis.^{6,7} In addition to cancer itself, other factors such as treatment modalities (chemotherapy and surgery), and venous access devices may contribute to the risk of VTE in these patients.⁸ Studies have suggested that development of VTE in pancreatic or upper gastrointestinal cancer patients is associated with a poor prognosis.^{8,9}

Several studies have demonstrated that thromboprophylaxis can significantly decrease the rate of VTE events in patients with pancreatic and gastric cancer, especially in outpatients¹⁰⁻¹⁴. However, the management of VTE risk in cancer patients represents a major challenge for clinicians, as the use of anticoagulants can increase the risk of potentially dangerous haemorrhage¹⁵. This risk is even higher in outpatients because they are beyond the observation of medical staff most of the time. Furthermore, although patients with pancreatic cancer have a higher risk for VTE compared to other types of cancer¹⁶, generally, they have twice the risk of major bleeds⁷. This highlights a need for the assessment of the risk of VTE in ambulatory cancer patients before starting anticoagulation. This can be attained through using sensitive and reliable VTE risk prediction models.

Predictive models in health care are statistical tools that use individual patient data (e.g., demographics, patient history, and biomarkers) to help estimate the likelihood of occurring an event, such as VTE, in a defined time^{17,18}. An appropriately built and validated model can improve clinical decision-making and improve patient management. Examples of clinical prediction models include the updated Vienna prediction model for the recurrence of VTE¹⁹; the Wells rule to predict DVT and PE in hospitalised patients^{20,21}; and a well-known risk stratification tool called the Khorana score (KS)²², designed to stratify cancer outpatients prior to the start of chemotherapy according to their risks of developing VTE.

A reliable predictive model for VTE in ambulatory patients with cancer may help reduce the number of patients needed to be treated for VTE by guiding clinicians towards taking a prophylactic approach in high-risk patients. As noted above, a widely used clinical VTE risk assessment tool is the KS which was derived and validated based on a split-sample method.²² The KS was developed in 2008, using the data from a cohort of 2,701 ambulatory patients with different types of cancer and it was further validated in another cohort of

1,365 patients²². In the development of this score, a logistic regression model was used with five clinical and laboratory variables including the type of cancer, the patient's Body Mass Index (BMI), the pre-treatment platelet count, leukocyte count and hemoglobin levels as well as the administration of erythropoietin stimulating agents.²² Notably, for pancreatic and gastric cancers they assigned a score of 2 points, which means that these types of cancer are associated with very high risk of VTE. In the derivation as well as validation cohorts, rates of VTE were 0.8% and 0.3% in the low-risk category (score=1), 1.8% and 2% in the intermediate category (score 1-2), and 7.1 and 6.7% in the high-risk category (score ≥ 3) for a median follow up period of 2.5 months. The two biggest advantages of KS are that firstly it uses patient data which are routinely available during the diagnosis or at the start of chemotherapy; and secondly, it has a high specificity of 93%²³. However, the disadvantages include the model's low sensitivity (23%)²⁴ and its failure in differentiating cancer patients with a low from those with a high risk of VTE.

Several independent investigators have validated the Khorana score²⁵⁻²⁷, but its generalisability to all types of tumors remains controversial as different cancer types have produced mixed results. Studies in pancreatic cancer patients have shown that the KS failed to discriminate high risk from those at intermediate risk for VTE²⁸⁻³⁰. A possible explanation for the poor performance of this score in pancreatic cancer patients may be that only <2% of patients who were included in the development and validation cohorts were patients with pancreatic cancer²². Furthermore, recent studies have reported no significant association between VTE risk and KS³⁰⁻³³. For instance, in a randomized control trial enrolling 312 pancreatic cancer patients showed that none of the Khorana score parameters was associated with risk of VTE.²⁹ Similarly, a study including 112 participants found that risk stratification using Khorana score was not predictive of VTE in the cohort of gastric cancer patients.³³

For outpatients with cancer, initially, a KS cutoff ≥ 3 was suggested to identify patients who are at high risk of VTE³⁴. However, as mentioned above, it was realised that the KS has low sensitivity for certain types of cancer such as pancreatic cancer³⁰ and gastric cancer³³. This issue is also applied to lung cancer^{31,35}. A key reported disadvantage of KS was that more than 50% of patients fell into the intermediate risk group, making it difficult for the physicians to decide whether to use anticoagulation. To alleviate those shortcomings, in two independent trials,^{36,37} undertaken to evaluate the effects of direct oral anticoagulation (DOAC) in ambulatory patients with cancer, a modified KS cutoff value of ≥ 2 was used. CASSINI³⁷ (Clinical Trials.gov identifier: NCT2555878) assessed the use of rivaroxaban in patients with solid tumours (over 50% of the study participants had diagnosis with very high-risk cancer types i.e, pancreatic or gastro-oesophageal) starting systemic anti-neoplastic therapy. The results not only showed significantly reduced VTE and VTE-related death during the treatment period, but also showed that the revised cut off was able to identify cancer patients who were at high risk of VTE both at baseline (4.53%) and during study 8.79% (HR:0.66;95% CI,0.40 to 1.09). The practicability of this revised cutoff value was recently confirmed by Mulder et al in a meta-analysis, using the KS cutoff value of two points or more reported a marked increase in proportion of patients from 17% to 47% in high-risk group with a decreased absolute risk of VTE from 11% (95% CI: 8.8-13.8) to 9% (95% CI: 7.3-10.8) in this group.³⁸

To improve the predictive performance of KS, several modifications have been proposed, such as the addition of D-dimer and P-selectin by the Vienna group of Cancer And

179 Thrombosis Study investigators (CATS score)²⁵, the inclusion of chemotherapeutic agents
 180 such as platinum-based regimens and gemcitabine as in the PROphylaxis of
 181 ThromboEmbolism during CHemoTherapy (PROTECHT) score³⁹, or replacing BMI with the
 182 performance status (used to quantify general wellbeing and daily life activities in cancer
 183 patients) as in the Charité-ONKOlogie (CONKO) score²⁹. The clinical usefulness of these risk
 184 assessment models remains a matter of debate because most of these models performed
 185 well in the initial derivation studies but when externally validated, showed conflicting
 186 results^{28,40}. A multinational prospective cohort study evaluated and compared the
 187 performances of all the above-mentioned risk scores for VTE in patients with solid cancer
 188 and found a poor discriminatory performance of all the scores. However, Vienna CATS and
 189 PROTECHT scores were found to distinguish better in low-risk and high-risk patients⁴¹.

190 Several clinical trials have also demonstrated that the risk of VTE can be reduced in
 191 pancreatic cancer patients on anticoagulant prophylaxis^{10,12-14,42}. Based on the results of
 192 these studies, the National Comprehensive Cancer Network recommended prophylactic
 193 treatment for patients with locally advanced or metastatic pancreatic cancer who are
 194 receiving chemotherapy⁴³. The American Society of Clinical Oncology's (ASCO) practice
 195 guidelines does not recommend routine thromboprophylaxis in all ambulatory cancer
 196 patients; however, they do recommend thromboprophylaxis for patients with Khorana
 197 score of ≥ 2 ⁴⁴ if there are no contraindications. On the other hand, the National Institute for
 198 Health and Care Excellence (NICE) recommended thromboprophylaxis only for patients with
 199 myeloma or pancreatic cancer⁴⁵.

200 Because of the above-mentioned controversies, a better understanding of the strengths and
 201 limitations of the available published VTE risk prediction models applicable to the
 202 ambulatory patients with pancreatic or gastro-oesophageal cancer will be highly useful. To
 203 date, no systematic review has been conducted to assess the predictive performance of risk
 204 assessment models of VTE in those groups of cancer patients. Therefore, this systematic
 205 review will seek to analyse and synthesise information regarding the predictive performance
 206 measures of the available models in assessing the risk of VTE in ambulate patients with
 207 pancreatic or gastro-oesophageal cancer.

208

209 Research question

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211 In adult ambulatory patients with pancreatic or gastro-oesophageal cancer, which VTE risk
 212 prediction model has the best predictive performance (discrimination and calibration)
 213 during the first year following cancer diagnosis?

214 The research question has been outlined according to the PICOTS system⁴⁶ in Table 1
 215 below.

216 **TABLE 1. PICOTS system for predictive models**

Population	Adult ambulatory patients with pancreatic, gastric or oesophageal cancer receiving one or more of the treatment options including systemic chemotherapy, radiation therapy, immunotherapy, and targeted therapy.
Intervention	Use of internally/externally validated predictive models for VTE

Comparator	No predefined comparator. However, models will be compared to each other.
Outcome to be predicted	Venous thromboembolism within 12 months from the cancer diagnosis
Follow up period	12 months from diagnosis of cancer
Setting	Models used in ambulatory settings.

217

218

219 Objectives of the systematic review

220

221 The objectives are as follows.

222

- 223 1. Identify all internally and/or externally validated prediction models in the published
224 literature, which can be used to predict the risk of VTE in ambulatory patients with
225 pancreatic, gastric, or oesophageal cancer separately.
- 226 2. Summarise the characteristics of these prediction models according to valid
227 guidelines such as “Critical Appraisal and Data Extraction for Systematic Reviews of
228 Prediction Modelling Studies: The CHARMS Checklist”⁴⁷.
- 229 3. Appraise the predictive accuracy (calibration, discrimination, and classification
230 measures) for the identified models.
- 231 4. If possible, compare the model performance measures of available risk prediction
232 models by meta-analysing the reported performance statistics for the same time
233 points across the studies.
- 234 5. Identify the predictors/risk factors for the occurrence of VTE in patients with
235 ambulatory pancreatic, gastric or oesophageal cancers.

236

237 METHODS AND ANALYSIS

238

239 This study protocol is prepared in compliance with the Preferred Reporting Items for
240 Systematic Reviews and Meta-analysis Protocol (PRISMA-P)⁴⁸ and the outcomes of the
241 review will follow Preferred Reporting Items for Systematic Reviews and Meta-analysis
242 (PRISMA) statement 2020⁴⁹. The methodology for data extraction and evaluation will be
243 guided by the CHARMS checklist⁴⁷ and the recommendations reported by Debray and
244 colleagues⁴⁶. The start date for this review is 1 August, 2021, and the anticipated completion
245 date will be the end of July 2022.

244

245 Eligibility criteria

246

247 Inclusion criteria

248 *Study design*

249 This review will include cohort studies (prospective or retrospective), case-control studies
250 and clinical trials with at least one prediction model developed and/or validated. For

251 randomised trials evaluating thromboprophylaxis, only control arms will be included for
252 analysis. Also, reference list of systematic reviews and included articles will be searched to
253 identify additional original studies which were not found through the standard database
254 searching.

255

256 *Patient group*

257 We will include studies which have developed or validated a prediction model for VTE on
258 patients ≥ 18 years of age with pancreatic, gastric, or oesophageal cancers diagnosed by
259 histopathology, who were receiving one or more of the treatment options including
260 systemic chemotherapy, radiation therapy, immunotherapy, and targeted therapy. For a
261 study to be included, the diagnosis of VTE should be confirmed by appropriate reference
262 methods (e.g., ultrasonography or computerised tomography). There is no restriction on the
263 stage or grade of cancer. Studies with mixed population/cancer types will also be included
264 provided that they report the relevant information for pancreatic, gastric, or oesophageal
265 cancer subgroups.

266

267 *Intervention*

268 Studies must report a prognostic model using multiple prognostic factors to predict the risk
269 of VTE in ambulatory patients with pancreatic or gastro-oesophageal cancer.

270 *Outcome*

271 Primary outcome to be predicted: Composite of VTE events which includes symptomatic or
272 incidentally detected VTE (including upper and lower deep and superficial venous
273 thrombosis, splanchnic thrombosis and PE) and catheter-related thrombosis.

274

275 *Settings*

276 Studies developing models to be used in adult ambulatory patients with cancer.

277

278 **Exclusion Criteria**

279 The review will exclude the following:

- 280 1. Studies enrolling patients under 18 years of age only.
- 281 2. All other cancers other than pancreatic, gastric, and oesophageal cancers.
- 282 3. Animal models, and *in vitro* studies.
- 283 4. Studies of VTE diagnosed 6 months prior to or more than 12 months after the
284 diagnosis of cancer.
- 285 5. Studies enrolling patients on long-term (>2 months) anticoagulants, anti-thrombotic
286 or thrombolytic treatment within 3 months prior to recruitment or within the follow-
287 up period.
- 288 6. Studies on mixed types of cancer with no subgroup analysis for pancreatic, gastric or
289 oesophageal cancers.
- 290 7. Studies occasionally reporting VTE as an adverse effect of intervention rather than a
291 study outcome.

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3 292 8. Studies purely focused on finding potential predictors of VTE rather than estimating
4 293 the predictive performance of associated models.
5 294 9. Studies based on genetic profiling only.
6 295 10. Studies published in languages other than English.
7 296 11. Full text unavailable.
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12 299 **Information sources**

13 300 We will search all records in the following databases.

- 14 301 1. Medline via EBSCOhost
15 302 2. Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost
16 303 3. Web of science
17 304 4. EMBASE(Scopus)
18 305 5. Cochrane library

19 306 Use of multiple databases will minimize the selection bias^{50 51}.
20
21 307

22 308 **Search strategy**

23 309 We will use both electronic search and manual search strategies to identify relevant articles.
24 310 The search strategy (below) has been designed with assistance from a liaison librarian at the
25 311 Faculty of Health, University of Canberra, and was approved by the co-authors AZ, NN, KT,
26 312 TN, NB, and RM.
27
28 313

29 314 One reviewer (AZ) will search the above-mentioned databases using a combination of
30 315 subject terms with free-text terms and search filters suggested by Geersing et al⁵². The
31 316 following search words are adopted for each data base : (“Venous Thromboembolism” OR
32 317 VTE OR Thromboemboli* OR “cancer associated thrombosis” OR CAT OR thrombosis OR
33 318 “Pulmonary embolism” OR PE OR “deep vein thrombosis” OR DVT) AND (“pancreatic
34 319 cancer*” OR “pancreatic carcinoma*” OR “carcinoma of pancreas” OR “pancreatic tumor*”
35 320 OR “pancreatic tumour*” OR “upper gastrointestinal cancer*” OR “upper gastrointestinal
36 321 carcinoma*” OR “upper gastrointestinal neoplasm*” OR “Pancreatic Neoplasm*” OR
37 322 “stomach cancer*” OR “gastric cancer*” OR “oesophageal cancer*” OR “esophageal
38 323 cancer*” OR “cancer of the pancreas”) AND (“risk model*” OR “risk assessment” OR “risk
39 324 stratification” OR “risk prediction” OR “risk scor*” OR “predict* model*” OR “predictive
40 325 scor*” OR “prediction tool*” OR “nomogram” OR “scoring system*” OR “score system*” OR
41 326 “prognos* predict*” OR “multivaria* predict*” OR “stratification” OR “ROC curve” OR
42 327 “discriminate” OR “c-statistics” OR “ c statistic” OR “ area under the curve” OR “AUC” OR
43 328 “calibration” OR “indices” OR “algorithm” OR “Multivariable”).
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51 329
52 330 Boolean and proximity operators, parentheses, truncation commands will be used in line
53 331 with the interfaces used for searching the databases. The search will cover from the start of
54 332 indexing up to the date of publication submission. We will read the reference lists of
55 333 included studies and relevant review articles to identify additional studies. If required,
56 334 forward or backward citation will be used in the searching. Furthermore, relevant ‘grey
57 335 literature’ will be searched via Google or MedNar. Each of the stages of systematic review
58 336 including title and abstract screening, full text screening, risk-of-bias assessment, and data

337 extraction will be undertaken by two of the reviewers and the conflicts at each stage will be
338 referred to a third reviewer for resolution.

339
340 An example of Medline search strategy is provided in the online supplementary additional
341 file 1. The outcomes of the review will be reported using 'Preferred Reporting Items for
342 systematic Review and Meta-analysis'(PRISMA) checklist 2020⁴⁹ and PRISMA flow diagram
343 will be used to show the selection process.

344

345

346 **Study Records**

347 *Data management*

348 All study records will be processed through an electronic reference tool, EndNote 20
349 (Clarivate Analytics), which will facilitate removing the duplicate results. Covidence (Veritas
350 Health Innovation, Melbourne, Australia) will be used for streaming, extracting and
351 recording included and excluded studies.

352

353 *Study selection and data collection process*

354 Title, abstract, and full text screening will be performed by two researchers independently
355 (AZ & RM) according to predefined criteria for inclusion and exclusion. Any disagreement
356 will be resolved by a third researcher (KT). Data extraction will be conducted by two
357 researchers (AZ) and (RM). The extracted data will be checked by TN and NN.

358 **Data Items**

359 Data extraction from selected studies will be guided primarily by CHARMS checklist⁴⁷. The
360 data extraction, where available, will include author, year of publication, study design,
361 sample size, source of participants (e.g., country, facility type, setting), eligibility criteria of
362 selected participants, treatment or type of chemotherapy and description, study
363 outcome(s), patient's performance status, stage of cancer, grade of cancer, missing data and
364 methods of handling missing data, follow-up period, lost to follow-up, type of VTE risk
365 model(s) and candidate predictors, number of events/sample size, incidence of VTE as well
366 as odds ratios or risk ratios for the predictors, the modeling method and evaluation, model
367 validated internally or externally (yes/no), model presentation (e.g., full presentation of
368 model is given including all variables and their beta weights), model performance such as
369 discrimination (assessed using area under the receiver operating characteristic (ROC) curve
370 or C-statistics (Harrell's C-index)⁵³, calibration measures (e.g., calibration plot and Hosmer-
371 Lemeshow test), and classification measures (i.e., sensitivity, specificity, positive predictive
372 value and negative predictive values). Where an essential piece of information has not been
373 reported for a study, the corresponding author will be contacted via an e-mail for enquiries.
374 Data from all included studies will be extracted using a Microsoft Excel spread sheet (version
375 2016, Microsoft Office).

376

377 **Risk of bias assessment**

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3 378 Two researchers AZ and RM will independently assess the risk of bias and applicability of
4 379 each included study using the Prediction model Risk of Bias ASsessment Tool (PROBAST).⁵⁴
5 380 Difficulties encountered, and the conflicts will be discussed and resolved by TN or NB. The
6 381 PROBAST tool consists of signaling questions divided to four different domains: participants,
7 382 predictors, outcome, and statistical analysis. Risk of bias in each of the domains will be
8 383 considered low if signaling questions can be answered with ('probably') 'yes'. Applicability
9 384 assessment examines whether the model development/validation study matches our
10 385 systematic review question in terms of the target population, predictors, or outcome of
11 386 interest. An overall rating for each domain will be assigned as low, high, or unclear risk of
12 387 bias.

13 388

14 389 **Data Synthesis**

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16
17 390 For each individual study, we will provide a qualitative overview of the model used. Study
18 391 characteristics and results extracted using CHARMS ⁴⁷checklist, as guidance will be
19 392 tabulated. This will include: (1) source of data; (2) participant population; (3) number of
20 393 events /sample size; (4) type of model; (5) outcome type; (6) follow-up time; (7) number of
21 394 predictors; (8) discrimination; (9) calibration; (10) internal/external validation (yes/no); and
22 395 (11) presentation of the risk model.

23 396

24 397 We will use qualitative information synthesis to evaluate the performance characteristics of
25 398 the models both individually and in comparison, to each other. The odds ratio (OR) or
26 399 hazard ratios (HR) of risk factors/predictors (derived from published articles) will also be
27 400 reported.

28 401

29 402 Clinical and methodological heterogeneity across studies will be assessed by considering
30 403 variability in the participant's characteristics (e.g., age and sex distribution, setting),
31 404 definition and measurement methods of outcome assessments and risk of bias. Statistical
32 405 heterogeneity will be identified using Cochran's Q statistic, which indicates the presence (p
33 406 < 0.05) or absence ($p > 0.05$) of heterogeneity. To quantify statistical heterogeneity, I^2
34 407 statistic test will be done. I^2 values between 0–30%, 31–50% and $>50\%$ will indicate mild,
35 408 moderate, and marked heterogeneity, respectively. A high amount of clinical or statistical
36 409 heterogeneity may affect our choice of meta-analysis.

37 410 Meta-analysis will be undertaken to combine the reported performance measures of the
38 411 individual models and estimate the overall performance index. If there is clinical
39 412 homogeneity among the included studies (or sub-sets of them), the random effects model
40 413 approach will be used instead of the fixed effect approach. Depending on the availability of
41 414 data, we will undertake separate meta-analyses for prospective and retrospective studies.

42 415

43 416 **Meta-Biases**

44 417 If more than 10 studies are included in the review, reporting bias will be explored
45 418 graphically using funnel plot, and statistically by Egger's test. As suggested, $p < 0.05$ will be
46 419 considered to indicate publication bias.

47 420

420 **DISCUSSION**

421 Studies have shown that VTE incidence is highest among pancreatic and gastro-oesophageal
422 cancer. Several risk assessments models have been developed to help assess the risk of VTE
423 in ambulatory patients with these types of cancer, but their predictive performance is less
424 known. To the best of our knowledge, no systematic review or VTE prediction models in
425 pancreatic or gastro-oesophageal patients has been published. Thus, we plan to conduct a
426 systematic review and meta-analysis on this subject topic. This review will identify various
427 risk models currently in existence/use, identify their methodological strengths and
428 limitations, and compare their performance measures. The results of this review will provide
429 the clinicians and researchers with clearer evidence about the usefulness of the current VTE
430 prediction models which can be used in ambulatory patients with pancreatic or gastro-
431 oesophageal cancers. This protocol provides a detailed and complete description of the
432 methodology of our intended systematic review.

433 This systematic review will have some limitations. First, only studies published in English will
434 be included, which could make us lose data published in other languages. Second, we expect
435 to find some heterogeneity across the included studies in the study population study design,
436 or other elements which may affect the feasibility of a meta-analysis. This could limit the
437 generalisability of our systematic review's findings. The assessment of bleeding risk and
438 identification of its predictors and risk factors will not be reviewed as it was considered to
439 be out of scope of this review.

440

441

442 **Ethics and Dissemination**

443 The proposed systematic review and meta-analyses will collect and analyse data from the
444 published literature; therefore, ethical approval is not required. The results will be
445 submitted for publication in a peer-reviewed journal and presented in a relevant
446 conference. Data generated during the research will be available from the corresponding
447 author upon reasonable request.

448 **Acknowledgements**

449 The authors would like to acknowledge the contribution of Mr Murray Turner, the liaison
450 librarian for the faculty of health, University of Canberra, for his support and guidance in
451 designing the search methodology.

452

453 **Author Contributions**

454 AZ and RM conceived the research idea and planned the entire method of undertaking the
455 study. AZ wrote the draft protocol. AZ, RM, KT, NN, TN, DY, and NB designed and finalized

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2
3 456 the search strategy and planned the data extraction. All authors made contributions to the
4 457 critical analysis of the manuscript as well as its conceptual development. All authors revised
5 458 and approved the final version of the manuscript.
6
7

8 459 **Funding**

9
10 460 The research receives no specific grant from any funding agency in the public, commercial or
11 461 non-profit sectors.
12

13 462 **Declaration of competing interests**

14
15
16 463 The authors have no competing interests to declare.
17

18 464 **Patient and public involvement**

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20 465 Patients and/or public were not involved in the design, or conduct, or reporting, or
21 466 dissemination plans of this research.
22
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24 467 **Patient consent for publication**

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26 468 Not required.
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29 469 **Data availability statement**

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31 470 No data were generated in writing this protocol.
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472 **REFERENCES:**

- 473 1. Martin LK, Bekaii-Saab T. Management of venous thromboembolism in patients with
474 advanced gastrointestinal cancers: what is the role of novel oral anticoagulants?
475 *Thrombosis* 2012;2012
- 476 2. Trousseau A. Lectures on clinical medicine at the Hotel-Dieu, Paris, translated from the
477 1868 edition by Cormack JR, London. *The New Sydenham Society* 1872;5:287.
- 478 3. Al-Samkari H, Connors JM. The role of direct oral anticoagulants in treatment of cancer-
479 associated thrombosis. *Cancers* 2018;10(8):271.
- 480 4. Blom J, Osanto S, Rosendaal F. High risk of venous thrombosis in patients with pancreatic
481 cancer: a cohort study of 202 patients. *Eur J Cancer* 2006;42(3):410-14.
- 482 5. Rollins K, Peters C, Safranek P, et al. Venous thromboembolism in oesophago-gastric
483 carcinoma: incidence of symptomatic and asymptomatic events following
484 chemotherapy and surgery. *Eur J Surg Oncol* 2011;37(12):1072-77.
- 485 6. Lyman GH. Venous Thromboembolism in the Patient With Cancer Focus on Burden of
486 Disease and Benefits of Thromboprophylaxis. *CANCER* 2011;117(7):1334-49. doi:
487 10.1002/cncr.2571
- 488 7. Lyman GH, Eckert L, Wang Y, et al. Venous thromboembolism risk in patients with cancer
489 receiving chemotherapy: a real-world analysis. *Oncologist* 2013;18(12):1321.
- 490 8. Larsen AC, Brøndum Frøkjær J, Wishwanath Iyer V, et al. Venous thrombosis in
491 pancreaticobiliary tract cancer: outcome and prognostic factors. *J Thromb Haemost*
492 2015;13(4):555-62.
- 493 9. Maraveyas A, Muazzam I, Noble S, et al. Advances in managing and preventing
494 thromboembolic disease in cancer patients. *Curr Opin Support Palliat Care*
495 2017;11(4):347-54.
- 496 10. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin
497 thromboprophylaxis in pancreatic cancer. *Eur J cancer* 2012;48(9):1283-92.
- 498 11. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight
499 heparin for ambulatory patients with advanced pancreatic cancer: outcomes from
500 the CONKO-004 trial. *J Clin Oncol* 2015;33(18):2028-34.
- 501 12. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of
502 thromboembolic events in ambulatory patients with metastatic or locally advanced
503 solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-
504 blind study. *Lancet Oncol* 2009;10(10):943-49.
- 505 13. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients
506 receiving chemotherapy for cancer. *N Engl J Med* 2012;366(7):601-09.
- 507 14. van Doormaal FF, Di Nisio M, Otten H-M, et al. Randomized trial of the effect of the low
508 molecular weight heparin nadroparin on survival in patients with cancer. *J Clin Oncol*
509 2011;29(15):2071-76.
- 510 15. Fuentes H, Oramas D, Paz L, et al. Meta-analysis on anticoagulation and prevention of
511 thrombosis and mortality among patients with lung cancer. *Thromb Res*
512 2017;154:28-34.
- 513 16. Dallos MC, Eisenberger AB, Bates SE. Prevention of venous thromboembolism in
514 pancreatic cancer: breaking down a complex clinical dilemma. *The oncologist*
515 2020;25(2):132.
- 516 17. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy
517 (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10(2):e1001381.

18. Hendriksen JM, Geersing G-J, Moons KG, et al. Diagnostic and prognostic prediction models. *J Thromb Haemost* 2013;11:129-41.
19. Tritschler T, Méan M, Limacher A, et al. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model. *Blood* 2015;126(16):1949-51.
20. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350(9094):1795-98.
21. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(03):416-20.
22. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111(10):4902-07. doi: 10.1182/blood-2007-10-116327
23. Haltout J, Awada A, Paesmans M, et al. Predictive factors for cancer-associated thrombosis in a large retrospective single-center study. *Support Care Cancer* 2019;27(4):1163-70.
24. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica* 2019;104(6):1277-87. doi: 10.3324/haematol.2018.209114
25. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010;116(24):5377-82. doi: 10.1182/blood-2010-02-270116
26. Posch F, Riedl J, Reitter E-M, et al. Hypercoagulability, venous thromboembolism, and death in patients with cancer. A Multi-State Model. *Thromb Haemost* 2016;115(4):817-26.
27. Lustig DB, Rodriguez R, Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. *Thromb Res* 2015;136(6):1099-102.
28. Muñoz Martín AJ, García Alfonso P, Rupérez Blanco AB, et al. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana's predictive model. *Clin Transl Oncol* 2014;16(10):927-30. doi: 10.1007/s12094-014-1165-y
29. Pelzer U, Sinn M, Stieler J, et al. Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy? *Dtsch Med Wochenschr* 2013;138(41):2084-88.
30. Van Es N, Franke V, Middeldorp S, et al. The Khorana score for the prediction of venous thromboembolism in patients with pancreatic cancer. *Thromb Res* 2017;150:30-32.
31. Mansfield A, Tafur AJ, Wang CE, et al. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. *J Thromb Haemost* 2016;14(9):1773-78.
32. Rupa-Matysek J, Lembicz M, Rogowska EK, et al. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. *Med Oncol* 2018;35(5):1-10.
33. Fuentes HE, Paz L, Wang Y, et al. Performance of current thromboembolism risk assessment tools in patients with gastric cancer and validity after first treatment. *Clin Appl Thromb Hemost* 2018;24(5):790-96.

- 1
2
3 564 34. Khorana A, Otten H, Zwicker J, et al. Prevention of venous thromboembolism in cancer
4 565 outpatients: guidance from the SSC of the ISTH. *J Thromb Haemost*
5 566 2014;12(11):1928-31.
6
7 567 35. Noble S, Alikhan R, Robbins A, et al. Predictors of active cancer thromboembolic
8 568 outcomes: validation of the Khorana score among patients with lung cancer:
9 569 comment. *J Thromb Haemost* 2017;15(3):590-91.
10
11 570 36. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous
12 571 thromboembolism in patients with cancer. *N Engl J Med* 2019;380(8):711-19.
13 572 37. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban thromboprophylaxis in high-risk
14 573 ambulatory cancer patients receiving systemic therapy: results of a randomized
15 574 clinical trial (CASSINI). *Blood* 2018;132(Supplement 1):LBA-1-LBA-1.
16
17 575 38. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of
18 576 venous thromboembolism in cancer patients: a systematic review and meta-analysis.
19 577 *Haematologica* 2019;104(6):1277-87.
20
21 578 39. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous
22 579 thromboembolism in cancer patients receiving chemotherapy: the Protecht score.
23 580 *Intern Emerg Med* 2012;7(3):291.
24 581 40. Simanek R, Vormittag R, Ay C, et al. High platelet count associated with venous
25 582 thromboembolism in cancer patients: results from the Vienna Cancer and
26 583 Thrombosis Study (CATS). *J Thromb Haemost* 2010;8(1):114-20.
27
28 584 41. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous
29 585 thromboembolism in cancer patients: a prospective cohort study. *Haematologica*
30 586 2017;102(9):1494-501.
31 587 42. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of Prophylactic Low-Molecular Weight
32 588 Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From
33 589 the CONKO-004 Trial. *J Clin Oncol* 2015;33(18):2028-34. doi:
34 590 10.1200/JCO.2014.55.1481
35
36 591 43. Streiff MB, Holmstrom B, Angelini D, et al. NCCN guidelines insights: cancer-associated
37 592 venous thromboembolic disease, version 2.2018. *J Natl Compr Canc Netw*
38 593 2018;16(11):1289-303.
39
40 594 44. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and
41 595 treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin*
42 596 *Oncol* 2020;38(5):496-520.
43
44 597 45. National Institute of Health and Care Excellence. Venous Thromboembolism over 16s:
45 598 Reducing the Risk of Hospital-acquired Deep Vein Thrombosis or Pulmonary
46 599 Embolism. NICE Guideline (NG89). 2018 [Available from:
47 600 [https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer)
48 601 [for-people-with-cancer](https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#interventions-for-people-with-cancer) accessed 11 August 2021.
49
50 602 46. Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-
51 603 analysis of prediction model performance. *BMJ* 2017;356:i6460. doi:
52 604 10.1136/bmj.i6460
53
54 605 47. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for
55 606 systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med*
56 607 2014;11(10):e1001744.
57
58 608 48. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review
59 609 and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4(1):1-9.
60

- 1
2
3 610 49. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated
4 611 guideline for reporting systematic reviews. *Syst Rev* 2021;10(1):89. doi:
5 612 10.1186/s13643-021-01626-4
6
7 613 50. Zhao J-G. Combination of multiple databases is necessary for a valid systematic review.
8 614 *Int Orthop* 2014;38(12):2639-39. doi: 10.1007/s00264-014-2556-y
9
10 615 51. Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and
11 616 the Effective Health Care Program. *J Clin Epidemiol* 2011;64(11):1168-77.
12 617 52. Geersing G-J, Bouwmeester W, Zuithoff P, et al. Search filters for finding prognostic and
13 618 diagnostic prediction studies in Medline to enhance systematic reviews. *PloS one*
14 619 2012;7(2):e32844.
15 620 53. Harrell FE, Califf RM, Pryor DB, et al. Evaluating the yield of medical tests. *JAMA*
16 621 1982;247(18):2543-46.
17
18 622 54. Wolff RF, Moons KG, Riley RD, et al. PROBAST: a tool to assess the risk of bias and
19 623 applicability of prediction model studies. *Ann Intern Med* 2019;170(1)
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Appendix 1: Medline search via EBSCOhost

S1: (MH "Venous Thromboembolism" OR VTE OR Thromboembolism OR "cancer associated thrombosis" OR CAT OR thrombosis OR MH "Pulmonary Embolism" OR PE OR MH "Venous Thrombosis" OR "deep vein thrombosis" OR DVT)

S2: (MH "Pancreatic Neoplasms" OR "pancreatic cancer*" OR "pancreatic carcinoma*" OR "carcinoma of pancreas" OR "pancreatic tumor*" OR "pancreatic tumour*" OR "cancer of the pancreas" OR MH "Stomach Neoplasms" OR "stomach cancer*" OR "gastric cancer*" OR MH "Esophageal Neoplasms" OR "oesophageal cancer*" OR "esophageal cancer*" OR "upper gastrointestinal cancer" OR "upper gastrointestinal carcinoma*" OR "upper gastrointestinal neoplasm*")

S3: ("risk model*" OR "risk assessment" OR "risk stratification" OR "risk prediction" OR "risk scor*" OR MH "Risk Factors" OR "predict* model*" OR "predictive scor*" OR "prediction tool*" OR MH "nomogram" OR "scoring system*" OR "score system*" OR "prognos* predict*" OR "multivaria* predict*" OR MH "Clinical Decision Rules" OR "stratification" OR MH "ROC curve" OR "discriminate" OR "c-statistics" OR "c statistic" OR "area under the curve" OR "AUC" OR "calibration" OR "indices" OR "algorithm" OR "Multivariable")

S4: S1 AND S2 AND S3

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

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

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

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

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11

Amendments

[#4](#) If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments n/a

Support

Sources [#5a](#) Indicate sources of financial or other support for the review 11

Sponsor [#5b](#) Provide name for the review funder and / or sponsor n/a

Role of sponsor or funder [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol n/a

Introduction

Rationale [#6](#) Describe the rationale for the review in the context of what is already known 3-5

Objectives [#7](#) Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) 6

Methods

Eligibility criteria [#8](#) Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review 6-7

Information sources [#9](#) Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage 7

Search strategy [#10](#) Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated 8

Study records - data management [#11a](#) Describe the mechanism(s) that will be used to manage records and data throughout the review 8-9

Study records - selection process [#11b](#) State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) 9

Study records - data [#11c](#) Describe planned method of extracting data from reports (such as
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1	collection process		piloting forms, done independently, in duplicate), any processes for	
2			obtaining and confirming data from investigators	
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4	Data items	#12	List and define all variables for which data will be sought (such as	9
5			PICO items, funding sources), any pre-planned data assumptions and	
6			simplifications	
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9	Outcomes and	#13	List and define all outcomes for which data will be sought, including	7
10	prioritization		prioritization of main and additional outcomes, with rationale	
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13	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	9
14	individual studies		studies, including whether this will be done at the outcome or study	
15			level, or both; state how this information will be used in data synthesis	
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18	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	9-10
19			synthesised	
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22	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned	10
23			summary measures, methods of handling data and methods of	
24			combining data from studies, including any planned exploration of	
25			consistency (such as I ² , Kendall's τ)	
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29	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or	10
30			subgroup analyses, meta-regression)	
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33	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of	10
34			summary planned	
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37	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication	10
38			bias across studies, selective reporting within studies)	
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41	Confidence in	#17	Describe how the strength of the body of evidence will be assessed	n/a
42	cumulative		(such as GRADE)	
43	evidence			
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