VENOUS THROMBOPROPHYLAXIS IN HOSPITALIZED MEDICAL PATIENTS

ELECTRONIC STRATEGIES TO ENHANCE VENOUS THROMBOPROPHYLAXIS IN

HOSPITALIZED MEDICAL PATIENTS: A RANDOMIZED CONTROLLED TRIAL

By

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ABSTRACT

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most preventable cause of death in hospitalized patients. Due to its high mortality, morbidity, and cost, health care providers are obligated to not only effectively diagnose and treat VTE, but also to prevent it if possible. This has been reinforced by a number of national and international quality initiatives to prevent hospital-acquired VTE.

Despite the existence of well-accepted clinical practice guidelines on VTE prophylaxis, 1 in 3 hospitalized medical patients receives an inappropriate VTE prophylaxis strategy. Both underuse of prophylaxis in patients with VTE risk, and overuse of prophylaxis in patients without VTE risk are problems. The use of inappropriate VTE prophylaxis strategies is likely due to the complexity and heterogeneity of hospitalized medical patients, and the difficulty of applying "one size fits all" practice guidelines to this group. Institution-wide knowledge translation strategies are required to close the gap between evidence and practice, and promote evidence-based VTE prophylaxis strategies in hospitalized medical patients.

The objective of this thesis is to design a cluster randomized controlled trial to determine if a standardized electronic order set, with an embedded computerized decision support system and audit and feedback component, affects the use of appropriate VTE prophylaxis in hospitalized medical patients. The unit of randomization in this study is the hospital, which serves as the cluster. The unit of observation in this study is the individual patient. The primary outcome of this study is the proportion of in-hospital days during which appropriate VTE prophylaxis is administered, in intervention versus control hospitals. Secondary outcomes are the rates of hospital-acquired VTE, major bleeding and mortality, in intervention versus control hospitals. Design, analytic and ethical challenges unique to cluster randomized trials will also be discussed. Strategies to overcome them in this trial will be presented.

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LIST OF ABBREVIATIONS

ACCP, American College of Chest Physicians

AHRQ, Agency for Healthcare Research and Quality

AUC, area under the receiver operating characteristic curve

CCDSS, computerized clinical decision support system

CHF, congestive heart failure

CI, confidence interval

DVT, deep vein thrombosis

EMR, electronic medical record

EPOC, Cochrane Effective Practice and Organisation of Care Group

GRADE, Grading of Recommendations Assessment, Development and Evaluation

HR, hazard ratio

ICC, intracluster correlation coefficient

ICD-9, International Classification of Diseases, Ninth Revision

IF, variance inflation factor

LHIN, local health integration networks

LMWH, low molecular weight heparin

MESH, medical subject headings

MI, myocardial infarction

N/A, not available

OIS, optimal information size

OR, odds ratio

PE, pulmonary embolism

PGY, postgraduate year

RCT, randomized controlled trial

RR, relative risk

SD, standard deviation

UFH, unfractionated heparin

VTE, venous thromboembolism

DECLARATION OF ACADEMIC ACHIEVEMENT

The following is a declaration that the content of this document has been completed by Menaka Pai. The contributions of Ms. Nancy Lloyd, Ms. Ji Cheng, Dr. James Douketis, Dr. Mark Crowther, Dr. Deborah Cook, Dr. Lehana Thabane, Dr. Frederick Spencer, Dr. Brian Haynes, Dr. Holger Schünemann, Professor Nancy Heddle, Dr. Sam Schulman and Dr. Rob Lloyd in the preliminary work, research process and completion of the thesis are recognized and appreciated.

PART I. STUDY BACKGROUND

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a concerning problem for patients, health care providers and the general public. Deep vein thrombosis occurs when a thrombus (blood clot) forms in one of the body's large veins, usually in the lower limbs. The thrombus can partially or completely block local blood circulation. If a fragment of this thrombus breaks off, it can migrate through the heart and into the lungs. The resulting blockage of a pulmonary artery or one of its branches is called a pulmonary embolism, and can impair the body's ability to circulate blood through the body and provide it with vital oxygen. VTE has a significant impact on hospitalized medical patients, and both pharmacologic and mechanical prophylaxis play a role in its prevention. The goal of this thesis is to present the design of a cluster randomized controlled trial to reduce the rate of VTE in hospitalized medical patients.

Section 1. The problem of VTE

Blood clots carry high mortality and morbidity, and are a major driver of healthcare costs.VTE has often been called the "silent epidemic."[1] An epidemiologic study of 18,954 VTE events showed that 14% were first diagnosed as fatal events. When pulmonary emboli alone were considered, nearly 25% presented as sudden death.[2] Even if one survives the initial diagnosis of PE, the 90-day mortality rate is still 18%.[3] Non-fatal

VTE results in considerable morbidity as well. The prevalence of postphlebitic syndrome – chronic, potentially disabling leg swelling and pain – is estimated to be 17% to 50% by the first year after an acute deep vein thrombosis.[4] Chronic thromboembolic pulmonary hypertension, which manifests as progressive dyspnoea and exercise intolerance, can cause significant disability after pulmonary embolism. Its cumulative incidence is estimated at 1% within six months of a pulmonary embolism, 3% at one year and 4% at two years.[5]

The costs associated with VTE are considerable. The U.S. Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Projects' estimates that VTE costs the United States healthcare system more than $1.5 billion per year.[3] The cost of an initial episode of deep vein thrombosis, in U.S. dollars, is estimated at $7,712 to $10,804; the cost of managing an initial pulmonary embolism event is $9,566 to $16,644.[3] The incremental cost rises further still when the long-term complications of VTE are considered. Approximately 25% of venous ulcers are secondary to DVT. The annual cost for treating venous ulcers in the United States has been estimated to be more than $600 million.[6]

Section 2. The problem of VTE in hospitalized medical patients

VTE is a common disease, with an age and sex adjusted overall annual incidence of 16 per 10,000 adults.[7] Recent population-based epidemiologic studies have found that

the incidence of VTE is higher in hospitalized patients. Forty-six percent of cases of VTE develop in hospital or in the 30 days after hospitalization, and 25 to 37% of all cases of symptomatic VTE occur in patients who have been hospitalized in the preceding 3 months.[8,9] Hospitalization confers a 6- to 11-fold increased risk of VTE, and autopsy studies have shown that 5 to 10% of in-hospital deaths are a direct result of PE.[9,10] VTE is the most common preventable cause of death in hospital.[3,11]

Why is VTE so common in hospitalized patients? It is likely because this population has a higher prevalence of VTE risk factors than community dwelling individuals.VTE risk factors have classically been grouped into three broad categories, dubbed "Virchow's Triad:" endothelial injury; hemodynamic changes (including stasis and turbulence); and hypercoagulability.[12] Hospitalized patients often have risks in all three categories. These patients may have undergone surgery, procedures or have received drugs that cause endothelial damage. They may be immobile, have abnormal positioning or have central venous catheters leading to vascular stasis. Concurrent illnesses such as malignancy, infection and inflammation induce a hypercoagulable state.

The prevalence (absolute risk) of symptomatic VTE is considered to be highest among surgical patients, particularly those undergoing bariatric surgery, oncologic surgery, major abdominal or pelvic surgery, and orthopaedic surgery. In these patients, the baseline risk of symptomatic VTE is greater than 3%. In contrast, the absolute risk of symptomatic VTE in medical patients is far lower.

Our information on the actual thromboembolic risk in medical patients comes from the placebo arms of large randomized controlled trials of pharmacologic prophylaxis in the hospitalized medical population. Three trials – MEDENOX, PREVENT and ARTEMIS – enrolled a total of 2129 patients in their placebo arms.[13] MEDENOX (prophylaxis in MEDical patients with ENOXaparin) was a randomized, double-blind, placebo-controlled study that compared the incidence of venous thromboembolism with 40 mg of enoxaparin, 20 mg of enoxaparin or placebo.[13] MEDENOX showed that there was a 15% incidence of VTE (both symptomatic and asymptomatic) in the 288 patient placebo arm. The PREVENT study was a randomized, double-blind, placebo-controlled study comparing 5000 IU of dalteparin versus placebo.[14] The 1518 patients in the placebo arm had a 5% incidence of venous thromboembolism (including symptomatic DVT and PE, and asymptomatic proximal DVT). Finally, ARTEMIS was a randomized, double-blind, placebo-controlled study comparing 2.5 mg of fondaparinux versus placebo.[15] The 323 patients in the placebo arm had a 6% incidence of VTE, and a 1% incidence of symptomatic VTE.

A recent meta-analysis by Lederle et al summarized data from these studies, and others.[16] It showed that in hospitalized medical patients receiving no active prophylaxis, the absolute risk of symptomatic DVT was 1.0% (27 cases in 2791 included patients), and the absolute risk of PE was 1.2% (127 cases in 10 251 included patients). Lederle et al highlighted the general characteristics of patients included in the meta-analyzed studies. The mean age was generally more than 70 years. Many studies restricted entry to patients

with certain diagnoses (e.g., congestive heart failure, sepsis, stroke), or to patients who had a minimum length of hospital stay. Patients were generally excluded from these trials if they had a definite indication for therapeutic dose anticoagulation (e.g., atrial fibrillation), a contraindication to anticoagulation (e.g., thrombocytopenia), expected short survival or recent surgery. Thus, included patients were highly selected, and likely at higher risk of VTE than the heterogeneous population more typically found on inpatient medical wards.

Though the incidence of symptomatic VTE in medical patients is low, the absolute number of hospitalized medical patients results in a considerable burden of risk. In 2003, there were 38.2 million patients discharged from hospital in the United States alone; 15.2 million of these were medical patients, and 7.7 million (51%) had at least one of the 2008 American College of Chest Physicians' (ACCP) risk criteria for VTE.[2,7] Based on these numbers, an absolute risk for symptomatic DVT in medical patients of 1.0% still translates into a large number of clots.[17] This absolute risk, based on the meta-analysis by Lederle et al, may be lower in unselected medical patients. However, the DVT FREE Registry confirmed that 35% of hospitalized patients suffering from VTE had no surgical procedures in the preceding 3 months.[18] That is, their VTEs were associated solely with *medical* disease. Due to its considerable morbidity and mortality, health care practitioners are obligated to not only effectively diagnose and treat VTE, but also to prevent it if possible.

Section 3. Options for VTE Prophylaxis

There are two broad categories of VTE prophylaxis options available to health care practitioners: mechanical and pharmacologic. Mechanical methods of VTE prophylaxis consist of graduated compression stockings, which provide a distributed amount of compression from the ankle upwards, and intermittent pneumatic compression devices, which consist of calf-length or thigh-length compressible sleeves or foot pumps. Mechanical methods of VTE prophylaxis are a good option when anticoagulants are contraindicated (i.e., because of bleeding risk). However they can be uncomfortable and constrictive for patients, and can lead to increased skin breakdown.[16] Compliance with mechanical prophylaxis is also poor, especially in non-ICU patients.[19] Based on these considerations, mechanical prophylaxis is generally not considered a first line prophylaxis option in patients with risk factors for hospital-acquired VTE.

Pharmacologic prophylaxis consists of subcutaneously administered anticoagulants – unfractionated heparin (UFH), low molecular weight heparins (LMWH), or fondaparinux. All three of these agents are administered by subcutaneous injection when used for VTE prophylaxis. They prevent the formation of blood clots by inhibiting the body's coagulation pathways. UFH is the oldest of these three anticoagulants. It is a polymer with a variable molecular weight, ranging from 3 kDa to 30 kDa, and acts by binding to antithrombin III, a naturally occurring enzyme in the body. Antithrombin III inactivates enzymes involved in blood clotting, including thrombin and factor Xa. When it is bound to heparin, antithrombin III's rate of action increases by up to 1000-fold.[20]

LMWHs are derived by depolymerisation or cleavage of UFH. Therefore, they consist only of the shortest chains.[21] There are several commercially-available LMWHs available in Canada. They also exert their anticoagulant effects by binding to antithrombin III. Fondaparinux is a synthetic pentasaccharide molecule that is chemically related to UFH and LMWH.[21] It also binds avidly to antithrombin III, and predominantly causes factor Xa inactivation.

The choice of anticoagulant for VTE prophylaxis is determined by clinical factors and physician preference. One particular group of patients that frequents medical wards are those with renal insufficiency; prophylactic dose LMWH was previously thought to bioaccumulate in patients with impaired renal function, so UFH became a more common choice in these patients. However a recent prospective cohort study showed that neither prophylactic-dose LMWH nor UFH produced an excessive anticoagulant effect when used in patients with reduced creatinine clearance.[22] A recent large multicentre clinical trial in critically ill patients with a range of renal function showed that there was no evidence of excess bleeding when prophylactic dose dalteparin (5000 international units once daily) was compared to UFH (5000 international units twice daily), even in patients requiring dialysis.[23] Further studies exploring this issue are ongoing. Heparin-induced thrombocytopenia – a potentially fatal immune reaction associated with a platelet drop and both arterial and venous thromboses - is reported to occur in 0.5% of medical patients who receive prophylactic dose UFH.[24] The risk of heparin-induced thrombocytopenia is lower when LMWH and fondaparinux are used.[23-26] Fondaparinux may also be a

reasonable choice for VTE prophylaxis in patients with prior heparin-induced thrombocytopenia, though this remains an off-label use.[27]

Section 4. The evidence for VTE prophylaxis in medical patients

Hospitalized medical patients face a considerable burden of venous thromboembolic disease, but there is also considerable potential for disease prevention. Two recent meta-analyses, by Dentali et al and Lederle et al, summarized available evidence for prophylaxis in this population.[16,28] Table 1 critically appraises these two meta-analyses, while Table 2 summarizes their findings.

Critical appraisal of the two recent meta-analyses of VTE prophylaxis in hospitalized medical patients was done using AMSTAR ("A measurement tool to assess systematic reviews"), a tool developed and externally validated by Shea et al in 2007.[29,30] Both meta-analyses were well-designed. (Table 1) They addressed clearly stated, specific clinical questions, ensured that important, relevant studies were included, and presented the results of included studies appropriately. The quality of included studies was carefully assessed, and considered in the authors' conclusions. Appropriate methods were used to pool the studies in both meta-analyses; heterogeneity did not exist for any of the key outcomes. Both meta-analyses addressed the issue of publication bias, and potential conflicts of interest were clearly identified.

Table 2 summarizes the findings of both meta-analyses, and assesses the quality of the evidence using the GRADE approach.[31] (Table 3) Both meta-analyses found that pharmacologic VTE prophylaxis significantly reduces PE in hospitalized medical patients. The absolute risk reduction is about 0.3%. That is, one must give pharmacologic VTE prophylaxis to 333 patients during hospitalization to prevent one pulmonary embolus. However, pharmacologic prophylaxis has no significant effect on symptomatic DVT (though there appears to be a trend towards benefit in the Dentali study) or mortality. The authors of both meta-analyses noted that anticoagulants may increase both major bleeding and all bleeding in this population. The risk for heparin-induced thrombocytopenia was not routinely assessed in included studies. Dentali et al did not comment on mechanical prophylaxis, while Lederle et al showed that this strategy did not reduce VTE, and was significantly associated with lower extremity skin damage.[16]

The GRADE approach was used to assess the quality of the evidence in the meta-analyses. Because both meta-analyses included randomized controlled trials, they yielded evidence that was high quality, at baseline. However, when GRADE was applied, data quality for most of the outcomes had to be lowered, due to imprecision. For systematic reviews, imprecision refers to a lack of confidence in the estimates of the effect. Guyatt et al suggest that in a systematic review, imprecision in the effect of an intervention on a binary variable exists if any one of the following criteria are met:[32]

a) The systematic review does not meet the optimal information size (OIS) threshold. That is, the total number of patients included in the systematic review is less than

the number of patients generated by a conventional sample size calculation for a single adequately powered trial.

b) The OIS is met, but the 95% CI crosses 1.0.

c) The total number of events is small. For the relative risk reductions (RRRs) in the two meta-analyses of VTE prophylaxis in hospitalized medical patients, <300 events across both control and intervention arms would be considered small.

The quality of evidence for most of the outcomes in the two meta-analyses was downgraded to "moderate," because of imprecision due to a small number of events and/or an inadequate optimal information size. The quality of evidence for only one outcome - "all bleeding" in the meta-analysis by Lederle et al – remained high after application of GRADE criteria.

It is clear from the abovementioned well-designed meta-analyses that VTE prophylaxis does not *uniformly* benefit hospitalized medical patients. This is not surprising, as hospitalized medical patients are not a uniform population. The absolute risk reductions for clinically important outcomes in this group appear modest, but this must be considered in light of the quality of evidence, and the population included in the meta-analyses. The effect size may have been diluted because prophylaxis was administered to patients with a broad range of VTE risk. Much of the data were imprecise, due to low event rates which demanded high optimal information sizes. The challenge for health care practitioners is to identify groups of medical patients at highest thrombotic risk, who are likely to derive the most benefit from VTE prophylaxis.

Section 5. Identifying hospitalized medical patients at highest risk of VTE

Several studies have attempted to identify risk assessment models that predict VTE in hospitalized medical patients. Table 4 summarizes their findings. The three largest randomized controlled trials of pharmacologic prophylaxis in hospitalized medical patients are MEDENOX, PREVENT and ARTEMIS. These randomized controlled trials did not provide physicians with any guidance on the individual risk-benefit ratio of anticoagulation in a specific patient, nor did they discuss which features conferred the highest thrombotic risk in the highly selected groups of patients that they included.[13-15] A number of studies have applied regression analysis techniques to randomized controlled trial data, to determine which risk factors independently predict VTE. The largest of these studies was published in 2004, when Alikhan et al performed a logistic regression analysis of the MEDENOX trial to evaluate independent risk factors for VTE in hospitalized medical patients.[33] The initial regression model included the following variables: age > 75 years, cancer, history of VTE, obesity, varicose veins, hormone therapy, chronic heart failure, chronic respiratory failure, acute infectious disease without septic shock, an acute rheumatic disorder, and an acute episode of inflammatory bowel disease. These independent variables were given binary values (i.e., present or not present), and their effect on the dependent variable (i.e., the presence of symptomatic or asymptomatic VTE within 14 days of admission) was subject to univariate regression analysis. Variables identified by the univariate analyses as potential risk factors (P < 0.10 for relationship to the dependent variable) were then considered for inclusion in a multivariate logistic regression analysis. Univariate analyses showed that only age > 75

years, cancer, previous VTE, and the presence of an acute infectious disease were significantly associated with an increased risk of VTE. The multivariate regression model showed that age > 75 years, cancer, previous VTE, acute infectious disease, and chronic respiratory disease were all independently related to risk of VTE, with previous VTE being the strongest predictor for future VTE events (odds ratio (OR) 2.06; 95% confidence interval (CI) 1.10 to 3.69). Alikhan et al used the 5-factor model to stratify patients into low, high and medium risk for VTE. Unfortunately, they did not comment on the risk of *symptomatic* VTE in each of these strata.

A major barrier to using randomized controlled trial populations to identify thrombotic risk factors is that the patients in these trials are highly selected. They do not reflect the "average" medical patient, nor do they provide useful data to clinicians caring for individual patients. A number of studies have avoided this bias by using observational data to identify independent risk factors for VTE. In 2011, Woller et al reviewed the charts of 143,000 internal medicine admissions, and identified patients with objectively confirmed VTE during hospitalization or within 90 days following discharge.[34] A risk assessment model with four risk factors (previous VTE, an order for bed rest, a peripherally inserted central venous catheterization line and a cancer diagnosis) was found to have an area under the receiver operating characteristic curve [AUC] of 0.874 (95% CI 0.869 to 0.880). (The AUC is a measure of diagnostic accuracy - the ability of a model or diagnostic test to correctly classify those with and without a disease.[35] An AUC can range from 0.5 to 1, with a higher number indicating that the model or test is more

accurate.) When the risk assessment model was validated in a new cohort of 46,000 medicine admissions, it retained its excellent performance characteristics with an AUC of 0.843 (95% CI, 0.833 to 0.852).

Rothberg et al conducted another large retrospective cohort study of adults admitted with one of a selection of primary diagnoses typical of medical admissions (pneumonia, heart failure, chronic obstructive pulmonary disease, stroke, and urinary tract infection).[36] The dependent variable was an International Classification of Diseases, Ninth Revision [ICD-9] code for VTE, plus a confirmatory diagnostic test and a record of appropriate treatment. A total of 242,738 patient records were reviewed, with 80% randomly assigned to a derivation set and 20% randomly assigned to a validation set. Using multivariate regression analysis, they found that the most strongly predictive risk factors for VTE were inherited thrombophilia (OR 4.0), length of hospital stay ≥6 days (OR 3.2), inflammatory bowel disease (OR 3.1), presence of a central venous catheter (OR 1.9), and cancer (OR 4.6). Their final model consisted of 11 risk factors independently associated with VTE; it was used to produce deciles of observed risk ranging from 0.2% to 1.8% for the dependent variable. Using a risk threshold of 1% for the dependent variable, the model had sensitivity of 28% and specificity of 93%.

Recently, Spyropoulos et al used data on the 15,516 medical patients in the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) to determine the cumulative incidence of clinically observed VTE within 92 days of

admission.[37] Multivariate regression analysis identified that previous VTE, known thrombophilia, cancer, age >60 years, lower limb paralysis, immobilization ≥7 days, and admission to an ICU or coronary care unit were all independent predictors of symptomatic VTE. The authors assigned points to each of the 7 risk factors, and found that a score ≥2 was associated with higher overall and VTE-related mortality. They suggested that medical patients in this high risk category should receive VTE prophylaxis during hospitalization.

A major strength of Spyropoulos' study is that it also describes a shorter "predictive risk model," in addition to the 7-factor model outlined above. The predictive risk model contains only four items: previous VTE (3 points); known thrombophilia (3 points); cancer (1 point); and age >60 (1 point). Many risk assessment models can only be applied retrospectively – they contain some risk factors that can only be determined during or after hospitalization. However, all four items on the predictive risk model can be scored at the time of admission. Spyropoulos et al found that patients with a score of <2 on the predictive risk model had an observed rate of ≤1% for VTE within 92 days of admission, and an observed rate of ≤0.5% for PE within 92 days of admission. Conversely, patients with a score of ≥2 on the predictive risk model had an observed rate of ≥2.1% for VTE within 92 days of admission, and an observed rate of ≥1.2% for PE within 92 days of admission. It is important to note that these are rates for *symptomatic* events.

Only one risk assessment model has been endorsed by the ACCP.[38] This model was published by Barbar et al in 2010.[39] They did not derive their risk model through statistical analysis. Instead, they modified the Kucher score, a VTE risk model for medical and surgical patients that was itself not based on statistical methods, but on expert opinion. The dependent variable in the Barbar study was objectively confirmed, symptomatic VTE within 90 days of admission. Barbar et al assigned points to each factor in the risk model, and found that it could be used to stratify patients into high and low VTE risk categories. Without prophylaxis, they found that the hazard ratio of VTE in high versus low risk patients was 32 (95% CI 4.1 – 251).

In 1997, the Journal of the American Medical Association published a set of methodological standards for clinical prediction rules.[40] When these standards are applied to existing risk assessment models for VTE in hospitalized medical patients, it is clear that the models have serious limitations. (Table 5) In general, the risk assessment models use a clinically relevant outcome (symptomatic or clinically evident VTE), however the study by Alikhan et al includes asymptomatic VTE. Many of the risk assessment models did not blind their assessment of the outcome. This is problematic, as knowledge of a subject's potential risk factors could bias the assessor's judgment of the outcome. None of the studies commented on reproducibility of their findings – either in the assessment of the predictor variables, or in the use of the model itself. Many of the risk assessment models do not provide useful data to clinicians on the course of action. That is, they suggest the probability that a patient will experience the VTE outcome, but not whether

VTE prophylaxis would be useful in preventing it. Finally, only a few of the risk assessment models have been internally validated, and none have been externally validated. The authors of many of the risk assessment models do admit that their findings are preliminary, and that rigorous validation in other centres, and in other groups of patients, is important.

Section 6. The (under)use of VTE prophylaxis in medical patients

In the past decade, there has been a major push for VTE prophylaxis in medical patients from healthcare agencies and accrediting bodies. Since 2001, the Agency for Health Research and Quality ranked VTE prophylaxis as the #1 priority to improve patient safety in medical patients, and the American College of Chest Physicians has given a Grade 1A recommendation for the use of low-dose anticoagulants or compression devices to prevent VTE in at-risk medical patients.[3,41] Many U.S. agencies have moved from recommending VTE prophylaxis to mandating it. The Joint Commission is moving towards standards that will hold medical centres accountable for ensuring that patients have VTE prophylaxis orders in place (prophylaxis prescribed, or a risk assessment to justify why it has not been prescribed) within 24 hours of hospital admission.[42] The Centers for Medicare and Medicaid Services have ruled that if a patient develops VTE during hospitalization for total knee or hip replacement, the hospital will not be paid for the added expense of this complication.[43]

Once these calls to action were released, a number of observational studies were conducted to establish the uptake of VTE prophylaxis in hospitalized medical patients. The 2006 Canadian Anticoagulant Survey gathered data from 195 hospitals across Canada.[44] It claimed that there was a massive "care gap" for VTE prophylaxis in hospitalized medical patients, since orthopedic surgery patients received recommended prophylaxis in over 84% of cases, but hospitalized medical patients received it in only 11% of cases. However, it should be underscored that "recommended" prophylaxis was defined as pharmacologic prophylaxis administered as per the 2004 ACCP guidelines, which recommend prophylaxis for a very broad range of medical patients.[45] Kahn et al followed up this research with the CURVE study, a multicenter evaluation of the use of VTE prophylaxis in Canadian medical patients.[46] Their audit of 29 Canadian hospitals found that 23% of patients received some form of prophylaxis, but only 16% received appropriate thromboprophylaxis. Again, appropriate prophylaxis was defined as pharmacologic prophylaxis administered as per the 2004 ACCP guidelines.[45] International studies confirmed these rates of VTE prophylaxis in hospitalized medical patients, however they also used outdated and broad criteria to determine who was eligible for prophylaxis.[47,48]

A 2010 study by our research group used a more up-to-date definition of appropriate prophylaxis.[49] Appropriate prophylaxis was defined as the receipt of prophylaxis (pharmacologic or mechanical) when it *was* indicated by the 2008 ACCP guidelines, the most current at the time of the study, OR the non-receipt of prophylaxis

when it was *not* indicated by the 2008 ACCP guidelines.[41] The findings of our study are summarized in Table 6. We found that 71% of hospitalized medical patients in Hamilton received appropriate prophylaxis. Conversely, 29% of hospitalized medical patients in Hamilton received *inappropriate* VTE prophylaxis.[49] Fifty-nine percent of these inappropriately managed patients were subject to errors of commission – *they did not need prophylaxis, yet they received it*. Errors of commission are costly, as they waste resources (e.g., anticoagulants, compression stockings). Furthermore, they expose patients to harm (e.g., bleeding from anticoagulants, skin breakdown from compression stockings). Twenty-eight percent of patients who received inappropriate prophylaxis were subject to errors of ommission – *they did need prophylaxis, but did not receive it*. Errors of ommission can also cause patient harm (e.g., mortality and morbidity from preventable VTE). The remaining errors include prescribing pharmacologic prophylaxis when mechanical prophylaxis was indicated (exposing patients to undue bleeding risk) and prescribing mechanical prophylaxis when pharmacologic prophylaxis was indicated (exposing patients to suboptimal prophylaxis). We concluded that VTE prophylaxis in hospitalized medical patients was a problem. However, overly enthusiastic use was as much of a concern as underuse.

Section 7. Barriers to VTE prophylaxis in medical patients

There are several possible barriers to optimal VTE prophylaxis in medical patients. A 2009 qualitative study by our group explored this, using in-depth interviews

with 15 nurses, 6 pharmacists, 12 physicians and 3 hospital administrators in academic and community hospitals.[50] Physicians and pharmacists stated that they understood the strong evidence supporting pharmacologic prophylaxis in high risk patients. However, they believed that depending on individual physicians to implement prophylaxis was insufficient. Though multidisciplinary care was perceived as a barrier to effective VTE prophylaxis (since it could lead to unclear accountability), participants believed that a comprehensive, systems approach was necessary to optimize prophylaxis. Suggestions given by interviewees included screening and risk-stratifying all patients, offering orders at hospital admission, and performing audit and feedback. A follow-up study, published in 2011, surveyed over 1500 healthcare professionals in Ontario, to determine their perceptions about the importance of VTE prophylaxis, and difficulties adopting VTE prophylaxis guidelines.[51] Again, VTE prophylaxis was viewed as important by respondents. However, they had concerns about how to implement it. Reported barriers to adopting VTE prophylaxis guidelines included concerns about bleeding, lack of clear indications and contraindications, and lack of time to consider prophylaxis in every patient.

The barriers identified in the abovementioned interview and survey studies are all valid concerns. Medical patients are a heterogeneous patient group, so implementing a "one size fits all" prophylaxis strategy can be problematic. Risk factors for both bleeding and thrombosis in these patients have not been fully explored, so it is not surprising that health care providers feel unsure of the indications and contraindications for

pharmacologic prophylaxis in a given patient. Additionally, meta-analyses confirming the efficacy and safety of VTE prophylaxis in medical patients have been done, but the effect sizes are not large, patients are not representative of "typical patients" and little guidance has been given to the medical community on high-risk groups that may derive special benefit for prophylaxis.

The natural history of VTE itself may also colour healthcare providers' willingness to use prophylaxis. Because VTE is often clinically silent, and often presents itself after hospital discharge, healthcare providers may perceive that it is very rare. On the other hand, the side-effects of prophylaxis (e.g., haemorrhage, inconvenience and thrombocytopenia) are immediate and easily detectable. Therefore, healthcare providers may perceive that they are very common. Lack of time is another often cited reason for not using VTE prophylaxis. This lack of time is particularly pronounced in medical patients, who often have multiple health issues competing for healthcare providers' attention.[10-14] As they try to juggle diet orders, pain control regimens, bowel protocols and polypharmacy, VTE prophylaxis often falls off healthcare providers' priority lists.

Finally, VTE prophylaxis guidelines themselves may be a barrier to uptake of VTE prophylaxis in individual patients. The most recent ACCP guidelines (published in 2012), and the large randomized trials and observational studies that helped shape it, use terms like "immobility" when describing eligibility for VTE prophylaxis.[38] Yet these terms are extremely broad, and not easily applicable to the clinical setting. How immobile

is a truly "immobile" patient? Does an order for bed rest put them in this category? What if a patient has not been put on bed rest, but only gets out of bed to ambulate to the bathroom? What if a patient has been put on bed rest, but does leg exercises? The terms used in clinical guidelines are often too nonspecific to be of practical use to the busy clinician.

All of these factors can make VTE prophylaxis in hospitalized medical patients seem daunting to busy clinicians. The challenge is to create strategies to overcome these barriers, and promote evidence based practice. The field of research that does this is called "knowledge translation". In the following sections, knowledge translation will be discussed – in general terms, and as it applies to the problem of VTE prophylaxis.

Section 8. The use of knowledge translation to improve clinical practice

VTE is associated with considerable morbidity and mortality, hospital readmission, increased hospital costs, and prolonged length of stay. Yet there is still a large gap between evidence and practice.[15-17] At first glance, "care gaps" seem paradoxical. If evidence exists, why do physicians not adopt it? Why do they not "do the right thing?" Many models have attempted to explore this.

One of the most comprehensive was published in 1999, when Cabana et al performed a systematic review to address why physicians do not follow clinical

guidelines.[52] They suggested that the explanations fell into one of three categories: knowledge; attitudes; and behaviour. The "Knowledge" category encompassed a lack of familiarity with the evidence, or a lack of awareness about the evidence. (Lack of familiarity or awareness could be due to difficulty keeping up with the sheer volume of medical information, a lack of time to stay informed, or inaccessibility of the evidence.) The "Attitudes" category encompassed a lack of agreement with the evidence, a lack of self-efficacy, or a lack of motivation (i.e., inertia of previous practice). The "Behaviour" category encompassed a host of patient factors (e.g., patient preferences opposed the evidence), evidence factors (e.g., contradictory or poorly constructed guidelines), and environmental factors (e.g., lack of time, lack of resources, lack of reimbursement, organizational constraints). Cabana et al concluded that there were often multiple barriers at work in any one setting. Furthermore, studies on improving physician adherence to "best evidence" may not be generalizable, since barriers in one setting may not be present in another.

Cabana's model acknowledges the realities of modern medical practice, and is directly applicable to the field of VTE prophylaxis. (Figure 1) Clinical evidence (of varying quality) is generated at an increasingly rapid rate. Physicians may find it difficult to efficiently access this information as it becomes available. And even if they can access it, they may infrequently or incorrectly apply it in clinical arena. This creates a "care gap." The field of knowledge translation developed in response to the challenge of closing this gap, and bringing clinical evidence to the bedside.

The Canadian Institutes of Health Research have defined knowledge translation as: "a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the healthcare system."[53] (Figure 2) Essentially, knowledge translation involves moving evidence into practice. This can take a number of forms. The Cochrane Effective Practice and Organisation of Care (EPOC) Group has created a taxonomy of knowledge translation interventions, grouping them as follows: distribution of educational materials; educational meetings; local consensus processes; educational outreach visits; local opinion leaders; patient mediated interventions; audit and feedback; reminders; marketing; and mass media.[54] (Table 7) To this, one more knowledge translation strategy can be added: computerized clinical decision support systems, which will be discussed shortly.

Many of the abovementioned interventions have been the subject of systematic reviews, looking at how they affect clinical practice. Distribution of educational materials is an appealing knowledge translation strategy, since it is cheap, and can easily target a large group of health care providers. However, it appears that passive distribution of educational materials does not improve patient outcomes.[55] Educational meetings (including courses, conferences, lectures, workshops, seminars, and symposia) are more resource intensive, but also have the appealing quality of targeting large groups. A Cochrane review showed that they have a small, variable effect on professional practice, and an even smaller effect on clinically relevant patient outcomes.[56] Educational

outreach, also called "academic detailing," involves face-to-face visits between clinicians and trained individuals. Educational outreach has been shown to improve both process outcomes and clinically important patient outcomes, including medication prescription and providing screening tests.[57] However, these effects varied between studies. The use of local opinion leaders attempts to capture the unique effects of normative social influence, and apply it to clinical practice. Opinion leaders are people who are seen as likeable, trustworthy and influential by a group. When studies that used them to persuade health care providers to adopt certain behaviours were reviewed, it was found that they were often successful in promoting evidence-based practice.[58] However, the heterogeneity of the included studies made it impossible to determine how an opinion leader can best change behaviour. Audit and feedback, which provides healthcare professionals with data about their performance, has also been found to improve professional practice.[59] However, the results are extremely variable, and often small.

The computerized clinical decision support system (CCDSS) is a novel knowledge translation strategy that is currently under a great deal of study. CCDSSs are computer programs that algorithmically apply an electronic knowledge base to individual patient data. In doing so, they generate suggested "optimal actions" and present them to healthcare providers.[60] The goals of a CCDSS include facilitating evidence-based care, minimizing errors and improving the efficiency of healthcare delivery. The first systematic review of CCDSSs was published in 2005 by Garg et al.[60] They included 100 studies in their review. The authors found that many CCDSSs improved practitioner

performance. Those that actively prompted users (versus requiring them to activate the system), and those that were developed by the study authors were more commonly successful. The CCDSS Systematic Review Team, based at McMaster University's Health Information Research Unit, has been redoing the 2005 systematic review. Their goal is to determine the impact of CCDSSs on both provider and patient important outcomes in different clinical situations. In a systematic review that looked at the impact of CCDSSs on drug prescribing and management, the team found that CCDSSs inconsistently improved process of care measures and rarely improved patient outcomes.[61]   Another systematic review published by the team looked at the impact of CCDSSs on acute care management (including the use of preventive therapies).[62] Most CCDSSs demonstrated improvements in provider or process outcomes. However, the effect on patient outcomes was generally poor or not evaluated.

Though many systematic reviews have summarized the efficacy of knowledge translation strategies, few studies have looked at how factors *external* to the strategy can impact its performance. Baseline compliance is one potentially important external factor. It seems that lower baseline compliance with a clinical guideline is associated with increased effectiveness of implementation.[59] Thus, if baseline compliance is already high, there may not be any more "room for improvement." The characteristics of clinicians and their environment may also be important. Younger physicians are often viewed as more receptive to practice change, while older clinicians often resist it.[59] This effect may be even more pronounced if a knowledge strategy involves computer technology. Clinicians

in a very litigious practice environment, or in one that financially rewards guideline adherence, may be more amenable to guideline uptake.[63]

In 2006, Grimshaw et al published a comprehensive systematic review of the effectiveness and costs of different guideline dissemination strategies.[64] They combined data on a wide range of knowledge translation strategies, targeted at a wide range of clinical problems. They found that, consistent with previous reviews, passive dissemination of educational materials was largely ineffective in changing practice. Reminders (both paper-based and computer-generated) were more likely to improve care, as were audit and feedback and educational outreach. (The authors noted that benefits from this last strategy had to be offset against resource-use implications.) Multifaceted interventions did *not* appear to be more effective than single interventions. Importantly, Grimshaw and his co-authors noted that, though studies on knowledge translation were being published at a rapid rate, the quality of these studies was poor. They identified frequent unit of analysis errors, small sample sizes, and incomplete statistical analysis. The bottom line of the systematic review was that decision makers needed to exercise considerable judgement when choosing knowledge translation strategies, considering the likely benefits and costs of the strategy, and the likely benefits and costs as a result of any changes in provider behaviour. Incorporating the findings of the CCDSS Systematic Review Team, decision makers must also determine if their chosen knowledge translation strategy will impact clinically important patient outcomes.

There are many options available to knowledge translation researchers wishing to address any given clinical problem, and a growing body of data that explore the efficacy of each option. However, the conclusion of Cabana's systematic review ultimately holds true: knowledge translation interventions may not be generalizable, and what works in one setting may not work in another. It is useful to explore the impact of knowledge translation interventions in the field of VTE prophylaxis in hospitalized medical patients.

Section 9. Knowledge translation in VTE prophylaxis

Several studies of knowledge translation techniques to optimize VTE prophylaxis have been published. In 2010, Mahan et al published a systematic review of knowledge translation studies to improve VTE prophylaxis and decrease VTE events in hospitalized patients.[65] A systematic search yielded over 25 studies published since 2006 in this area. Though the outcomes proved to be too heterogeneous to formally combine in a meta-analysis, they found that, in general, many types of interventions appeared to improve VTE prophylaxis rates and/or decrease VTE events in hospitalized medical patients. Active interventions were far more effective than passive interventions. Computerized tools were most effective; however simpler paper-based interventions could work if supplemented with continued provider education, audit, and feedback. Human alerts (especially those delivered by pharmacists) also appeared effective. Though Mahan et al found numerous knowledge translation studies aimed at improving appropriate type and dose of VTE prophylaxis in hospitalized medical patients, there was a paucity of studies

that evaluated the impact of prophylaxis duration. Though several studies reported overall VTE rates, few studies reported bleeding rates, and none reported potentially preventable VTE – those that occurred in the setting of thrombotic risk factors and the absence of appropriate prophylaxis. (This is an important metric to consider, as potentially preventable VTE is now a key recommendation of The Joint Commission.) There were also no studies that looked at interventions with mandatory stops, which require the physician to complete VTE prophylaxis orders before other orders can be signed or implemented, or at alert fatigue, the process by which physicians stop responding to alerts. (Mahan et al postulated that ongoing audit and feedback may reduce alert fatigue, but this has not been formally studied.) Importantly, Mahan et al found many observational single-site studies in this field, but few randomized or multi-site trials.

The findings of key knowledge translation studies aimed at optimizing VTE prophylaxis will be outlined below. These studies have used two general types of strategies: "high-tech" interventions (e.g., electronic alerts, CCDSSs); "low-tech" interventions (e.g., paper-based tools, person-based alerts); and multifaceted strategies.

The first "high-tech" knowledge translation study in VTE prophylaxis was published in 2005, by Kucher et al.[66] This single center randomized trial was targeted at hospitalized medical and surgical patients. Patients in the intervention group had electronic alerts of their VTE risk broadcast to physicians, while patients in the control group received no electronic alerts. More patients in the intervention group than the

control group (33.6% vs. 14.5%, P < 0.05) received either pharmacologic or mechanical prophylaxis, and the relative risk reduction for clinically diagnosed, objectively confirmed VTE after 90 days was 41%. This primary end point occurred in 4.9% of patients in the intervention group and 8.2% of patients in the control group. Kucher's study was the first to look at electronic alerts in increasing uptake of VTE prophylaxis. However, it did not determine the appropriateness of prophylaxis – simply whether it was prescribed or not. It also combined data from medical and surgical patients. A group from a U.S. military hospital used a similar electronic alert at their centre, consisting of a table listing indications and contraindications to VTE prophylaxis as well as suggested orders.[67] The alert screen appeared before physicians wrote their electronic medical record (EMR) admission note. This group found that the alert improved the rate of appropriate prophylaxis in hospitalized medical patients from 51.0% to 68.9% (P < 0.001).

A recently published multicentre before-after study of hospitalized medical and surgical patients went beyond alerts, to implement a more comprehensive electronic VTE risk assessment tool (elVis). elVis was accompanied by brief educational outreach, and was implemented in 6 hospitals across Australia.[68] The use of appropriate VTE prophylaxis increased from 66.8% in the "before" phase of the study to 71.8% in the "after" phase of the study. (Adjusted OR 1.27, 95% CI 1.07 to 1.49.) When different patient types were considered, the adjusted OR for appropriate prophylaxis in medical patients was 1.56 (95% CI 1.15 to 2.10). As the use of elVis was not mandatory, only

20.5% of patients in the "after" phase were assessed using this knowledge translation strategy. The authors conducted a logistic regression analysis to determine the impact of elVis, and found that 78% of patients in the "after" phase of the study who were assessed with elVis received appropriate prophylaxis, versus 70.2% of patients who were not assessed with elVis. (Adjusted OR 1.44, 95% CI 1.04 to 1.99.) elVis had a weak positive effect on optimizing VTE prophylaxis in hospitalized medical patients. A small single centre before-after study conducted locally, by O'Connor et al, also used a non-mandatory electronic tool to improve VTE prophylaxis in hospitalized medical patients.[69] However, the order set did not have a decision support component, nor was there an education component to the intervention. The appropriateness of prophylaxis was also not assessed. The authors found that the use of VTE prophylaxis (either heparin 5000 units subcutaneously bid or compression stockings) increased from 12.8% of patient-days before order set implementation to 25.8% of patient-days. Data specifically on medical patients was not provided.

Though the results of these high-tech studies are compelling, they are not applicable to hospital sites without the necessary computer infrastructure. Low-tech studies, with potentially more generalizable results, have also been published. In 2009, in follow-up to the successful electronic alert study by Kucher et al, Piazza et al published a multicentre randomized controlled trial of "person-based alerts."[70] They enrolled 2493 patients from 25 study sites, and randomized them to either the intervention or the control group. Patients were risk stratified using a validated point score system. In the

intervention group, a hospital staff member alerted the physician (by phone) if a patient at high risk for VTE was not receiving prophylaxis. In the control group, no alerts were issued. Piazza et al found that patients in the intervention group were more than twice as likely to receive VTE prophylaxis as control subjects (46.0% versus 20.6%, P < 0.0001). Rates of appropriate prophylaxis were not assessed. There was no statistically significant difference in symptomatic VTE rates or bleeding rates. The authors postulated that this was due to the fact that human alerts (when compared to computer alerts) are "easier to ignore." They also commented that on the basis of the VTE event rate in their trial, they would have had to enrol over 9000 patients to detect a statistically significant difference in this outcome. Therefore, their study was underpowered.

Educational meetings are another low-tech strategy that has found success in published studies. Dobesh et al described an educational program focusing on the importance of VTE prophylaxis in medically ill patients, developed by clinical pharmacists and presented to nurses, pharmacists, and physicians in a single community teaching hospital.[71] The authors found that pharmacy education was associated with an increase in the utilization of any VTE prophylaxis (43% in the before phased versus 58% in the after phase, P < 0.001). Appropriate prophylaxis use increased from 38% in the "before" phase to 49% in the "after" phase (P = 0.006). An Australian study used a paper-based order sheet with a risk stratification table, and a dedicated space to prescribe VTE prophylaxis.[72] The intervention, which was conducted at a single site, resulted in an increase in prophylaxis utilization in hospitalized medical patients (52.7% to 66.5%),

which was sustained twelve months post-intervention. There was also an increase in appropriate prophylaxis in this group (55.6% to 71.0%). The authors were unable to detect any significant change in the incidence of VTE or prophylaxis-related complications.

Though it is not clear that multifaceted knowledge translation interventions are generally more effective than single knowledge translation interventions, many authors have explored if VTE prophylaxis can be optimized by combining multiple strategies.[64] In 2006, Cohn et al published a single center before-after study of hospitalized medical patients.[73] The multifaceted intervention consisted of education sessions, a paper-based decision support tool, and audit and feedback sessions. These interventions resulted in a dramatic increase in the proportion of patients receiving appropriate VTE prophylaxis – from 43% at baseline, to 68% after 12 months of the intervention, and 85% after 18 months. In 2010, Maynard et al implemented a similar knowledge translation intervention at their academic hospital.[74] However, their risk assessment module was electronic, and the linked computerized provider order entry set was mandatory. Maynard et al also added an audit and feedback component that they dubbed "measure-vention," where patients who received inappropriate prophylaxis were flagged by the ward pharmacist, and brought to the attention of nursing and medical staff. Using randomly sampled inpatient audits, the authors found that the percent of patients on appropriate prophylaxis improved during each of the 3 years of the study (58%, 78%, and 93%; $P < 0.001$).They found a significant reduction in hospital-acquired VTE (RR 0.69; 95% CI 0.47 to 0.79),

and no increase in HIT or prophylaxis-related bleeding. These data were not broken down by patient type. Schiro et al pared down the intervention by Maynard significantly, but they retained the "measure-vention" theme.[75] They used an automated VTE risk assessment tool to identify patients at risk of VTE in real time. Data were then passed on to a nurse case manager, who helped physicians identify high-risk patients, and advocated for appropriate pharmacologic prophylaxis in the absence of contraindications. Before the intervention, 47.9% of at risk patients received pharmacologic prophylaxis. (19.1% had contraindications to anticoagulation.) After the intervention, 64.9% of at risk patients received pharmacologic prophylaxis. (36.2% had contraindications to anticoagulation.)

There has only been one published study that explicitly looked at the *harm* associated with use of knowledge translation strategies in VTE prophylaxis. Khanna et al described their centre's use of a paper-based admission order set, which included a module on VTE prophylaxis.[76] The VTE prophylaxis module was based on the 2008 ACCP guidelines, provided decision support as well as specific recommendations on prophylaxis, and was mandatory for all patients. The authors divided patients into three categories: those with potential benefit from pharmacologic prophylaxis, who had risk factors for VTE and no bleeding risk factors; those with potential harm from pharmacologic prophylaxis, who had either active haemorrhage or a bleeding diathesis; and those with unclear benefit from pharmacologic prophylaxis, who fit into neither category. The module did result in a small overall rise in pharmacologic prophylaxis use after implementation (51% to 58%, $P < 0.001$).However, in multivariable models with

interrupted time series analysis, patients with potential harm from pharmacologic prophylaxis had the *largest* increase in pharmacologic prophylaxis use at the time of implementation (adjusted OR 1.6; 95% CI 1.1 to 2.2). The increased likelihood of receiving prophylaxis in this subgroup gradually returned to baseline. There was a significant increase in bleeding events after the VTE prophylaxis module was implemented – however events were still sufficiently infrequent that they could not be broken down by subgroup. The authors postulated that the new VTE prophylaxis module may have initially created the impression that anticoagulants were the "default" decision, despite the fact that the module had apparent, evidence-based decision support that argued otherwise. This enthusiasm for VTE prophylaxis seemed to have had the maximum impact on patients with the maximum risk of harm.

Are there some general findings that can be taken from the abovementioned knowledge translation studies? The results of many of the high-tech studies (e.g., Kucher's electronic alert study, Maynard's multifaceted electronic order study) are compelling, as they show improvements in both process outcomes and clinically important patient outcomes. However, the authors did not conduct subgroup analyses to look at the effect of electronic alerts on hospitalized medical patients. The benefits of these strategies (on both the process and the patient outcomes) may have been driven by the population that had the highest VTE risk, such as surgical and critical care patients. Many of the successful studies were conducted at a single centre. Knowledge translation strategies may be more effective in a single centre, as there is a concentration of

resources, a specific hospital-based culture and a focused goal. However, such studies have limited generalizability.

The study by Janus et al, which looked at the elVis CCDSS, was well-designed as it attempted to look at different patient groups and the appropriateness of prophylaxis. However, elVis had only modest success. This may have been because its use was not mandatory, and it was not used to assess a large proportion of patients. Knowledge translation strategies that health care practitioners cannot "opt out" of may be more viable than those that are optional. Finally, the findings of Khanna's study should be heeded by future knowledge translation studies in this area. VTE prophylaxis is not a benign intervention, so knowledge translation in this area can be dangerous if it is over-exuberant and not carefully audited.

Section 10. Background work in knowledge translation and VTE prophylaxis by our research group

In 2006, the Thromboembolism Group at McMaster University, under the direction of Dr. J. Weitz, was awarded a CIHR Team Grant in VTE. The grant spanned the spectrum from basic science to clinical investigation to knowledge translation. A key goal of this grant was to investigate barriers to implementing VTE prophylaxis guidelines in hospitalized medical patients, as the need to bridge the gap between existing knowledge and actual practice was considered to be the greatest in this group. To

determine the barriers and identify potential solutions to implementing VTE prophylaxis

in medical patients, we conducted three preliminary studies. In Phase I, a retrospective

chart audit of VTE prophylaxis patterns was conducted in a representative sample of 6

Ontario hospitals (2 large academic hospitals, 2 large community hospitals and 2 small

community hospitals). Of 1,257 adult patients hospitalized on a general internal medicine

ward for at least 3 days, only 60% received *appropriate* prophylaxis (i.e., prophylaxis in

the presence of risk factors and no contraindications, and no prophylaxis in the presence

of contraindications or no risk factors). In Phase II, described in Part 1, Section 7 of this

protocol, 1,553 questionnaires were sent to physicians, nurses, pharmacists and

physiotherapists, to assess their perception of the importance of VTE prophylaxis in

medical patients, barriers to optimal prophylaxis, and the potential success and feasibility

of interventions to optimize utilization.[51] Phase III, also described in Part 1, Section 6 of

this protocol, involved face-to-face interviews with members of these groups and with

hospital administrators.[50] Attitudes towards VTE prophylaxis, logistic barriers,

interprofessional communication and possible intervention strategies were explored.

Phases I to III of our research provided the groundwork for phase IV, a 16-week

pilot cluster randomized control trial of a multifaceted knowledge translation

intervention. SENTRY (Strategies to Enhance Venous Thromboembolism Prophylaxis in

Hospitalized Medical Patients) was conducted in a representative sample of 6 Ontario

hospitals from January to April 2009.The goal was to determine the proportion of medical

patients that were appropriately managed for thromboprophylaxis (according to the 2008

American College of Chest Physician guidelines) within 24 hours of admission, and determine the feasibility of conducting this study on a larger scale. The SENTRY intervention was anchored on a *paper-based* VTE prophylaxis order sets available on the internal medicine wards – a 'low-tech' approach potentially generalizable to a broad spectrum of hospitals. Hospitals in the intervention group received educational sessions conducted by a haematologist and a research coordinator, posters, a VTE risk assessment algorithm and standardized physician order sets. A real-time chart audit of all admitted medical patients was conducted, and feedback sessions were delivered at 4, 12 and 16 weeks to relay performance results to clinical staff. Hospitals in the control group received usual care. The impact of the intervention was assessed by comparing the rate of appropriate VTE prophylaxis in intervention versus control hospitals.

2,611 patients (1,154 in the intervention and 1,457 in the control group) were eligible and included in the SENTRY analysis. We found that the multifaceted intervention did not lead to a significant difference in appropriate VTE prophylaxis rates between intervention and control hospitals (appropriate management rate OR 0.80; 95% CI 0.88, 1.83; $P = 0.413$; intra-class correlation coefficient = 0.022). It was thus not considered feasible. Errors of commission (patients without VTE risk factors receiving prophylaxis) and prescribing errors (patients receiving the wrong type of prophylaxis) were the most common problem in both intervention and control hospitals (51% of all errors in intervention hospitals, and 52% of all errors in control hospitals). Overall, this multifaceted intervention, which incorporated both active and passive strategies, did not

successfully increase the rate of appropriate VTE prophylaxis in medical patients. Major barriers to effective knowledge translation were poor attendance by clinical staff at education and feedback sessions, difficulty locating pre-printed orders and lack of involvement by clinical and administrative leaders. We identified several factors that may have increased the uptake of a VTE prophylaxis strategy, including local champions, support from clinical and administrative leaders, mandatory use, and a simpler risk assessment tool that was more universally available.

There are several explanations for SENTRY's findings. First, despite concerted efforts to incorporate the paper-based VTE prophylaxis order set into all patients' admission orders, they were placed on only 27% of charts in the intervention hospitals. This suggests that for an order set to be successful, it must be embedded within a standardized and mandatory patient admission package. Second, though our order set was modeled on the widely accepted ACCP guidelines for VTE prophylaxis, clinicians stated it was cumbersome and not easily applicable to everyday clinical situations. (This alludes to comments from the phase II and phase III studies, that VTE prophylaxis is not "one size fits all" in medical patients.) Third, despite efforts to engage members of the healthcare team, there was a lack of awareness of the study. Certain groups were not well represented at educational sessions, as they could not take time off from their clinical activities. There was also little involvement from clinical and administrative leaders, resulting in the lack of a sustained internal push to improve practice. Fourth, logistical issues, including placement of the paper-based order sets in accessible areas, was

challenging. This further reinforced the need for order sets to be part of a standard patient admission package which healthcare providers could not 'opt out' of using.

SENTRY showed that a non-mandatory, low-tech intervention that relies on the voluntary cooperation of front-line clinicians (i.e., a bottom-up approach) is unlikely to improve VTE prophylaxis in medical patients. And while the involvement of different health care professionals may be useful to increase accountability, diffusing responsibility to the entire team is clearly not an effective way to optimize VTE prophylaxis. To streamline and unify VTE prophylaxis in medical patients, we believe that a 'top-down', system-based approach is needed. In part 2, a cluster randomized controlled trial of a standardized electronic VTE prophylaxis module will be described. This module will incorporate two promising knowledge translation strategies: an evidence-based CCDSS with variables that meaningfully impact VTE risk; and a multidisciplinary audit and feedback component to ensure medical patients receive evidence-based VTE prophylaxis during hospitalization.

PART 2. STUDY DESIGN

Section 1. Study objectives

Many hospitals are in the process of implementing order sets, which are pre-formatted electronic order sheets for physicians, advanced practice nurses and midwives. It would be useful if these order sets could be designed to work in diverse hospital settings (including academic centres, large community hospitals and small community hospitals). Order sets are believed to: improve safety by reducing error; enhance workflow by streamlining and standardizing care; encourage compliance with best practices; and reduce costs.[61,62] However, order sets have yet to be tested in multicentre randomized controlled trials, to determine if they can optimize VTE prophylaxis in hospitalized medical patients. We believe that order sets should be rigorously studied to evaluate their effect on clinical decision making and patient and provider outcomes. We also believe that it is imperative that content experts take part in the creation of order sets, to ensure promotion of evidence-based care.

We propose a cluster randomized controlled trial to answer the following question: *Does the availability of a standardized electronic order set with an embedded computerized decision support system and audit and feedback component, promoting evidence-based VTE prophylaxis, affect the use of appropriate VTE prophylaxis in hospitalized medical patients?* The primary objective of this study is to determine the impact of this knowledge translation intervention on the rate of evidence-based VTE

prophylaxis. The secondary objective is to determine the impact of this knowledge translation intervention on hospital-acquired VTE, major bleeding and mortality. The population of interest will include all patients aged 18 years or older admitted to the general medical service, either directly through the emergency room or from another ward or facility.

Section 2. Study methods

a)   Study design, recruitment and randomization

The knowledge translation intervention will be studied in a cluster randomized controlled trial. (Figure 3) The unit of randomization (i.e., the cluster) will be the hospital. A cluster design has been chosen for this trial, because the knowledge translation intervention (the electronic Order Set and the audit and feedback component) is naturally applied at the cluster level. Ensuring that all individuals in the hospital cluster either experience, or do not experience, the intervention is administratively convenient, and avoids contamination between the intervention and control groups.[77,78]

North American acute care hospitals will be included in this study if they have the basic computer infrastructure to support the electronic Order Set. (Study personnel will install required software at intervention sites, and provide information technology staff with training in routine software maintenance.) Hospitals will be recruited using two methods:

i) The research coordinator and principal investigator of the study will contact the Chief of Medicine at each eligible hospital, requesting participation.

ii) The research coordinator and principal investigator of the study will contact the Board and senior administration at each eligible hospital, requesting participation.

Participating hospitals will be randomized to either the intervention or control groups in a 1:1 allocation ratio.[79] Stratified randomization will be used, to ensure that there is a balance of hospital size and type in each group. Participating hospitals will be divided into three strata, based on the Ontario Ministry of Health's classification of hospitals: Group A (teaching hospitals); Group B (non-teaching hospitals having greater than 100 beds); and Group C (non-teaching hospitals having fewer than 100 beds). Before randomization, each hospital's Chief of Medicine will fill out a Site Information Form. (Appendix 3) The study research coordinator will divide participating hospitals into three strata. A separate block randomization list will be produced by the study statistician for each stratum, who will then randomize hospitals within each stratum. Allocation concealment will be in place until the study intervention begins.

b)   Participants

Participants in this study are health care providers to whom the knowledge translation intervention applies - those who write orders that apply to hospitalized medical patients. The unit of analysis will be the individual hospitalized medical patient. Eligible

patients include all adults (≥18 years of age), admitted to a general medical ward, either directly through the emergency room or from another ward or facility. Patients will be excluded if they are receiving therapeutic-dose anticoagulation at the time of hospital admission (i.e., as recorded on their medicine admission orders), such as unfractionated heparin (UFH), low-molecular-weight heparin (LWMH), fondaparinux, warfarin, dabigatran, thrombolytics or another anticoagulant.

c)   Intervention

The intervention in this study will be applied at the cluster level. Baseline comparator data will be collected for six months at each hospital site *before* the intervention is introduced. Once the intervention period begins, all eligible patients and physicians at the control hospitals will receive "usual care" (non-standardized, physician-driven admission and daily orders), while all eligible patients and physicians at the intervention hospitals will receive the electronic order set, CCDSS and audit and feedback component. The intervention will not be administered in a blinded fashion.

The core of the knowledge translation intervention is an electronic order set with an embedded CCDSS to guide VTE prophylaxis. (Figure 4a) Physicians will be asked to fill out the electronic order set – which consists of a risk assessment section and a prophylaxis recommendation section – on each eligible patient at admission and every 48 hours. At this time, there is no single widely accepted, externally validated risk assessment model to identify those hospitalized medical patients at highest risk for VTE.

The model by Barbar et al, which has been promoted in the 2012 ACCP guidelines, is not methodologically superior to other models and was not derived using any statistical methods.[38,39] There are also no clear guidelines on which patients can be safely excluded from receiving prophylaxis, since they will receive minimal benefit (or unacceptable harm). Therefore, the VTE risk factors in this study's electronic order set are taken from the 7-factor risk assessment model by Spyropoulos et al.[37] (Figure 4b) This risk assessment model has well-defined, clinically relevant independent variables. It also has a clinically important dependent variable (objectively confirmed, symptomatic VTE), and was developed using sound statistical methodology. This model is based on a simple point system, and divides hospitalized medical patients into high and low VTE risk categories. Importantly, 6 of the 7 risk factors can be determined at the time of admission. The 7th risk factor (immobility for $\geq$7 days) cannot, but in this study, clinicians will be asked if they expect their patient to be immobilized for 48 hours. These risk factors must all be entered into the VTE order set by the health care provider.

Bleeding risk factors are taken from the 2012 ACCP Guidelines: acute bleeding (e.g., GI, intracranial), increased risk for bleeding (e.g., brain lesion, falls, serious bleeding less than 1 month ago), on therapeutic anticoagulation, coagulopathy (INR $\geq$1.5 or aPTT $\geq$40 sec), thrombocytopenia (platelets $\leq 75 \times 10^9$/L) and anemia (Hb $\leq$ 80 g/L).[38] (Figure 4b) The first three risk factors must be entered into the VTE order set by the health care provider. The latter three are automatically entered into the VTE order set by the hospital's laboratory information system (LIS).

The electronic order set will automatically tally the thrombotic risk factors. (Table 8) When they developed their 7-factor risk assessment model, Spyropoulos et al showed that patients with a risk score of ≥2 points had a ≥2% risk of developing objectively confirmed, symptomatic VTE at 92 days, while patients with a risk score of <2 points had a ≤1% risk of this outcome. In this study, the electronic order set will recommend VTE prophylaxis for all patients with a thrombotic risk score of ≥2 points. If the patient has any bleeding risk factors, mechanical prophylaxis with graduated compression stockings will be recommended. (Figure 4c) If the patient has no bleeding risk factors, pharmacologic prophylaxis will be recommended. (Figure 4d) If the patient's thrombotic risk score is <2 points, no prophylaxis will be recommended. (Figure 4e) To reflect current practice patterns and evidence-based guidelines, both LMWH and UFH have been included as pharmacologic VTE prophylaxis options.[38] A systematic review has demonstrated that these agents have similar efficacy and safety.[16] As neither prophylactic-dose LMWH nor UFH have been shown to produce an excessive anticoagulant effect when used in patients with reduced creatinine clearance[22], we have not recommended dose adjustment for reduced creatinine clearance. Fondaparinux is also included as a VTE prophylaxis option for those patients with heparin-induced thrombocytopenia (HIT) who cannot safely receive heparinoids.

Physicians will always have the opportunity to "overrule" the electronic order set's recommendations and prescribe the VTE prophylaxis strategy of their choice. (This

includes the option of prescribing no VTE prophylaxis.) They must fill out a reason for doing so, before they are allowed to submit the order. Regardless of what VTE prophylaxis strategy is chosen, the computer system will prompt physicians to re-assess VTE prophylaxis every two days. This prompt will be enforced by not permitting physicians to submit any new orders that day unless the patient has had a VTE prophylaxis order filed within the last 48 hours.

In order to involve different disciplines in VTE prophylaxis, and encourage accountability and evidence-based practice, an audit and feedback component will be built into the knowledge translation intervention. (Figure 4a) This component will be modeled after the "measure-vention" described by Maynard et al.[80] Every 96 hours, a list of participating patients who are receiving "non-recommended" prophylaxis will be flagged by the computer system. The resulting VTE report card will be reviewed by the ward pharmacist, and brought to the attention of nursing and medical staff. (Figure 5)

d)   Outcomes

All study outcomes pertain to the individual subject level, not the cluster level. The primary outcome of interest is the *proportion of in-hospital days during which appropriate VTE prophylaxis was administered*. This continuous variable, modeled after the primary outcome in the BEHAVE study, is a clinical care or "process" indicator.[81] "Appropriate VTE prophylaxis" is defined as:

(i)   non-receipt of any form of prophylaxis when the patient has <2 VTE risk

        factors; or

(ii)   receipt of pharmacologic prophylaxis, in the correct dose, when ≥2 VTE

        risk factors are present and the patient has no bleeding risk factors; or

(iii)   receipt of mechanical prophylaxis, when ≥2 VTE risk factors are present

        and the patient has any bleeding risk factors.

"Inappropriate VTE prophylaxis" is defined as:

(i)   receipt of any form of prophylaxis when the patient has <2 VTE risk

        factors; or

(ii)   non-receipt of pharmacologic prophylaxis in the correct dose, or receipt of

        mechanical instead of pharmacologic prophylaxis, when ≥2 VTE risk

        factors are present and the patient has no bleeding risk factors; or

(iii)   non-receipt of mechanical prophylaxis, or receipt of pharmacologic

        instead of mechanical prophylaxis, when ≥2 VTE risk factors are present

        and the patient has any bleeding risk factors.

Secondary outcomes are hospital-acquired VTE, major bleeding and death. These

event rates are clinically important "patient" indicators. VTE is defined as the presence of

DVT (lower extremity) or PE objectively confirmed by at least one of compression

ultrasonography, venography, ventilation-perfusion lung scanning, CT pulmonary

angiography, or a conventional pulmonary arteriogram. Data on upper extremity DVT

will be collected, but will not be included in the secondary outcome. Hospital-acquired VTE is VTE that is not clinically evident or suspected at the time of admission, but is diagnosed from 24 hours after hospital admission up to 30 days after hospital discharge. Major bleeding is defined using the International Society of Haemostasis and Thrombosis Scientific and Standardization Committee criteria: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or packed red blood cells.[82]

e)   Data collection

Chart review will be used to ascertain outcomes. Charts will be reviewed for the duration of hospitalization, and for 30 days after discharge from hospital. (The assumption is that patients will return to hospital if they experience a clinical event.) If a patient is hospitalized more than once during the study period, all eligible admissions will be reviewed. We will request Health Records and Decision Support assistance at each site to pull charts for patients who meet our eligibility criteria.

Patient data will be abstracted by a data management assistant, using a modification of the paper-based standardized case report form that was piloted in the SENTRY study. (Appendix 1) All data will be scanned into an electronic Microsoft Access database using Teleform, an electronic data capture system. To ensure data

quality, duplicate data extraction and data entry will be conducted on a randomly selected sample of 5% of charts at each site.

Section 3. Statistical analysis

The analysis and reporting of the results will follow the CONSORT guidelines.[83] All analyses will be done using SAS 9.2 (SAS Institute, Cary, NC).

a) **Sample size**

In the SENTRY study, we found that 70% of patients in the control group received appropriate VTE prophylaxis.[49] These results will be extrapolated, and we will assume that in this study, appropriate VTE prophylaxis will be received by hospitalized medical patients on 70% of in-hospital days**.** We estimate that the standardized electronic order set will increase this proportion to 80%. The sample size calculation for this cluster randomized trial is in Appendix 2.[78,84,85] For a 2-sided alpha of 0.05 and a power of 0.80 in a chi-square test comparing two proportions, the required sample size is approximately 100 hospital admissions in each cluster, and the required number of clusters is 19. *Therefore, this trial will include 10 clusters in each of the usual care and standardized order set groups. 100 hospital admissions will be reviewed in each cluster.* Based on SENTRY, the smallest hospital sites (which also had the fewest hospital admissions) accrued at least 30 eligible admissions per site per month. The largest hospital sites accrued at least 100 eligible admissions per site per month. Therefore, it will be feasible to reach the total required sample size within 16 weeks.

b) **Descriptive statistics**

Individual patient and cluster demographics, and study outcomes (both primary and secondary) will be summarized using descriptive measures. Continuous variables will be expressed as means (standard deviation (SD)) or medians (minimum-maximum, inter-quartile range). Proportions (e.g., proportion of in-hospital days during which appropriate VTE prophylaxis was administered) and event rates (e.g., rates of hospital-acquired VTE) will be expressed as percentages. Results will be expressed as odds ratios with 95% confidence intervals.

c) **Statistics to describe differences between control and intervention group outcomes**

A direct adjustment of the standard chi-square test will be used to analyze the primary and secondary outcomes, which are expressed as proportions and event rates, respectively. This approach is intuitively attractive, since it would be used if the study was a standard randomized trial looking at proportions and event rates. The standard chi-square test would yield a P value that is biased downward in the presence of clustering. However, the adjustment proposed by Donner and Klar[85] takes into account a clustering correction factor (C) for each group. C can be thought of as a group-specific variance inflation factor, or measure of sampling inefficiency in a cluster randomized trial. C_i, the clustering correction factor for study group i, is given by:

$$C_i = \frac{\sum m_{ij}(1 + (m_{ij} - 1) \, ICC)}{\sum m_{ij}}$$

where m_{ij} is the number of individuals in group i, cluster j, and ICC is the intracluster correlation coefficient for the study. In this study, i = 1 or 2 (corresponding to the intervention or control groups), j = 1 through 10 (corresponding to 10 clusters in each group), m = 100 (as each cluster contains 100 subjects), and ICC = 0.022, based on the value calculated in the SENTRY study.[48]

The adjusted chi-square statistic is then given by:

$$X_A^2 = \sum_{i=1}^{2} \frac{n_i(p_i - p_0)^2}{C_i(p_o(1 - p_0))}$$

where C_i is the clustering correction factor for group i, n_i is the number of individuals in group i, p_i is the event rate in group i, and p_o is the expected event rate (corresponding to the overall proportion or event rate in both groups). The adjusted chi-square statistic, X_A^2, will be considered significant if it corresponds to a P value of ≤ 0.05.

Section 4. Ethical considerations

The design of this trial considers the unique ethical challenges inherent to cluster randomized controlled trials: waivers of informed consent; gatekeeper consent; clinical equipoise; and data privacy. Research ethics are primarily concerned with protecting the interests of a trial's research subjects. Therefore, before we discuss this trial's ethical concepts, we must first identify its research subjects.

In randomized placebo controlled trials of drugs, it is fairly simple to identify the research subjects – they are the individuals who either receive the study drug or receive the placebo. In cluster randomized controlled trials, particularly those of knowledge translation interventions aimed at health care providers, identifying research subjects is more difficult. This trial involves several groups of individuals who could be considered research subjects: health care providers in control or intervention hospitals; all patients in control or intervention hospitals; and patients eligible for VTE prophylaxis in control or intervention hospitals. Who are the research subjects?

McRae et al have set out a definition of a human research subject, based on regulatory definitions and ethical concepts. They define human research subjects as those whose interests may be compromised as a result of interventions in a research study.[86] The definition of "intervention" is purposely broad, encompassing procedures in both the control and experimental arms of a study, as well as non-therapeutic data collection procedures. McRae et al elaborate that, under this definition, all human research subjects meet at least one of the following criteria: they are directly intervened upon by an investigator; their environment is deliberately manipulated by an investigator; investigators interact with them for the purpose of collecting data; and investigators obtain their identifiable private information while collecting data.[86] According to this definition, health care providers in all hospitals in this trial are human research subjects. They are the "target" of the experimental knowledge translation intervention, and their environment is being deliberately manipulated. In this trial, the patients are *not* human

research subjects, though their care is indirectly affected by the knowledge translation intervention. Using the McRae definition, the patients are not the direct target of the intervention, their environment is not being deliberately manipulated, and they are not directly interacting with the investigators. McRae et al reinforce that if an individual's identifiable private information has been anonymized, and is used solely to generate aggregate outcome measures, they are not a human research subject unless they are intervened upon in some other way.[86] Patient level effects are an outcome measure in this trial, but identifiable private information is not being used for data analysis.

Generally, we seek informed consent for study participation from research subjects, or their surrogate decision makers. However, obtaining informed consent can be difficult in cluster randomized controlled trials, as it may not be feasible, and it may compromise data integrity. In this trial, obtaining informed consent from health care providers will be difficult, as the clusters (hospital sites) will be randomized before individual cluster members can be identified or approached. Each cluster will likely contain many physicians, and it will not be feasible to obtain informed consent from all of these individuals. Additionally, since it will be difficult for individual cluster members to avoid participating in the intervention (or lack of intervention) once their cluster is randomized, refusal of informed consent would not be meaningful. Finally, obtaining informed consent in this trial would compromise data integrity.[87] The act of explaining the intervention and control groups may influence research subjects' behaviour, obscuring the effect of the knowledge translation intervention. It may also introduce authorisation

bias. This term was coined by Jacobsen et al to describe statistically significant differences between participants and non-participants in research that used medical records.[88] It is a risk in this trial as well. Intuitively, those who refuse to participate in a high-tech intervention that may enhance their knowledge and application of VTE prophylaxis evidence may have different attitudes towards adoption of health technology, towards the use of standardized care modules, and even towards the utility of VTE prophylaxis in general.

We will request each participating research ethics board to grant our study a waiver of consent. We will justify this based on the fact that the informed consent process could potentially introduce bias, and because this study confers minimal risk to research subjects (and the patients they care for). Clinical research studies must uphold the ethical principle of beneficence (the moral obligation not to harm needlessly, and if possible, promote the welfare of research subjects) by ensuring clinical equipoise.[87] Clinical equipoise is defined as "a state of professional disagreement among the community of experts" about a diagnostic or therapeutic question.[87,90] In this trial, there is clinical equipoise in regards to the knowledge translation intervention. We do not have convincing evidence that this intervention does, or does not improve provider behaviour or patient outcomes in the field of VTE prophylaxis. Therefore, administering the intervention to healthcare providers in the intervention group does not needlessly harm them, and if possible, may promote their welfare by enhancing their knowledge. Though the healthcare providers in the control group may not gain any benefits from knowledge

enhancements, they are not being harmed. They are also free to care for their patients using the best clinical evidence available. The study thus poses minimal risk to healthcare providers. The patients in this study are not human research subjects. However their interests also cannot plausibly be compromised by the study intervention, which is in line with, and promotes best clinical evidence. Patients in this study are thus also at minimal risk. Since the study intervention may potentially increase patients' access to evidence-based VTE prophylaxis, they are being treated in a beneficent way.

Though individual informed consent will not be sought in this trial, we will seek "gatekeeper consent." This concept, unique to cluster randomized trials, recognizes that there may be individuals who have the authority to "speak on behalf of" the cluster. These individuals, called gatekeepers, advocate on behalf of clusters, and must be in an administrative position to effectively give consent for those within a cluster to be randomized.[86,89] In this trial, the gatekeepers are the Chiefs of Medicine at each hospital site. They will be approached before the trial begins, and after reviewing the study protocol with the principal investigator, will make a decision on whether or not to participate in the trial.

Ensuring privacy of research data is another important area of consideration in this trial. Privacy advocates have cogently argued that the use of a waiver of informed consent not only denies study participants the choice to have their personal information collected, it denies them the choice to accept or refuse the risks that may result of a privacy breach

which could expose this data.[89,91] The use of a waiver of informed consent in this trial is justified above. However, such a waiver demands that stringent safeguards be used to ensure confidentiality of personal health data. Toronto's Institute for Clinical Evaluative Sciences and the Canadian Institute for Health Research have laid out a number of strategies to protect research data, and these strategies will be adopted in this trial.[92,93] (Table 9) Data collection forms will carry no personal identifiers (i.e., name, birth date, medical record number). Instead, they will be assigned an anonymous study ID. An encrypted list, accessible only to the principal investigator and research coordinator, will link anonymous study Ids to medical record numbers. This list will be stored on a secure, password-protected computer in a locked office, separate from the site used to store other study data. This secure computer will not have external server access. In order to ensure physical security, all data will be kept in locked filing cabinets within locked offices at the research coordinator's hospital site. Electronic security will be maintained by encrypting and password-protecting all files, and storing them on a password-protected computer. Virus-checking programs and regular server back-ups will be implemented. Paper documents will be securely shredded by a document management company after study closure, while electronic documents will be erased as per the each participating research ethics board. Access to the data will be limited to the principal investigator, the research coordinator and the study statisticians. To ensure that these individuals, as well as all other staff participating in the study, appreciate the importance of ethical research practices, they will be required to review the "Tri-Agency Framework: Responsible Conduct of Research," and participate in online Good Clinical Practice (GCP) training

administered by McMaster University. When study results are reported, they will be presented in aggregate. Finally, in order to ensure transparency and oversight, this trial's protocol will be submitted to Research Ethics Boards at all participating hospital sites.

Section 5. Study weaknesses and barriers

One potential weakness of this study is that rates of hospital-acquired VTE are not being measured to assess the efficacy of the intervention. This study is powered on the effect of the electronic order set on appropriate VTE prophylaxis (which includes appropriate administration of prophylaxis and appropriate avoidance of prophylaxis). Although VTE is clinically important to both patients and health care providers, the absolute risk reduction for VTE with pharmacologic prophylaxis in hospitalized medical patients is low (absolute risk reduction for PE with pharmacologic VTE prophylaxis during hospitalization is 0.3%). [16,28]This makes it infeasible to power a study based on clinical events alone. Nevertheless, hospital-acquired VTE has been included as a secondary outcome, as has major bleeding. This study may not show a statistically significant difference in clinical VTE rates with electronic order sets, but the collected data can be used in the design of future studies that *are* powered to assess effects of knowledge translation interventions on clinical outcomes.

Loss to follow-up is a potential barrier facing this study. Loss to follow-up can pose more of a problem in cluster randomized trials than in standard randomized trials; in

the former, not just individual participants, but entire clusters, may choose to drop out of the study. In this study, the possibility of cluster loss will be minimized at the time of cluster recruitment. Telephone meetings between the study research coordinator, the principal investigator of the study and the Chief of Medicine at each eligible hospital will take place before randomization, to evaluate the hospital's willingness to participate in the trial if it is randomized to either group. Hospitals will be encouraged to participate, and remain in the study, through communication with the Board and senior administration at each eligible hospital. Finally, the sample size calculation is sufficiently conservative to allow for a loss to follow-up rate of 5%. (Appendix 2)

Loss of individual participants is also a challenge. Abstracting a complete data set during hospital admission should not be an issue, as hospital records in developed countries (either electronic or paper-based) are generally comprehensive. Outcomes based on data abstracted during the hospital admission (e.g., proportion of in-hospital days of appropriate VTE prophylaxis) should therefore be very reliably detected. However, a major assumption of this study is that if patients experience one of the secondary outcomes within 30 days of discharge (e.g., hospital-acquired VTE, major bleeding and death), they will return to hospital and this information will again be detected in the hospital record. This assumption may not hold true, if the patient has an event within 30 days of discharge, but is not followed up in hospital. Therefore, the expectation is that outcomes based on data abstracted after the initial hospital discharge (e.g., all secondary outcomes) may not be very reliably detected. Given the expected funding and privacy

constraints of this study, it is not feasible to contact each patient by phone/letter to confirm secondary outcomes that take place out of hospital.

The final major barrier facing this study is inadequate computer infrastructure. The study intervention hinges on a robust computer infrastructure at each hospital, which is able to handle multi-step real-time electronic order entry, communication with the LIS, and generation of pharmacy reports. Thus, a computer infrastructure failure would have grave consequences for the study's feasibility. To mitigate this risk, the first 12 months of the study will be devoted to setting up computer software at each intervention site. Skilled developers (employed by the research study, not by the individual hospitals) will ensure that the system is running smoothly before it is launched for clinical use. They will work closely with the Computer Informatics Department at each intervention site. The next 2 months of the study will be a "run-in" phase, where no data are collected, but the system will be subject to routine clinical use. This run-in phase will give each hospital's Computer Informatics Department time to fix any software or hardware problems.

Section 6. Study strengths

This study has both methodologic and clinical strengths. A major methodologic strength is its cluster design, with reporting based on the rigorous CONSORT guidelines.[83] (Appendix 4) Cluster randomized trials are studies in which intact units of individuals (called clusters), rather than individual subjects, are randomly assigned to

intervention groups. This design is well-suited to the study of a health care knowledge translation intervention like electronic order sets. The cluster design minimizes treatment contamination that is likely to occur if individual patients are randomized within each hospital. In this trial, all individuals in the geographically contained hospital cluster will receive either the intervention (electronic order sets) or the control (usual care). The cluster design also allows the knowledge translation intervention to be maximally "promoted," since all practitioners in the geographically contained hospital clusters assigned to the intervention group can be educated about the electronic order sets, encouraged to use it, and targeted by the audit and feedback component. There is no need to shield certain practitioners from this promotion effort, for fear of treatment contamination. Compliance may also be enhanced by the cluster design. A 1988 study by Farr et al randomized families a viruscidal nasal spray or a placebo nasal spray, to determine if the incidence of respiratory disease could be reduced.[94] It was thought that compliance with the nasal spray would be more likely if all members of a family were assigned to the same treatment regimen. This "herd mentality" effect, a reaction to peer pressure that makes individuals act in order to avoid feeling left behind from the group, may similarly increase compliance with more complex interventions, such as the use of (and agreement with) electronic order sets.

The stratified cluster design is an additional methodologic strength. Stratification by Ministry of Health hospital type (i.e., teaching hospitals, non-teaching hospitals having greater than 100 beds, non-teaching hospitals having fewer than 100 beds) will achieve

overall balance in each study arm. This should improve the accuracy of the study results, since hospital type may be a surrogate for within-cluster dynamics that can affect the study outcome. An additional clinical strength of the inclusion of diverse hospitals is that the results of this study will be widely generalizable. In order to improve the precision of this cluster randomized trial, cluster-level eligibility restrictions have been put in place (i.e., North American acute care hospitals). These restrictions should reduce between-cluster variability. Baseline measurements of potentially important study site characteristics, such as hospital size, the presence of student physicians and residents, the presence of a hospital Patient Safety or Quality Improvement Team, and the presence of an inpatient thrombosis consulting service, will also be collected. These characteristics may have prognostic importance, and they will be taken into account when the data are analyzed.

The statistical analysis used in this study, which takes clustering into account, is a final methodologic strength. Analysis of binary data (i.e., comparing two proportions or event rates) in cluster randomized trials is challenging, since all available statistical methods are approximate. The strengths and weaknesses of several analytic approaches are described in detail by Donner and Klar, and Campbell.[95,96] The chi-square test is well-suited to the comparison of event rates, as it imposes no distributional assumptions on the data. It is therefore the most appropriate statistical test for this study's secondary outcomes. However, a fundamental assumption of the standard chi-square test is that sample observations are statistically independent. This study violates the assumption of

independence, since outcomes in subjects within a hospital will likely be more similar

than outcomes in subjects in different hospitals. Violation of this assumption would bias

the P value downwards, risking a falsely significant result with the standard chi-square

test. The magnitude of bias corresponds to the intracluster correlation coefficient (ICC),

outlined in Appendix 2. A two-sample t-test is also not appropriate to analyze the

outcomes in this study, since the data violate the core assumption required for the t-test's

validity: that cluster-specific event rates are normally distributed and have a homogenous

variance. Additionally, the t-test does not lend itself well to stating conclusions in terms

of odds ratios, which is the natural way that researchers discuss binary outcome data.

Using a modification of the chi-square statistic to analyze the outcomes in this

study is most appropriate, since these data are binary (event / no event), not continuous.

The adjusted chi-square statistic proposed by Donner and Klar takes group-specific

variance inflation factors into account. These factors reflect sampling inefficiency, cluster

size and cluster homogeneity, and group size.[95] An assumption behind the adjusted chi-

square approach is that the group-specific variance inflation factors (C_1 and C_2) are not

significantly different.[95] This is a reasonable assumption in this experimental study, as

stratification is used to balance treatment arms, and hospitals are recruited from the same

general pool (North American acute care hospitals). Donner and Klar do describe two

additional approaches to comparing event rates in cluster randomized trials: a likelihood

ratio test based on parametric modeling, and a generalized estimating equation.[95] Though

these approaches are very flexible and robust, they are computationally intensive. It

appears that these approaches do not offer much advantage over the adjusted chi-square approach, especially when the cluster sizes are equal.[95] That is, their results closely approximate X_A^2 under these conditions.

A clinical strength of this study is its use of an evidence-based VTE risk assessment tool, based on the 7-factor risk assessment model by Spyropoulos et al.[37] This risk assessment model has well-defined, clinically relevant independent variables. It also has a clinically important dependent variable (objectively confirmed, symptomatic VTE), and was developed using sound statistical methodology. This model is based on a straightforward summative point system, and divides hospitalized medical patients into high and low VTE risk categories. At this time, there is no single universally accepted guideline on which hospitalized medical patients can be safely excluded from receiving prophylaxis, since they will receive minimal benefit (or unacceptable harm). However, the VTE the model by Spyropoulos et al appears to be the most methodologically sound. There is no single widely accepted bleeding score for hospitalized medical patients either, however this study uses risk factors drawn from the widely accepted 2012 ACCP Guidelines.[38] No other studies in this area have combined risk assessment of both VTE and bleeding.

Finally, this study is strengthened by the fact that its intervention is based on best evidence from the field of knowledge translation in VTE prophylaxis. The 2010 systematic review of this field, conducted by Mahan et al, commented on several "best

practices" that appeared to optimize VTE prophylaxis and/or decrease VTE event rates: active interventions, computerized tools, human alerts (especially those delivered by pharmacists), and multifaceted interventions.[65] Mahan et al suggested that components like audit and feedback may augment an intervention's effect, and surmount alert fatigue.[65] The knowledge translation intervention in this study incorporates all of these features. It additionally incorporates mandatory stops, which require the physician to complete VTE prophylaxis orders before other orders can be entered, and to specify their reasons if they overrule the electronic order set's evidence-based recommendations. It is expected that the computerized order set and CCDSS will be more convenient for physicians to use than a manual, paper-based order set and CCDSS (such as the one that was used in the SENTRY pilot trial.) This study is one of few randomized, multi-site knowledge translation studies aimed at optimizing VTE prophylaxis. It is the only such study exclusively aimed at hospitalized medical patients.

Section 7. Study timeline

The expected timeline of this project is 2 years. (Figure 6) The first 12 months will be devoted to working with participating hospitals to develop the electronic order set software, embed it in each intervention group hospital's computer infrastructure, and ensure that the software is functional and linked to the hospital's LIS. Baseline data on VTE prophylaxis and clinical outcomes will be collected for 16 weeks at all participating hospitals, at the end of this period. Once the order set is introduced, a 2 month run-in

period will take place, where no data are collected, and any software or hardware errors are resolved. Data on VTE prophylaxis rates and clinical outcomes will then be collected for 16 weeks, to assess the intervention's impact. The final 4 to 6 months will be devoted to data analysis.

Section 8. Study impact

This study should have wide-ranging impact. Internationally, it will be one of few multicenter knowledge translation studies aimed at optimizing VTE prophylaxis. Locally, this study will determine if electronic order sets improve VTE prophylaxis in hospitalized medical patients, and whether their effect can be detected in a variety of different hospital settings. This study is also expected to streamline the process of care by standardizing the ordering of VTE prophylaxis in hospitalized medical patients. It is hypothesized that it the electronic order sets will result in a meaningful reduction in the delivery of inappropriate VTE prophylaxis, and a meaningful improvement in the delivery of appropriate VTE prophylaxis. Electronic order sets, if grounded in evidence-based clinical content and knowledge translation strategies, may be a tool for sustainable change in the delivery of patient care.

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Appendix 1. Data collection form

Data collection form		Study ID: __ - __ __ __		**PAGE 1**
	Sex: O male O female	Date of Birth (d/m/y):		
Admission (d/m/y):	Discharge (d/m/y):	Admission Diagnosis (ICD-10):		
Admission Diagnosis (ICD-10 code):				
Inclusion Criteria (ALL must be YES for inclusion)			**Yes**	**No**
Adult (age >18 years)			O	O
Hospitalized on general internal medicine ward			O	O
Exclusion Criteria (YES excludes patient)			**Yes**	**No**
Received therapeutic dose anticoagulation at time of admission			O	O

Section A: VTE Prophylaxis Assessment *See coding sheet for abbreviations of prophylaxis orders*			
	Suggested Order	**Entered Order**	**Administered Prophylaxis**
Admission			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			

You may append additional sheets if patient's length of stay exceeds 23 days

Appendix 1. Data collection form (continued)

Data collection form	Study ID: __ - __ __ __	PAGE 2

Section B: Outcomes Assessment
Check all events that occurred during the study period (within 30 days of discharge).
Answer all questions for each event.

Deep vein thrombosis
☐ No
☐ Yes: a. Date (d/m/y): _____
       b. Location: _____
       c. Confirmed by (check all that apply)
           ☐ a. Duplex ultrasound scan
           ☐ b. Venography

Pulmonary embolism
☐ No
☐ Yes: a. Date (d/m/y): _____
       b. Confirmed by (check all that apply)
           ☐ a. High probability VQ scan
           ☐ b. Pulmonary arteriogram
           ☐ c. Spiral CT scan

Major bleeding
☐ No
☐ Yes: a. Date (d/m/y): _____
       b. Nature of bleed (check all that apply)
☐ a. Clinically evident with drop in Hgb > 20 g/L or bleed necessitating ≥ 2U PRBC
☐ b. Bleeding into critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome)
☐ c. Fatal bleeding

Heparin-induced thrombocytopenia (confirmed with serotonin release test)
☐ No
☐ Yes: a. Date (d/m/y): _____

Death
☐ No
☐ Yes: a. Date (d/m/y): _____
       b. Cause of death: _____
       c. Was autopsy performed?
           ☐ No
           ☐ Yes. If Yes, describe findings:
_____

Appendix 1. Data collection form (continued)

Abbreviations to be used in Part A
GCS: GCS / bilateral graduated compression (anti-embolic) stockings
OTM: Other mechanical prophylaxis
DAL: Dalteparin 5,000 units subcut OD
HEP: Heparin 5,000 units subcut BID
FON: Fondaparinux 2.5 mg subcut OD
OTH: Other pharmacologic prophylaxis (different drug or different dose)
NON: No prophylaxis

Appendix 2. Sample size calculation

Cluster randomized trials are studies in which intact units of individuals (called clusters), rather than individual subjects, are randomly assigned to intervention groups. The sample size for this cluster randomized trial will be calculated as per the method suggested by Donner et al.[1] The number of subjects required in a cluster randomized trial is larger than a standard randomized trial. This is because, though the statistical inferences are intended to apply at the level of the individual subject, the unit of randomization is actually the cluster. Individuals within each cluster are generally more similar than individuals between clusters; this homogeneity must be taken into account when powering the study.

The intracluster correlation coefficient (ICC) is a measure of homogeneity within clusters. The formula for ICC is:

$$ICC = \frac{SD(between)^2}{SD(between)^2 + SD(within)^2}$$

where SD is the standard deviation between and within clusters. Estimating sample size in cluster randomized trials can be difficult if these standard deviations are not known. Investigators often have to estimate these values, if relevant literature or pilot data are not available. In this study, the ICC does not need to be based on estimated SDs. Instead, the ICC can be taken from the SENTRY study, which included large academic hospitals, medium-sized community hospitals and small community hospitals.[2] The ICC in SENTRY was calculated to be 0.022.

Donner et al describe another measure - the design effect term or variance inflation factor (IF). If the ICC is large and/or if the cluster sizes are large, then sampling will be inefficient in a cluster randomized trial. The IF is a measure of this inefficiency. The formula for IF is:

$$IF = 1 + (m - 1)ICC$$

where ICC is the intracluster correlation coefficient, and m is the number of subjects within each cluster. For this trial, ICC = 0.022, and m = 100. This value for m is based on the assumption that we can recruit 100 patients per site. (In SENTRY, we recruited approximately 30 to 100 patients per site, per month.) Therefore, the IF is 3.178.

To estimate the total sample size in a cluster sample, one must first estimate the unadjusted sample size. The traditional formula for a sample size, unadjusted n, in a trial comparing two binomial proportions or event rates, p_1 and p_2, is:

$$unadjusted\ n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \frac{p_1(1-p_1) + p_2(1-p_2)}{(p_1 - p_2)^2}$$

Where $Z_{1-\alpha/2}$ is the z score corresponding to the desired level of confidence, and $Z_{1-\beta}$ is the z score corresponding to the desired level of statistical power. For this trial, $\alpha = 0.05$, $\beta = 0.80$, $p_1 = 0.70$ and $p_2 = 0.80$. Therefore, the unadjusted sample size is 588, or 294 patients in each of the control and intervention groups.

This figure must be multiplied by the IF to get the adjusted sample size. The resulting formula is:

$$adjusted\ n = IF\ x\ unadjusted\ N$$

For this trial, IF = 3.178 and unadjusted n = 588. Therefore, the adjusted sample size is 1869.

To calculate the required number of clusters, c, the formula is:

$$c = \frac{adjusted\ n}{m}$$

For this trial, the adjusted sample size = 1869 and m = 100. Therefore, 19 clusters are required.

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Appendix 3. Site information form

1.   Name:_____

2.   Hospital/Institution:_____

3.   Is your hospital an… Academic hospital ☐ OR a Community hospital ☐

4.   How many total inpatient beds are at your site? (Including step-down beds)
     ☐☐☐

5.   How many general medical beds are at your site? (Including step-down beds)
     ☐☐☐

6.   Approximately how many general medicine admissions does your hospital have
     per night?
     ☐☐☐

7.   How many staff internists work on your general medical ward?
     ☐☐☐

8.   Does your hospital have medical residents?
     Yes ☐   No ☐

9.   Does your hospital have clinical clerks (i.e. senior medical students)?
     Yes ☐   No ☐

10.   Does your hospital have a dedicated Patient Safety or Quality Improvement
     Team?
     Yes ☐   No ☐

11.   Does your hospital have an inpatient thrombosis consulting service?
     Yes ☐   No ☐

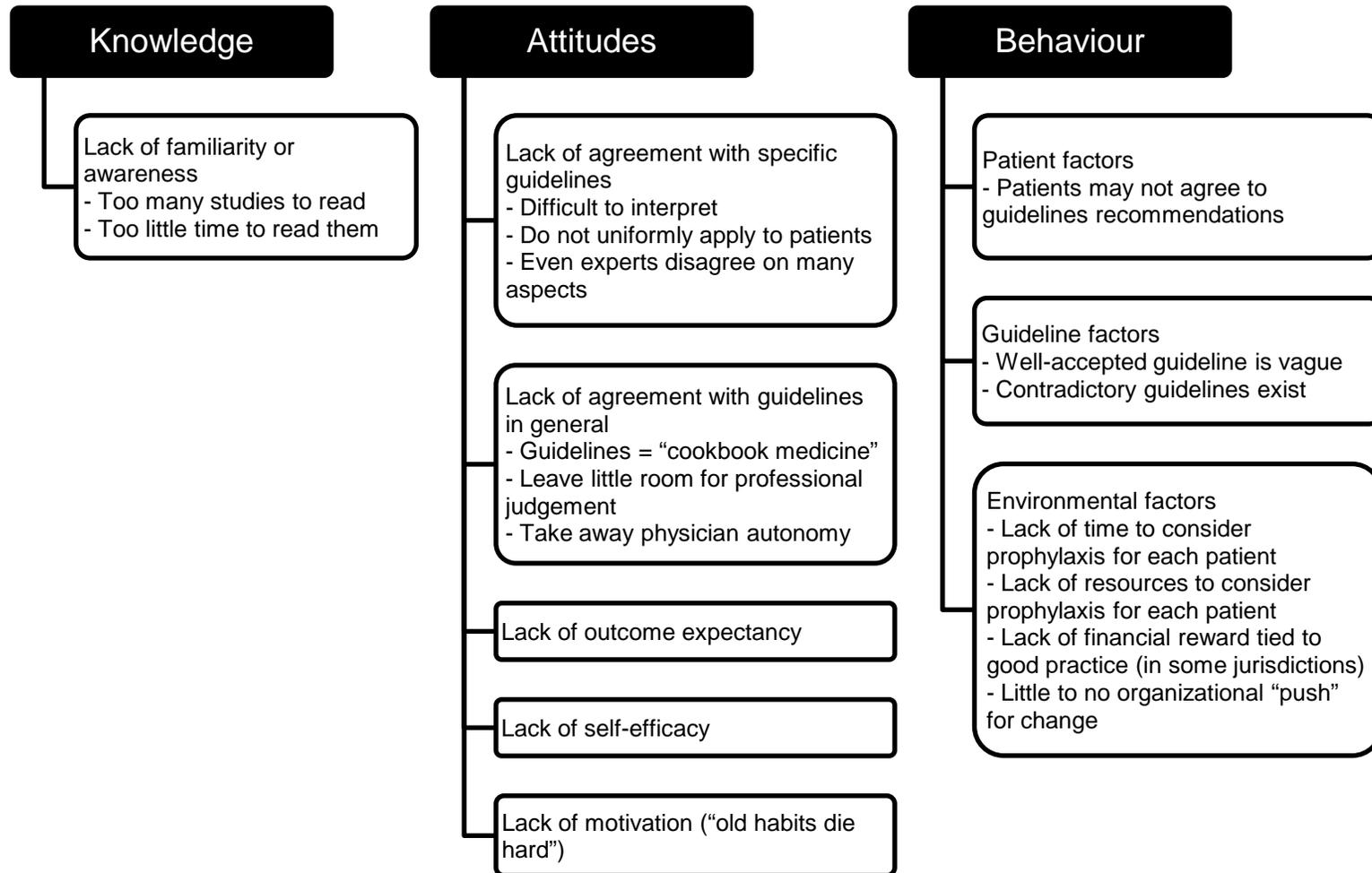## Appendix 4. CONSORT checklist for reporting of a cluster randomized trial

PAPER SECTION and topic	Item	Descriptor
TITLE & ABSTRACT	1*	How participants were allocated to interventions (e.g., "random allocation", "randomised", or "randomly assigned"), *specifying that allocation was based on clusters*
INTRODUCTION Background	2*	Scientific background and explanation of rationale, *including the rationale for using a cluster design.*
METHODS Participants	3*	Eligibility criteria for participants *and clusters* and the settings and locations where the data were collected.
Interventions	4*	Precise details of the interventions intended for each group, *whether they pertain to the individual level, the cluster level or both,* and how and when they were actually administered.
Objectives	5*	Specific objectives and hypotheses, *and whether they pertain to the individual level, the cluster level or both.*
Outcomes	6*	Report clearly defined primary and secondary outcome measures, *whether they pertain to the individual level, the cluster level or both*, and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).
Sample size	7*	How *total* sample size was determined *(including method of calculation, number of clusters, cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty*) and, when applicable, explanation of any interim analyses and stopping rules.
Randomisation. Sequence generation	8*	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification, *matching*).
Allocation concealment	9*	Method used to implement the random allocation sequence, *specifying that allocation was based on clusters rather than individuals and* clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (Masking)	11	Whether or not participants, those administering interventions, and those assessing outcomes were blinded to group assignment. If done, how success of blinding was evaluated.
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s) *indicating how clustering was taken into account*; methods for additional analyses, such as subgroup analyses and adjusted analyses.
RESULTS Participant flow	13*	Flow of *clusters and* individual participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of *clusters and* participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.

Appendix 4. CONSORT checklist for the reporting of a cluster randomized trial (continued)

PAPER SECTION and topic	Item	Descriptor
Baseline data	15*	Baseline information for each group *for the individual and cluster levels as applicable*
Numbers analyzed	16*	Number of *clusters and* participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).
Outcomes and Estimation	17*	For each primary and secondary outcome, a summary of results for each group measures *for the individual or cluster level as applicable*, and the estimated effect size and its precision (e.g., 95% confidence interval) *and a coefficient of intracluster correlation (ICC or k) for each primary outcome.*
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalisability	21*	Generalisability (external validity) *to individuals and/or clusters (as relevant)* of findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

From: Campbell MK, Elbourne DR, Altman DG, et al.. CONSORT statement: extension to cluster randomised trials. BMJ. 2004;328(7441):702-708.

Figure 1. Barriers to physician adherence to VTE prophylaxis guidelines in medical patients

Knowledge

Lack of familiarity or awareness
- Too many studies to read
- Too little time to read them

Attitudes

Lack of agreement with specific guidelines
- Difficult to interpret
- Do not uniformly apply to patients
- Even experts disagree on many aspects

Lack of agreement with guidelines in general
- Guidelines = "cookbook medicine"
- Leave little room for professional judgement
- Take away physician autonomy

Lack of outcome expectancy

Lack of self-efficacy

Lack of motivation ("old habits die hard")

Behaviour

Patient factors
- Patients may not agree to guidelines recommendations

Guideline factors
- Well-accepted guideline is vague
- Contradictory guidelines exist

Environmental factors
- Lack of time to consider prophylaxis for each patient
- Lack of resources to consider prophylaxis for each patient
- Lack of financial reward tied to good practice (in some jurisdictions)
- Little to no organizational "push" for change

Adapted from: Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA*. 1999;282(15):1458-1465

Figure 2. CIHR's model of knowledge translation
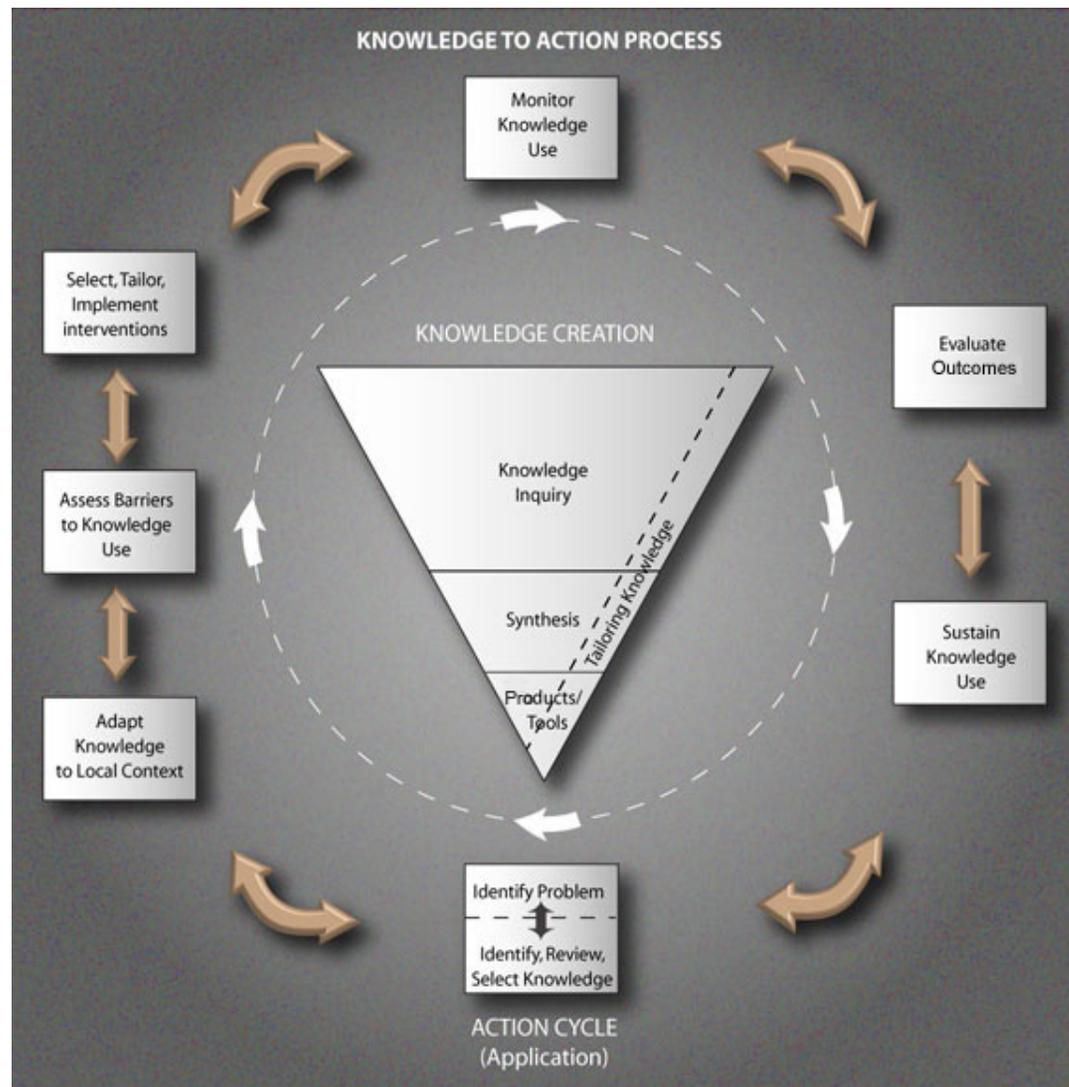
From: Graham ID et al. Lost in translation: Time for a map? *J Cont Educ Health Prof*. 2006: 26, 13–24.

Figure 3. Study design
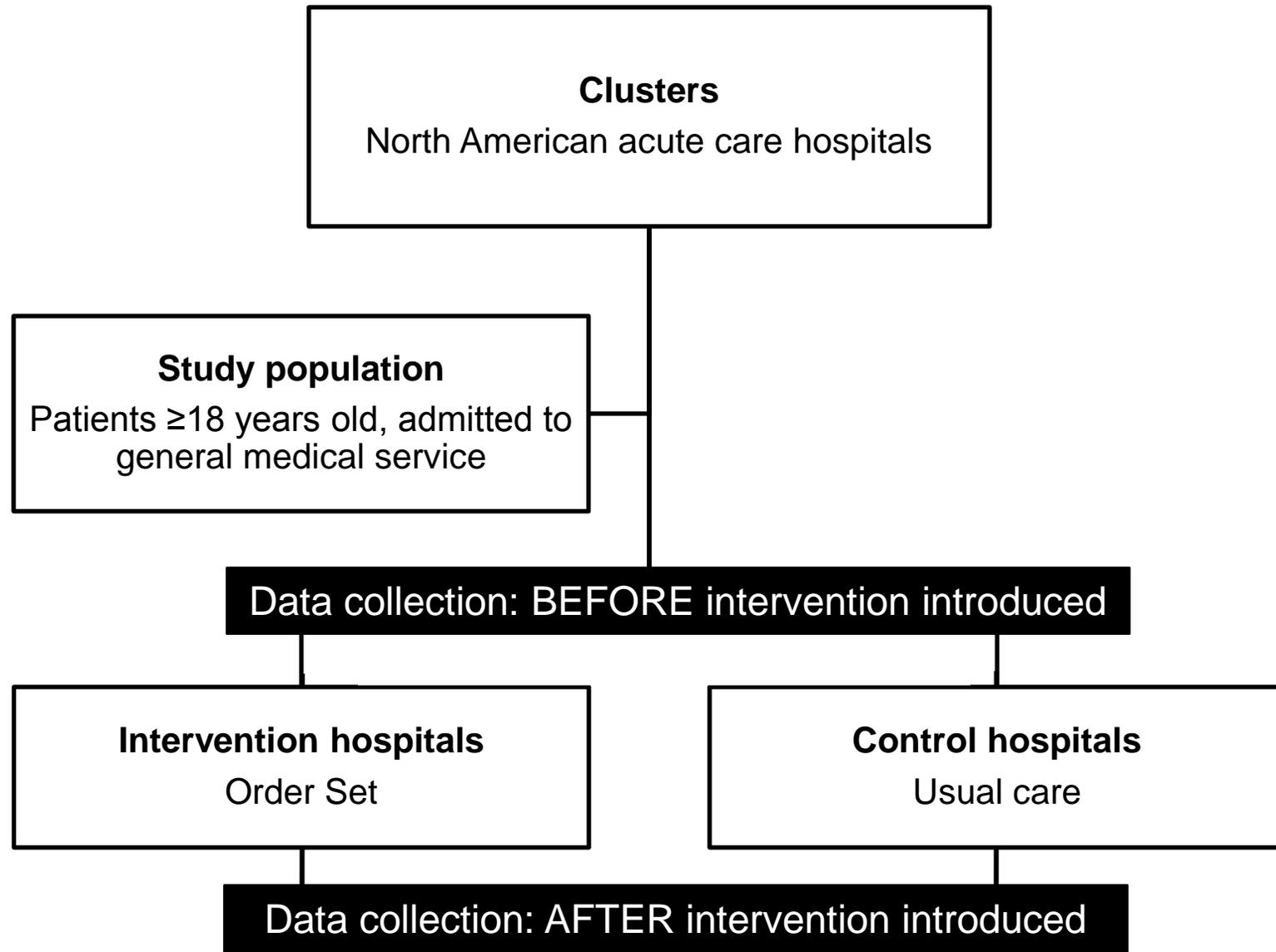
Figure 4a. Electronic order set – overview of use

Physician must complete VTE risk assessment at time of patient admission and every 48 hours

Based on risk assessment, physician is prompted to order pharmacologic, mechanical or no VTE prophylaxis.

Physician accepts recommended order OR overrules recommendation and writes own order.

Computer system flags patient every 96 hours if they are on "non-recommended" VTE prophylaxis. Ward pharmacist audits list, then gives feedback on flagged patients to MDs and RNs

Figure 4b. Electronic order set – risk assessment section

** Consider VTE prophylaxis in every patient, every day ***

Is your patient at risk of clotting?

Check all that apply

- Previous VTE
- Known thrombophilia (e.g., factor V Leiden, prothrombin mutation, antithrombin III deficiency, protein C/S deficiency, lupus anticoagulant)
- Active cancer
- Lower limb paralysis
- Age >60
- In ICU or CCU
- Immobility (confined to bed or chair) for at least 48 hours prior to admission, or expected for at least 48 hours post-admission

Is your patient at risk of bleeding?

Check all that apply

- Active bleeding (e.g., gastroduodenal ulcer, intracranial bleed)
- Increased bleed risk (e.g., brain lesion, falls, bleed <3 mos ago)
- On therapeutic anticoagulation, thrombolytics
- Coagulopathy (INR ≥ 1.5, aPTT ≥ 40 sec)
      Your patient's INR is: _____, PTT is: _____
- Thrombocytopenia (plt ≤ 50 × 109/L).
      Your patient's plt is: _____
- Anemia (Hb ≤ 80 g/L).
      Your patient's Hb is: _____

Figure 4c. Electronic order set – mechanical prophylaxis section

** Consider VTE prophylaxis in every patient, every day ***

Mechanical prophylaxis is recommended!

Choose:

- GCS: bilateral graduated compression (anti-embolic) stockings. Use continuously on both legs except during bathing, walking, TID skin care. Reassess daily for pharmacologic prophylaxis.

ACCEPT THIS ORDER

Or… OVERRULE RECOMMENDATION AND WRITE A DIFFERENT ORDER

Figure 4d. Electronic order set – pharmacologic prophylaxis section

** Consider VTE prophylaxis in every patient, every day ***

Pharmacologic prophylaxis is recommended!
Choose one of:

- Dalteparin 5,000 units subcut OD
- Heparin 5,000 units subcut BID
- Fondaparinux 2.5 mg subcut OD – ONLY if patient has history of HIT

ACCEPT THIS ORDER

Or… OVERRULE RECOMMENDATION AND WRITE A DIFFERENT ORDER

Figure 4e. Electronic order set – no prophylaxis recommendation section

** Consider VTE prophylaxis in every patient, every day ***

No VTE prophylaxis is recommended!

Choose one of:

- No prophylaxis. Reassess daily.

ACCEPT THIS ORDER

Or… OVERRULE RECOMMENDATION AND WRITE A DIFFERENT ORDER

Figure 5. Sample VTE report card from audit and feedback component

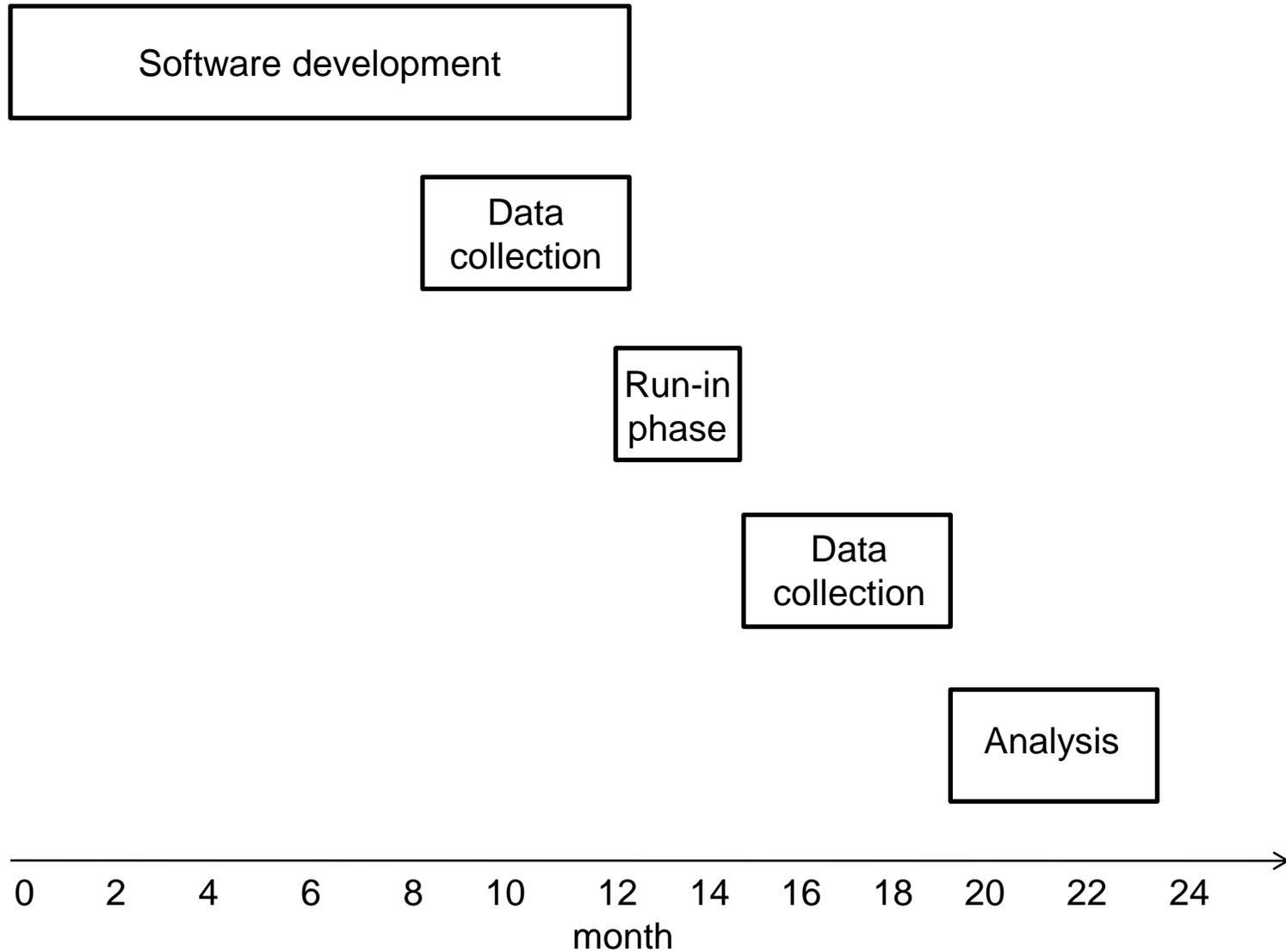| Patient	Staff physician	Status
STEIN, Gertrude	Dr. Zhivago	**Recommended**
HEMINGWAY, Ernest	Dr. Jekyll	**Recommended**
FITZGERALD, Zelda	Dr. Jekyll	**Recommended**
PORTER, Cole	Dr. Zhivago	**Recommended**
PICASSO, Pablo	Dr. Zhivago	**Non-recommended**
CHAGALL, Marc	Dr. Watson	**Non-recommended**
PARKER, Dorothy	Dr. Jekyll	**Non-recommended**

Figure 6. Study timeline

Table 1. Critical appraisal: Two systematic reviews of VTE prophylaxis in hospitalized medical patients

Critical appraisal criteria	Dentali et al	Lederle et al
Was *a priori* design provided? • Research question and inclusion criteria established before conduct of review	Yes	Yes
Was there duplicate study selection and data extraction? • At least two independent data extractors • Consensus procedure for disagreements	Yes	Yes
Was a comprehensive literature search performed? • At least two electronic sources searched, with years and databases specified • Key words, MESH terms and search strategy provided • All searches supplemented by consulting current contents, reviews, textbooks, specialized registers, experts, references of studies found	Yes	Yes
Was the status of publication (i.e. grey literature) used as an inclusion criterion? • Authors searched for reports regardless of their publication type • Authors state whether they excluded any reports based on publication status, language etc.	No *Only RCTs included* *Language not used to exclude studies*	No *Only RCTs included* *Only English language studies included*
Was a list of included and excluded studies provided?	No *List of excluded studies not provided*	No *List of excluded studies not provided*
Were characteristics of included studies provided (in aggregate form)?	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes
Were the methods used to combine the findings of studies appropriate? • For pooled results, a test of homogeneity should be performed • If heterogeneity exists a random effects model should be used and/or clinical appropriateness of combining should be taken into consideration	Yes	Yes
Was the likelihood of publication bias assessed?	Yes	Yes
Were conflict of interest and sources of support included?	Yes	Yes

Abbreviations: VTE, venous thromboembolism; MESH, medical subject headings; RCT, randomized controlled trial.

Table 2. Summary of findings: Two systematic reviews of VTE prophylaxis in hospitalized medical patients

What is the effect of any anticoagulant, versus placebo or no intervention, on VTE outcomes in hospitalized medical patients?
Included studies:
Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med. 2007;146(4):278-288.
Lederle FA, Zylla D, Macdonald R, Wilt TJ. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: a background review for an american college of physicians clinical practice guideline. Ann Intern Med. 2011;155(9):602-615.

Outcome	Study	Event rates, n/N (%)		Relative effect (95% CI)	Number of studies	Quality of the evidence (GRADE)
		Without Anticoagulant	**With anticoagulant**			
Any PE	Lederle et al	127 / 10,251 (1.2)	88 / 10,466 (0.8)	**OR 0.7 (0.5 to 0.9)**	10	⊕⊕⊕⊖, Moderate[2]
	Dentali et al	49 / 9,930 (0.5)	20 / 9,807 (0.2)	**RR 0.4 (0.3 to 0.7)**	8	⊕⊕⊕⊖, Moderate[2]
Fatal PE	Lederle et al	26 / 8,693 (0.3)	21 / 8,927 (0.2)	OR 0.8 (0.4 to 1.4)	5	⊕⊕⊕⊖, Moderate[1,2]
	Dentali et al	39 / 9,422 (0.4)	14 / 9,288 (0.2)	**RR 0.4 (0.2 to 0.7)**	5	⊕⊕⊕⊖, Moderate[1,2]
Symptomatic DVT	Lederle et al	27 / 2,791 (1.0)	25 / 3,166 (0.8)	OR 0.8 (0.5 to 1.4)	5	⊕⊕⊕⊖, Moderate[1,2]
	Dentali et al	21 / 2,167 (1.0)	10 / 2,190 (0.5)	RR 0.5 (0.2 to 1.0)	3	⊕⊕⊕⊖, Moderate[1,2]
Major bleeding	Lederle et al	25 / 10,116 (0.3)	41 / 10,331 (0.4)	OR 1.5 (0.9 to 2.4)	9	⊕⊕⊕⊖, Moderate[1,2]
	Dentali et al	19 / 4,254 (0.4)	25 / 4,251 (0.6)	RR 1.3 (0.7 to 2.4)	7	⊕⊕⊕⊖, Moderate[1,2]
All bleeding	Lederle et al	115 / 4,194 (2.7)	216 / 4,550 (4.7)	**OR 1.3 (1.1 to 1.7)**	8	⊕⊕⊕⊕, High
	Dentali et al	N/A	N/A	N/A	N/A	N/A
All-cause mortality	Lederle et al	679 / 10,251 (6.6)	679 / 10,466 (6.5)	0.8 (0.8 to 1.0)	10	⊕⊕⊕⊖, Moderate[1,2]
	Dentali et al	165 / 3,679 (4.5)	158 / 3,676 (4.3)	RR 1.0 (0.8 to 1.2)		⊕⊕⊕⊖, Moderate[1,2]

[1]Quality of evidence rated down, due to imprecision. Optimal information size is not met.

[2]Quality of evidence rated down, due to imprecision. <300 events in total.

Optimal information size was calculated using on-line sample size calculator at: http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; RR, relative risk; OR, odds ratio; CI, confidence intervals; N/A, not available; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Table 3. GRADE approach to rating quality of evidence

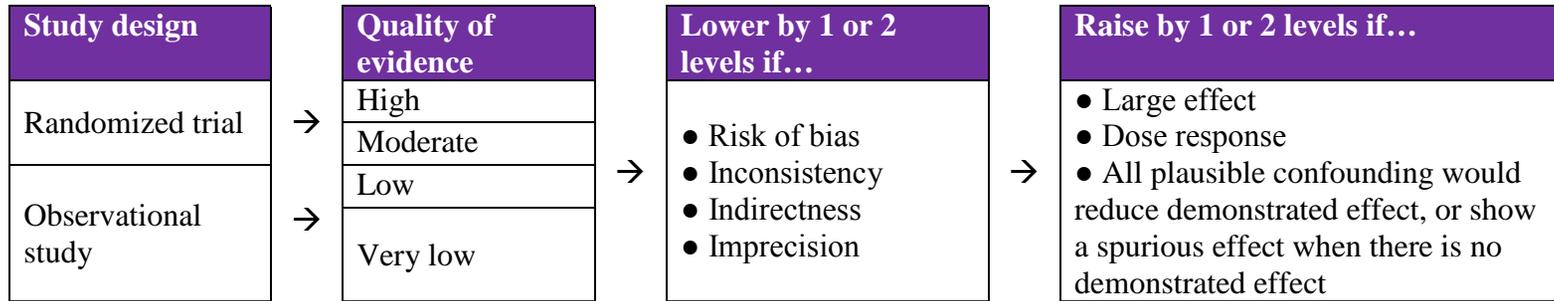| Study design		Quality of evidence	Lower by 1 or 2 levels if…	Raise by 1 or 2 levels if…
Randomized trial	→	High	● Risk of bias	● Large effect
		Moderate	● Inconsistency	● Dose response
Observational study	→	Low	● Indirectness	● All plausible confounding would reduce demonstrated effect, or show a spurious effect when there is no demonstrated effect
		Very low	● Imprecision	

Table 4. Summary of studies to develop VTE risk assessment models in hospitalized medical patients

Findings	Alikhan et al	Woller et al	Rothberg et al
Outcome	Objectively confirmed, symptomatic and asymptomatic VTE within 14 days of admission	Objectively confirmed VTE during hospitalization or within 90 days of discharge	ICD-9 code for VTE plus diagnostic test to objectively confirm and record of appropriate treatment
Predictive variables	Age >75 Cancer Previous VTE Acute infectious disease Chronic respiratory disease	Previous VTE Order for bed rest Peripherally inserted central venous catheter Cancer diagnosis	Age > 65, Male sex, Inherited thrombophilia, Length of stay ≥6 days, Pneumonia, Inflammatory bowel disease, Central venous catheter, Cancer, Mechanical ventilation Chemotherapy, Steroids
Included patients	1102 acutely ill, immobilized patients admitted over 18 months. Patients were enrolled in the MEDENOX study.	Derivation cohort: 143,000 medical admissions over 7 years. Validation cohort: 46,000 medical admissions over subsequent 2 years.	242,738 hospitalized medical patients admitted over 2 years. Subjects randomly assigned (80:20 ratio) to derivation or validation set.
Study site	Internal medicine wards, intensive care units and coronary care units of 60 hospitals in 9 countries	Internal medicine wards at 22 hospitals and >150 clinics in a not-for-profit, university-affiliated, integrated health care system in Utah and Idaho	Internal medicine wards at 374 U.S. hospitals
Statistical analysis	11 potential risk factors derived from MEDENOX data. Multivariate logistic regression analysis to determine which variables independently associated with outcome.	86 potential risk factors derived from 5 prospective clinical trials and a clinical consensus statement. Multivariate logistic regression analysis to determine which variables independently associated with outcome.	34 potential risk factors derived from published data on VTE risk, including 2004 ACCP guidelines. Multivariate logistic regression analysis to determine which variables independently associated with outcome.
Model performance	*Patients stratified into 0, 1 or ≥2 risk factors* 0 factors: 8.7% had outcome 1 factor: 10.9% had outcome ≥2 factors: 12.3% had outcome	Receiver operating characteristic curve constructed for this model. AUC = 0.87 (95% CI 0.87-0.88).	Model produced deciles of observed risk ranging from 0.2% to 1.8% for the outcome. Using a risk threshold of 1%, model had sensitivity of 28% and specificity of 93%.

Table 4 (continued). Summary of studies to develop VTE risk assessment models in hospitalized medical patients

Findings	Spyropoulos et al	Barbar et al
Outcome	Objectively confirmed, symptomatic VTE within 92 days of admission and crude all-cause death rate.	Objectively confirmed, symptomatic VTE within 90 days of admission
Predictive variables	Previous VTE = 3 points Known thrombophilia = 2 points Current cancer = 2 points Current lower limb paralysis = 2 points ICU/CCU stay = 1 point Immobilized ≥7 days = 1 point Age > 60 = 1 point	Active cancer = 3 points Previous DVT or PE = 3 points Reduced mobility = 3 points Known thrombophilia = 3 points Trauma, surgery <30 days ago = 2 points ≥70 years old = 1 point CHF, respiratory failure = 1 point Acute MI, ischemic stroke = 1 point Acute infection, rheumatologic disorder = 1 point Obesity (BMI ≥ 30) = 1 point Ongoing hormonal treatment = 1 point
Included patients	15,156 acutely ill hospitalized medical patients admitted over 4 years. Patients were enrolled in IMPROVE registry.	1180 medical patients admitted over 2 years
Study site	Internal medicine wards of 52 hospitals in 12 countries.	Internal medicine ward of a single academic hospital
Statistical analysis	25 potential risk factors derived from IMPROVE registry data. Multivariate logistic regression analysis to determine which variables independently associated with outcome.	None. Authors modified an existing VTE risk model designed for medical and surgical patients. The original model was developed using expert opinion, not statistical methods.
Model performance	*Patients stratified into high VTE risk (≥2 points) and low VTE risk (<2 points)* High risk: ≥2% had VTE outcome, 15% had mortality outcome Low risk: ≤1% had VTE outcome, 35% had mortality outcome	*Patients stratified into high VTE risk (≥4 points) and low VTE risk (<4 points)* HR of VTE in high versus low risk with prophylaxis = 0.1 (95% CI 0.04-0.4) HR of VTE in high versus low risk without prophylaxis = 32.0 (95% CI 4.1-251.0)

Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CHF, congestive heart failure; MI, myocardial infarction; HR, hazard ratio; ACCP, American College of Chest Physicians; AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; ICD-9, International Classification of Diseases, Ninth Revision.

Table 5. Critical appraisal: Studies to develop VTE risk assessment models in hospitalized medical patients

Critical appraisal criterion	Alikhan et al	Woller et al	Rothberg et al	Spyropoulos et al	Barbar et al
Outcome					
Well defined	Yes	Yes	Yes	Yes	Yes
Clinically important	No	Yes	Yes	Yes	Yes
Blinded assessment	Yes	No	No	No	Yes
Predictive variables					
Well defined	Yes	Yes	Yes	Yes	Yes
Patient characteristics					
Well described	Yes	Yes	Yes	Yes	Yes
Study site					
Well described	Yes	Yes	Yes	Yes	Yes
Statistical analysis					
Well described	Yes	Yes	Yes	Yes	Yes
Statistically valid	Yes	Yes	Yes	Yes	No
Model performance	OR, 95% CI, X^2 for each variable % with outcome in three strata of patients	OR, 95% CI, X^2 for each variable AUC for model	OR, 95% CI, X^2 for each variable % with outcome for deciles of patients, and sensitivity and specificity for model	OR, 95% CI, X^2 for each variable HR, 95% CI of outcome in two strata of patients	OR, 95% CI, X^2 for each variable HR, 95% CI of outcome in two strata of patients
Reproducibility					
Of detecting predictors	No	No	No	No	No
Of using model	No	No	No	No	No
Sensibility					
Clinically sensible	Yes	Yes	Yes	Yes	Yes
Easy to use	Yes	Yes	Yes	Yes	Yes
Suggests probability of outcome	Yes	No	Yes	Yes	Yes
Suggests course of action	No	No	No	Yes	No
Validation					
Prospectively validated	No	Yes	Yes	No	No
Effects of use					
Well described	No	No	No	No	No

Abbreviations: VTE, venous thromboembolism; OR, odds ratio; 95% CI, 95% confidence interval

Table 6. Appropriate and inappropriate use of VTE prophylaxis in consecutively admitted hospitalized medical patients in Hamilton from January to April 2009, based on the 2008 ACCP guidelines

	n/N (%)
Patients receiving appropriate VTE prophylaxis	**526/744 (71)**
Correct receipt of VTE prophylaxis	258/744 (35)
Correct non-receipt of VTE prophylaxis	268/744(36)
Patients receiving inappropriate VTE prophylaxis	**218/377 (29)**
Errors of commission (received VTE prophylaxis when it was not indicated)	124/744 (17)
Errors of omission (did not receive VTE prophylaxis when it was indicated)	57/744 (8)
Receipt of anticoagulant prophylaxis when mechanical prophylaxis was indicated	33/744 (4)
Receipt of mechanical prophylaxis when anticoagulant prophylaxis was indicated	4/744 (0.5)

Abbreviations: VTE, venous thromboembolism; ACCP, American College of Chest Physicians.

Table 7. Classification of Professional Interventions from the Cochrane Effective Practice and Organisation of Care (EPOC) Group

- **Distribution of educational materials -** distribution of published or printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials, and electronic publications
- **Educational meetings** - health care providers who have participated in conferences, lectures, workshops, or traineeships
- **Local consensus processes** - inclusion of participating providers in discussion to ensure that they agreed that the chosen clinical problem was important and the approach to managing the problem was appropriate
- **Educational outreach visits** - use of a trained person who met with providers in their practice settings to give information with the intent of changing the provider's practice
- **Local opinion leaders** - use of providers nominated by their colleagues as ''educationally influential.'' The investigators must have explicitly stated that their colleagues identified the opinion leaders
- **Patient mediated interventions** - new clinical information (not previously available) collected directly from patients and given to the provider, e.g., depression scores from an instrument
- **Audit and feedback** - any summary of clinical performance of health care over a specified period of time
- **Reminders** - patient or encounter-specific information, provided verbally, on paper or on a computer screen that is designed or intended to prompt a health professional to recall information
- **Marketing** - use of personal interviewing, group discussion ("focus groups"), or a survey of targeted providers to identify barriers to change and subsequent design of an intervention that addresses identified barriers
- **Mass media** - (i) varied use of communication that reached great numbers of people including television, radio, newspapers, posters, leaflets, and booklets, alone or in conjunction with other interventions; and (ii) targeted at the population level

Table 8. Weighted scoring of thrombotic risk factors in electronic order set

Item	Number of points
Previous venous thromboembolism	3
Known thrombophilia	2
Current cancer	2
Current lower limb paralysis	2
In intensive care / coronary care unit	1
Immobility	1
Age > 60	1

Table 9. Institute for Clinical Evaluative Sciences strategies to ensure confidentiality of personal health data

• De-identification of data or, if de-identification cannot occur, the substitution of an encrypted unique numeric identifier for personal identifiers by a designated data custodian
• Designation of a privacy officer to implement and monitor compliance with all security and confidentiality policies and practices
• Stringent physical and electronic security of data
• Limitation of physical and electronic access to the data
• Cultivation of an atmosphere of respect for privacy and confidentiality, inclusion of confidentiality and data protection obligations in employment contracts, requirements for employees to sign confidentiality pledges yearly and to receive adequate and ongoing training
• Implementation of strict policies and procedures to handle, access, use, disclose, retain and destroy data
• Established penalties for unauthorized attempts to access or disclose data, or to re-identify de-identified data
• Assessment of potential privacy and confidentiality risks for every observational study
• Limitations on data use to a need-to-use basis
• Controls on disclosure of study results including the stipulation that only aggregate results are allowed to be reported
• Regular reviews and audits, transparency to the public, firm oversight and approval by independent parties