STUDY PROTOCOL

*B*ridging Anticoagulation in Patients who *R*equire Temporary *I*nterruption of Warfarin Therapy for an Elective Invasive Proce*d*ure or Sur*ge*ry

The "BRIDGE" Trial

September 17, 2008

Amendment 1 January 28, 2009
Amendment 2 March 29, 2010

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1.0 Protocol Synopsis

VERSION DATE	Amendment 1 January 28, 2009 Amendment 2 February 17, 2010
PRINCIPAL INVESTIGATORS	Dr. Tom Ortel (Clinical Coordinating Center) Vic Hasselblad, PhD (Statistical Data Coordinating Center)
CO-PRINCIPAL INVESTIGATORS	Drs. David Kong and Rick Becker
PROTOCOL TITLE	**"BRIDGE":** *B*ridging Anticoagulation in Patients who *R*equire Temporary *I*nterruption of Warfarin Therapy for an Elective Invasive Proce*d*ure or Sur*ge*ry
STUDY OBJECTIVES	1) To compare the *efficacy* of bridging anticoagulation (therapeutic-dose LMWH) with no bridging anticoagulation (placebo) on the rate of ATE in patients with atrial fibrillation or atrial flutter who require temporary interruption of warfarin. 2) To compare the *safety* of bridging anticoagulation with no bridging anticoagulation on the rate of major bleeding in patients who require temporary interruption of warfarin.
STUDY PHASE	Phase III
STUDY DESIGN	Randomized double-blind, placebo-controlled, trial.
TREATMENT REGIMENS	Patients will be randomly allocated to: 1) bridging anticoagulation arm (dalteparin ~100 units/kg SC twice-daily) or 2) no bridging anticoagulation arm (matching placebo, SC twice-daily) for approximately 3 days before and approximately 6 days after procedure or surgery.
ROUTE OF ADMINISTRATION	Active study drug or placebo will be administered by subcutaneous injection.
PATIENT POPULATION	Patients with atrial fibrillation or atrial flutter who are receiving long-term warfarin therapy and require temporary interruption of warfarin because of an elective surgical or other invasive procedure.
PLANNED SAMPLE SIZE	3,626 patients (1,813 patients per treatment arm)
PATIENT INCLUSION /EXCLUSION CRITERIA	***Inclusion criteria*** ***All of the following 5 criteria must be satisfied for trial eligibility:*** 1) adult male or female, age 18 years or older 2) receiving warfarin therapy (for at least 3 months), administered to achieve a target INR range of 2.0-3.0

	3) require temporary interruption of warfarin for pre-specified elective procedure or surgery 4) have ***at least one*** of the following conditions: (a) chronic (permanent or paroxysmal) nonvalvular atrial fibrillation or atrial flutter, confirmed by at least one prior electrocardiography recording or pacemaker/ACD interrogation; or (b) chronic (permanent or paroxysmal) valvular atrial fibrillation or atrial flutter with evidence of mitral valvular heart disease, confirmed by same criteria as nonvalvular atrial fibrillation or atrial flutter 5) have ***at least one*** of the following major stroke risk factors: (a) age >75 years; (b) hypertension; (c) diabetes mellitus; (d) congestive heart failure or left ventricular dysfunction; or (e) previous ischemic stroke, systemic embolism or TIA ***Exclusion criteria*** One or more of the following criteria precludes trial eligibility: 1) any mechanical prosthetic heart valve 2) stroke (ischemic or hemorrhagic), systemic embolism or TIA within past 12 weeks 1) 3) venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) within past 12 weeks. 4) major bleeding within past 6 weeks 5) severe renal insufficiency (calculated creatinine clearance <30 mL/min) 6) thrombocytopenia (platelet count $<100 \times 10^9$/L) 7) life expectancy <1 month 8) condition that impairs compliance with trial protocol (e.g., cognitive impairment, uncontrolled psychiatric condition, geographic inaccessibility) 9) pregnancy 10) allergy to heparin or history of heparin-induced thrombocytopenia 11) patient is having one of the following surgeries/procedures during warfarin interruption: (a) cardiac surgery (*e.g.,* coronary artery bypass, heart valve replacement); (b) neurosurgery that is intracranial or intraspinal (*e.g.,* tumor resection, aneurysm repair); (c) high-risk non-surgical procedures (*e.g.,* brain biopsy) 12) other surgical or non-surgical procedure that, at the discretion of the surgeon or proceduralist, precludes administration of therapeutic-dose LMWH at any time in the post-procedure period 13) more than one surgery planned during the trial period 14) prior participation in this trial 15) inability or unwillingness to provide informed consent

INTERVENTION AND INTERVAL BETWEEN FIRST AND LAST DOSE OF ACTIVE STUDY DRUG	In the *bridging anticoagulation arm*, the treatment regiment will consist of: dalteparin, at a dose of ~100 units/kg administered twice-daily by SC injection. In the *no bridging anticoagulation arm*, the treatment regimen will of: matching placebo, administered twice-daily by SC injection. The ***first*** dose of study drug will be given approximately 3 days before the surgery or procedure; the ***last*** dose of study drug will be given approximately 6 days after the surgery or procedure.
STUDY OUTCOMES	Primary efficacy endpoint The primary efficacy outcome is ***ATE***, defined by one or more of: 1) ischemic stroke 2) transient ischemic attack 3) systemic embolism Primary safety endpoint The primary safety outcome is ***major bleeding***, defined by one or more of: 1) symptomatic (or clinically-overt) bleeding associated with: - transfusion of ≥2 units pRBCs or whole blood, or - decrease in hemoglobin level >20 g/L (>2 g/dL), or - need for re-operation or invasive intervention 2) symptomatic or clinically-overt bleeding at a critical anatomic site 3) fatal bleeding Secondary efficacy outcomes 1) acute myocardial infarction (ST- and non-ST-elevation) 2) deep vein thrombosis 3) pulmonary embolism 4) death Secondary safety outcomes 1) minor bleeding
DURATION OF STUDY PARTICIPATION	Participation in this trial commences when informed consent is obtained, between Day -30 to Day -5 before the surgery or procedure, and ends between Day +30 to Day +37.

2.0 SUMMARY of BACKGROUND and RATIONALE, TRIAL OBJECTIVES and METHODS, and SIGNIFICANCE

Background and Rationale:

- The management of patients who require temporary interruption of warfarin therapy for an elective surgical or other invasive procedure is a common clinical problem. In North America, approximately 2 million patients with chronic atrial fibrillation or atrial flutter are receiving long-term warfarin therapy [1].
- Each year, it is estimated that ~20% (~400,000) of these patients require temporary interruption of warfarin because of elective surgery, placing them at increased risk for arterial thromboembolic events (ATE) [2-6]. In approximately three-fifths of these patients, clinicians empirically use bridging anticoagulation, usually with therapeutic-dose subcutaneous (SC) low-molecular-weight heparin (LMWH), before and after surgery [7-10].
- The argument that bridging anticoagulation is needed to minimize the risk for perioperative ATE is questionable, because the time period for which there is sub-therapeutic anticoagulation after warfarin is withheld is short (~8 days) and the efficacy of bridging anticoagulation to reduce the risk for ATE is not established [11]. Bridging anticoagulation is also costly, and administering it in close proximity to surgery may increase the risk for bleeding [12-14].
- Despite the frequency of this clinical problem, good quality evidence to inform practice is lacking. Although a substantial number of observational studies (patient registries, cohort studies) have assessed bridging therapy, these studies only provide the weakest of evidence (Level 2C) [15] to guide clinical decision-making, particularly for those patients with atrial fibrillation or atrial flutter. This lack of high-quality evidence emphasizes the importance of the BRIDGE trial.
- Furthermore, guidelines from the American College of Chest Physicians (ACCP) and joint guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) are inconsistent [16, 17] and it is not surprising, therefore, that clinician practices vary [7-10].

Objectives:

- To compare the *efficacy* of bridging anticoagulation (therapeutic-dose LMWH) with no bridging anticoagulation (placebo) on the rate of ATE in patients with atrial fibrillation or atrial flutter who require temporary interruption of warfarin.
- To compare the *safety* of bridging anticoagulation with no bridging anticoagulation on the rate of major bleeding in patients who require temporary interruption of warfarin.

Methods:

- To address these objectives, the BRIDGE trial is a randomized double-blind, placebo-controlled, trial comparing '*bridging anticoagulation*' with '*no bridging anticoagulation*' in 3,626 patients (1,813 patients per arm) with chronic non-valvular or valvular atrial fibrillation or atrial flutter (hereafter referred to as 'atrial fibrillation or atrial flutter') who are receiving warfarin therapy and require temporary interruption of warfarin for a procedure or surgery.
- Patients will be randomly allocated to a bridging arm (dalteparin ~100 units/kg SC twice-daily) or to no bridging arm (matching placebo, SC twice-daily) between Day -14 to Day -5. Study drug/placebo will be administered for ~3 days before and ~6 days after surgery/procedure. Warfarin therapy will be interrupted 5 days before the surgery/procedure.

- For this trial to change practice in patients who are receiving bridging therapy and to establish a standard-of-care, it must demonstrate that, compared with a bridging therapy approach, a "no bridging" strategy will not expose patients to a clinically important increase in risk for ATE.

Significance:

- **BRIDGE** is the first randomized comparison of bridging anticoagulation with no bridging therapy and will provide Level 1A evidence regarding the therapeutic benefits and risks of this treatment approach. In doing so, this trial will establish an evidence-based standard-of-care for the large number of patients who require temporary interruption of warfarin because of elective procedure or surgery.

3.0 BACKGROUND and RATIONALE

3.1 Management Options for Patients who Require Temporary Interruption of Warfarin

In assessing a patient who requires temporary interruption of warfarin therapy prior to elective surgery, it is clear that interruption of warfarin is required to prevent bleeding complications during and after surgery [12-14]. It is not clear whether bridging anticoagulation should be administered before and after surgery. There are two principal management options for the clinician to consider in such patients:

- *Bridging anticoagulation*, defined as the administration of a short-acting anticoagulant in therapeutic doses, typically SC LMWH or intravenous (IV) unfractionated heparin (UFH), for the ~8 days before and after surgery that warfarin is interrupted and the international normalized ratio (INR) is sub-therapeutic. This approach is currently the dominant practice.
- *No bridging anticoagulation*, defined as simply withholding warfarin for ~4 days prior to surgery and restarting warfarin on the evening of (or the day after) surgery when hemostasis is secured.

3.2 Management of Patients who Require Interruption of Warfarin and Bridging is Common

In North America, approximately 2 million patients with atrial fibrillation are receiving warfarin therapy to prevent ATE, and 250,000 new patients with this condition are eligible to receive warfarin per year [1, 18]. An analysis of the Anticoagulation Clinic databases from two Steering Committee sites found that ~20% of patients with atrial fibrillation will require temporary interruption of warfarin for surgery, thereby suggesting that ~400,000 patients (2,000,000 × 0.20) with atrial fibrillation are assessed for bridging in North America per year. Clinician surveys of anticoagulation management show that bridging is used in 20-62% of patients with atrial fibrillation who require warfarin interruption and a survey of Steering Committee members' clinical centers, found the proportion of patients with atrial fibrillation who receive bridging is 50-75%. A conservative estimate is that 50% of patients with atrial fibrillation who are assessed for warfarin interruption actually receive bridging therapy, suggesting that ~200,000 patients will receive bridging therapy in North America each year.

3.3 Evidence Regarding Bridging is Poor Quality and Limits Treatment Recommendations

Two systematic reviews assessed 38 studies of perioperative anticoagulant management in patients receiving warfarin [19]. The quality of the studies was poor with no randomized trials. Taken together, the aggregate evidence from these studies provides the weakest level of evidence (Level 2C) [15], which is likely to have little or no impact on clinical practice. Due to the lack of high quality evidence and randomized trials, treatment recommendations from consensus groups and experts are inconsistent, unclear, and not justified (11, 19-30).

3.4 Rationale for Using Bridging Anticoagulation: Benefits and Risks

Empiric use of bridging anticoagulation has been rationalized by the theoretical premise that minimizing the time patients are not therapeutically anticoagulated will minimize patients' risk for ATE. Although this approach has some biological plausibility, there is no evidence that LMWH or UFH is efficacious in preventing cardioembolic stroke or systemic embolism [20-22].

Bridging anticoagulation may not decrease the risk for ATE. In one review, the pooled incidence of ATE with various bridging therapy regimens was 1.6% (95% confidence interval [CI]: 1.0-2.1) [19]. In the second review [23], the incidence of ATE with bridging was 1.2% (0.8-1.8%). To assess the incidence of ATE in patients who do not receive bridging, we assessed data from a community-based cohort study involving 550 patients with atrial fibrillation who had temporary warfarin interruption prior to an invasive procedure [24]. In this study, 97% of patients did not receive bridging anticoagulation and the 30-day incidence of postoperative stroke/ATE was only 0.7%. In another study, the 30-day incidences of postoperative stroke in patients with and without atrial fibrillation who had surgery or an invasive procedure were 1.2%, and 0.3%, respectively. It was presumed that most patients with atrial fibrillation had warfarin interruption before surgery *did not receive* bridging anticoagulation, which was not routinely done during the period of observation. Taken together, these data suggest that in patients with atrial fibrillation who require warfarin interruption before surgery, the risk for perioperative ATE without bridging is similar to the risk with bridging.

Bridging anticoagulation may increase the risk for bleeding. The argument that bridging therapy may cause harm is based on several observations that administration of anticoagulants in close proximity to surgery increases the risk for major bleeding. The rate of major bleeding was 9% and 30% in two studies of patients with postoperative venous thromboembolism who received therapeutic-dose IV UFH [25]. In a patient-level meta-analysis done by the **BRIDGE** Steering Committee, the pooled incidence of major bleeding was 2.3 [26], which appears higher than the ~1% risk of major bleeding in patients who receive only warfarin after major surgery [27]. Taken together, these data suggest that administering bridging anticoagulation with therapeutic-dose IV UFH or LMWH in close proximity to surgery may be associated with a significantly higher risk of major bleeding than just resuming warfarin after surgery.

4.0 PRELIMINARY STUDIES that GUIDE DEVELOPMENT of TRIAL PROTOCOL

4.1 Survey Data Assessing Bridging Anticoagulation after Interruption of Warfarin

Published survey data assessing bridging anticoagulation practices for patients with atrial fibrillation suggests there are significant practice differences among clinicians, especially with regard to whether (and for which patients) bridging therapy is needed [7,9,10]. Although the numbers from the different studies vary, the surveys consistently indicate that there is no consensus among clinicians about when to give bridging therapy.

*Implication of findings on **BRIDGE** design*:

- Bridging therapy is not consistently used in patients with atrial fibrillation, supporting the feasibility of enrolling such patients into a placebo-controlled trial.
- Therapeutic-dose LMWH is the dominant regimen used for bridging, which supports adopting this intervention as the standard-of-practice (or control) arm for the BRIDGE trial.

4.2 Systematic Reviews of Bridging Anticoagulation

To provide precise estimates of the incidence of ATE (efficacy) and major bleeding (safety) with bridging anticoagulation, we performed a patient-level meta-analysis of bridging anticoagulation

using source data from 4 prospective cohort studies involving 1,903 patients who had warfarin interruption [2, 5, 6]. The incidence (95% CI) of ATE in a sub-group with atrial fibrillation was 1.0% (0.5-1.8); the incidence of major bleeding in all patients was 2.3% (1.7-3.3) [26]. These estimates of ATE and major bleeding were comparable to those of a systematic review [23], in which the pooled incidence of ATE and major bleeding with various bridging regimens was 1.2% (0.8-1.8) and 2.9% (2.3-3.7), respectively.

Implication of findings on **BRIDGE** design:

- These reviews provide precise estimates of rates of ATE (~1%) and major bleeding (~2-3%) in patients who received bridging anticoagulation that can be used for determining trial sample size.

4.3 Observational Studies of Bridging Anticoagulation: Patient Registries and Cohort Studies

Patient registries. In a multi-center patient registry in North America that included 671 patients with atrial fibrillation or a mechanical heart valve who underwent a procedure requiring temporary interruption of warfarin [4], 80% of patients received LMWH and 20% received UFH. In the sub-group of 390 patients who received therapeutic-dose LMWH, the incidence of ATE was 0.8% and the incidence of major bleeding was 3.6% after 4 weeks of follow-up. Another bridging registry assessed if there is a residual anticoagulant effect just before surgery in 71 patients who received bridging with a LMWH [28]. In 37 patients who received therapeutic-dose LMWH (last dose ~24 hours before surgery), a residual anticoagulant effect (anti-Xa >0.10 units/mL) occurred in 11 (30%) patients. Therapeutic-dose LMWH was strongly associated with a residual anticoagulant effect (OR = 119; 5.8-999). In addition, compared to once-daily dosing of therapeutic-dose LMWH, a residual anticoagulant effect before surgery appeared less likely with twice-daily dosing (OR = 0.14; 0.02-1.1).

Cohort studies assessing twice-daily LMWH. Two prospective cohort studies assessed standardized bridging regimen with twice-daily LMWH. The first study involved 650 patients with atrial fibrillation or a mechanical heart valve who received dalteparin, 100 units/kg twice-daily [2]; the second study involved 220 patients with a mechanical heart valve who received enoxaparin, 1 mg/kg twice-daily [6]. A key feature in both studies was ensuring hemostasis was achieved before starting LMWH after surgery. This entailed delaying the start of LMWH in patients who had delayed hemostasis and not using LMWH after surgery in a small proportion (~10%) of patients empirically considered high-risk for postoperative bleeding (e.g., cardiac or major cancer surgery). With this regimen, the incidence for ATE was ~1% in both studies and the risk for major bleeding was 1% and 3.5% based on a patient follow-up in each study of 2 weeks and 12 weeks, respectively. In the study with a 12-week follow-up, all bleeding events occurred during the first 4 weeks after surgery. Two more recently published studies suggest that, among patients with atrial fibrillation, the risk of thromboembolism during short interruptions of warfarin may indeed be low, even without bridging therapy. However, these studies have important design flaws that prevent definitive conclusions about the relative risks and benefits of bridging anticoagulation.[7,8]

Cohort studies assessing once-daily LMWH. A standardized bridging regimen with once-daily enoxaparin (1.5 mg/kg) was investigated in a prospective cohort study of 176 patients with atrial fibrillation [5]. After 1 month of follow-up, the incidence of ATE and major bleeding with this bridging regimen was 1.6% and 4.5%, respectively, with all bleeds occurring within 1 week of surgery. Another study assessed 224 patients with atrial fibrillation or a mechanical heart valve who received dalteparin, 200 units/kg once-daily, with the dose after surgery reduced to 5,000 units in 37 (17%) patients at high-risk for bleeding [3]. This bridging regimen was associated with a high rate of major bleeding (6.9%), which was unexpected as most patients had minor surgery or procedures and 8 thromboembolic events, although only 3 were ATE (stroke, embolism, TIA).

Implication of findings on BRIDGE design:

- Systematic reviews provide precise estimates of rates of ATE (~1.0%) and major bleeding (~3%) when therapeutic-dose LMWH is used for bridging.
- Although head-to-head comparisons of bridging regimens with different LMWHs are lacking, it appears that twice-daily LMWH may be preferable to once-daily administration, based on modest evidence that the latter is associated with a higher risk for bleeding and is more likely to be associated with a residual anticoagulant effect before surgery. Consequently, twice-daily administration of LMWH (dalteparin) has been chosen. In addition, the evening dose of LMWH on the day before surgery has been omitted since giving LMWH up to 12 hours prior to surgery might result in a detectable anticoagulant effect at the time of surgery in a large proportion of patients, which would be undesirable and unsafe for patients.
- The available studies have methodologic limitations, including the lack of appropriate comparator groups and/or the potential for selection bias. The BRIDGE trial is needed because the imperfections in previously published studies will prevent them from affecting any standard clinical practice.
- A twice-daily bridging regimen is more appealing to because it allows clinicians greater flexibility in starting study drug after surgery when some flexibility is required depending on the type and extent of the surgery. Thus, concerns about post-surgical hemostasis would be more easily addressed with a twice-daily than once-daily LMWH regimen because the start of treatment could be delayed until the evening dose and started as 50% of the total daily dose.
- The most common treatment regimen used in patients who received bridging anticoagulation in North America is therapeutic-dose LMWH (usually enoxaparin or dalteparin), thereby supporting its use as the dominant standard practice to be compared against a 'no bridging' therapy approach.
- A 1-month period of patient follow-up in this trial is justified because the vast majority of bleeding events observed in the observational studies occurred within this time period. Extending the duration of follow-up beyond 1 month might include events that are unrelated to the perioperative bridging period, thereby obscuring any treatment effects that might be related to a bridging or a no bridging approach.
- These studies highlight the need for flexibility in administration of the study drug, especially in the postoperative period because of the heterogeneity in the types of surgery patients undergo and the wide spectrum of associated bleeding risk. Without this flexibility, the trial design will not reflect real-world bridging practice and, therefore, have limited generalizability and clinical impact.

5.0 STUDY METHODS

5.1 Study Design

BRIDGE is a randomized double-blind, placebo-controlled trial comparing '*bridging anticoagulation*' with '*no bridging anticoagulation*' during temporary interruption of warfarin in patients with atrial fibrillation or atrial flutter who are receiving warfarin and are undergoing an elective surgical or other invasive procedure.

Patients will be randomly allocated to a bridging arm (dalteparin 100 units/kg SC twice-daily) or to no bridging arm (matching placebo, SC twice-daily) between Day -14 to Day -5. Study drug/placebo will be administered for approximately 3 days before and approximately 6 days after surgery/procedure. Warfarin therapy will be interrupted 5 days before the surgery/procedure on Day -5. The surgery/procedure will be classified as a minor surgery/procedure or a major surgery/procedure.

Patients undergoing a ***minor*** surgery/procedure will have ***early initiation*** of dalteparin/placebo post-procedure (12-24 hours after procedure); patients undergoing a ***major*** surgery/procedure will have ***delayed initiation*** of dalteparin/placebo postoperatively (48-72 hours after surgery/procedure).

The aim of the BRIDGE trial is to compare a 'bridging anticoagulation' with a 'no bridging' management approach for efficacy (ATE) and safety (major bleeding) outcomes during the period commencing when patients receive the first dose of dalteparin/placebo and ending Day +30 to Day +37.

5.2 Study Population

5.2.1 Inclusion criteria

All of the following 5 criteria must be satisfied for trial eligibility:

- adult male or female, age 18 years or older
- has been receiving warfarin therapy for at least 3 months, given to achieve an INR range of 2.0-3.0
- requires temporary interruption of warfarin for pre-specified elective surgery or invasive procedure
- have ***at least one*** of the following conditions:
  - chronic (permanent or paroxysmal) nonvalvular OR valvular (evidence of mitral valvular disease) atrial fibrillation or atrial flutter, confirmed by at least one prior electrocardiography recording or pacemaker/ACD interrogation;
- have ***at least one*** of the following major stroke risk factors: (a) age ≥75 years; (b) hypertension; (c) diabetes mellitus; (d) congestive heart failure or left ventricular dysfunction; or (e) previous ischemic stroke, systemic embolism or TIA

5.2.2 Exclusion criteria

One or more of the following criteria precludes trial eligibility:

- any mechanical prosthetic heart valve
- stroke (ischemic or hemorrhagic), systemic embolism or TIA within past 12 weeks
- venous thromobembolism (deep vein thrombosis and/or pulmonary embolism) within past 12 weeks
- major bleeding within past 6 weeks
- severe renal insufficiency (calculated creatinine clearance <30 mL/min by Cockcroft-Gault equation)*
- thrombocytopenia (platelet count $<100 \times 10^9$/L)*
- life expectancy <1 month
- condition that impairs compliance with trial protocol (e.g., cognitive impairment, uncontrolled psychiatric condition, geographic inaccessibility)
- pregnancy
- allergy to heparin or history of heparin-induced thrombocytopenia
- patient is having one of the following surgeries/procedures during warfarin interruption: (a) cardiac surgery (*e.g.,* coronary artery bypass, heart valve replacement); (b) neurosurgery that is intracranial or intraspinal (*e.g.,* tumor resection, aneurysm repair); (c) high-risk non-surgical procedures (*e.g.,* brain biopsy)
- other surgical or non-surgical procedure that, at the discretion of the surgeon or proceduralist, precludes administration of therapeutic-dose LMWH at any time in the post-procedure period
- more than one surgery planned during the trial period
- prior participation in this trial

- inability or unwillingness to provide informed consent

***The BRIDGE trial mandates that within 90 days prior to the planned surgery/procedure, study patients have had the following laboratory tests done to allow an assessment of patient eligibility for the trial: complete blood count (CBC), to include platelet count; serum creatinine.**

5.3 Classification of Type of Surgery or Procedure

Patients who satisfy the trial eligibility criteria will be classified according to the planned surgery/procedure.

5.3.1 Minor surgery/procedure

- gastrointestinal endoscopy (with or without biopsy)
- cardiac catheterization (with or without percutaneous coronary intervention)
- dental surgery or other dental procedure
- dermatologic surgery or other dermatologic procedure
- cataract removal or other ophthalmologic procedure
- any other surgery or procedure lasting <1 hour

5.3.2 Major surgery/procedure

- intraabdominal surgery (e.g., bowel or visceral organ resection)
- intrathoracic surgery (e.g., lung resection)
- major orthopedic surgery (e.g., hip or knee replacement)
- peripheral arterial revascularization (e.g., abdominal aortic aneurysm repair, vascular bypass)
- urologic surgery (e.g., prostatectomy, bladder tumor resection);
- permanent pacemaker or internal defibrillator insertion
- major procedure (e.g., colonic polyp resection, biopsy of kidney or prostate)
- any other surgery or procedure lasting ≥1 hour

5.4 Justification for Study Population

5.4.1 Justification for studying patients with atrial fibrillation or atrial flutter

To maintain a simple study design, increase the homogeneity of the study population, and optimize the generalizability of the study results, the study population consists of patients who are (a) receiving warfarin for chronic atrial fibrillation or atrial flutter *and* (b) are having a surgery or procedure in which bridging therapy would be appropriate *before and after surgery/procedure* and would not be curtailed because of bleeding risk.

Focusing on patients with chronic atrial fibrillation or atrial flutter is based on 3 considerations.

- *First*, chronic atrial fibrillation is the dominant clinical indication for warfarin therapy, and, therefore, represents the patient group in which bridging therapy will be most often considered [2-6]. In support of this contention, patients with atrial fibrillation comprised 62% of patients in registries of bridging therapy [2-6], and 50-70% of patients assessed at clinical centers who would be participating in this trial. Patients with chronic atrial flutter, while less common than patients with chronic atrial fibrillation, are also treated with chronic anticoagulation and most likely have similar risk for thromboembolic complications when anticoagulation is withheld as patients with chronic atrial fibrillation. Patients with chronic atrial flutter are therefore being included in the study.

- *Second*, among patients with an arterial indication for warfarin therapy, the variability in bridging anticoagulation practices is greatest in patients with atrial fibrillation, and, therefore, studying such patients will have the greatest impact in standardizing clinical practice.
- *Third*, the uncertainty as to whether or not bridging anticoagulation is needed in patients with atrial fibrillation or atrial flutter will facilitate their recruitment into a placebo-controlled trial, thereby optimizing study feasibility.

5.4.2 Justification for patient inclusion/exclusion criteria

The patient inclusion criteria for this trial reflects (a) identifying a broad enough spectrum of patients with nonvalvular and valvular atrial fibrillation or atrial flutter that is representative of the population assessed in clinical practice, (b) excluding patients at the high extreme of risk for stroke and/or ATE (*i.e.,* recent stroke/ATE), in whom there likely would be reluctance to have them enrolled in a placebo-controlled trial, and (c) excluding patients at the low extreme of risk for stroke and/or ATE, in whom long-term warfarin therapy is not clinically indicated (i.e., atrial fibrillation or atrial flutter and no major stroke risk factors). Our decision to *include patients with at least one major stroke risk factor* is supported by findings from our investigation of the linked administrative database. [29]. When we examined in patients with atrial fibrillation who were undergoing surgery, the effects of each of these factors on the risk for postoperative stroke, expressed as an OR (95% CI), each risk factor was found to confer a statistically significant increase for stroke: age >75 years, OR = 1.88 (1.79-1.96); hypertension, OR = 1.38 (1.28-1.39); diabetes, OR = 1.38 (1.33-1.44); congestive heart failure, OR = 1.52 (1.44-1.60); previous stroke, OR = 2.48 (2.31-2.66). Taken together, these findings support our inclusion criteria of patients with atrial fibrillation or atrial flutter and at least one major stroke risk factor to assess the effect of LMWH bridging on the risk for ATE.

The patient exclusion criteria reflects the need to exclude patients who are (a) at high risk for perioperative bleeding (*i.e.,* recent bleeding or disease affecting hemostasis) or are (b) undergoing surgery associated with a high risk for bleeding (*e.g.,* neurosurgical), in whom perioperative bridging would be relatively contraindicated and would render them ineligible for this trial. We believe this balanced approach to patient eligibility will ensure that the trial results are generalizable to the widest possible spectrum of patients and will optimize trial feasibility, as trial eligible patients are likely to be recruitable for this trial.

5.5 Patient Recruitment

5.5.1 Patient screening, enrollment and consent

Screening of patients for this trial will be done by the site investigator or delegate at each participating site. Potentially eligible patients are those who are being managed for temporary interruption of warfarin before surgery and possible bridging anticoagulation. All potential BRIDGE sites will obtain Institutional Review Board or Ethics Committee (IRB/EC) approval of the protocol and the consent form, and any recruitment tools. The IRB will have OHRP assurance. Written informed consent will be obtained from each patient after clinical eligibility is established and prior to any study procedures.

Screening of patients for this trial will take place between Day -30 and Day -5 before the planned surgery/procedure. **If screening occurs in closer proximity to the surgery/procedure than Day -5 (e.g., Day -4 or Day -3), the patient will not be eligible for the BRIDGE trial.**

5.5.2 Randomization procedure and stratification

The Statistical and Data Coordinating Center will prepare a computer-generated randomization schedule for treatment allocation. Patients will be randomized by a pre-validated and configurable system that is accessed via the internet or telephone. Patient stratification will occur according to clinical site.

5.5.3 Screening log of patients excluded from trial

For a trial of this scope, we acknowledge the importance of ensuring that the trial results are generalizable to patients assessed in everyday clinical practice. The selected EDC system will maintain a log of all patients screened for this trial but are excluded for one or more of the following reasons: i) patient is ineligible because of not satisfying inclusion criteria or having one or more exclusion criteria; ii) patient is non-consenting; or iii) treating physician decision.

5.6 Trial Study Drug

Study patients will receive study drug, administered in a double-blind manner, before and after the surgery/procedure. The study drug treatment regimens will consist of either:

- In the *bridging anticoagulation arm*, the treatment regiment will consists of: **dalteparin, at a dose of ~100 units/kg administered twice-daily by SC injection**

OR

- In the *no bridging anticoagulation arm*, the treatment regimen will of: **matching placebo, administered twice-daily by SC injection**

5.7 Trial Activities and Processes

Trial activities and processes will be separated into 3 time periods:

- Day -30 to Day -1: Trial activities before the day of surgery/procedure
- Day 0: Trial activities on the day of surgery/procedure
- Day +1 to Day +37: Trial activities following the day of surgery/procedure

5.7.1 Trial Activities and Processes Before the Day of Surgery/Procedure **(Day -30 to Day -1)**

5.7.1.1 Patient Encounter 1 (hospital or clinic visit: Day -30 to Day -15)

- Patients will be screened for this trial when they are assessed for temporary interruption of warfarin prior to the planned surgery/procedure. Eligible patients will be approached for study participation and written informed consent will be obtained.
- For patients who consent to participate in this trial, a baseline patient assessment will be done **as per usual clinical practice** for patients who require perioperative management of warfarin. This assessment will typically include: reason for surgery/procedure; past medical history; listing of concomitant medications and allergies; physical examination; and laboratory testing.
- The decision to continue or interrupt antiplatelet therapy (e.g., aspirin, clopidogrel) and/or other drugs with antiplatelet effects (e.g., nonselective NSAIDs, COX-2 selective NSAIDs) will be determined by the Site Investigator **as per usual clinical practice.**
- Patients will be instructed to discontinue warfarin therapy as of Day -5. (In other words, the final preoperative dose of warfarin will be taken on Day -6.)

5.7.1.2 Patient Encounter 2 (hospital or clinic visit: Day -14 to Day -5)

- Patients will be randomly allocated to one of two perioperative anticoagulation strategies: *'bridging anticoagulation strategy'* or *'no bridging anticoagulation strategy'*.

- Study drug (dalteparin/placebo) will be dispensed and patients will be given instructions in regard to study drug administration. The amount of study drug supplied will depend on whether a visit encounter with study personnel is anticipated on Day 0 or Day +1 after a major or minor surgery/procedure.
  - For patients who are having a major or minor surgery/procedure in whom a visit encounter by study personnel *is not* expected to occur on Day 0 or Day +1 (e.g., dental extraction or colonoscopy at an outside clinic or eye surgery at an outside specialized facility), study drug may be dispensed for *both* the pre- and post-operative periods. The amount of study drug dispensed will be sufficient to allow administration of up to 19 doses (5 preoperative and 14 postoperative) of study drug.
  - For patients who are having a major or minor surgery/procedure in whom a visit encounter by study personnel *is* expected to occur on Day 0 or Day +1 (e.g., major surgery at the study investigator site) with subsequent hospitalization, study drug may be dispensed for *only* the pre-operative period (with the anticipation that study drug for the post-operative period will be dispensed after the surgery/procedure). The amount of study drug dispensed will be sufficient to allow administration of 5 preoperative doses of study drug with postoperative doses of study drug given after the surgery/procedure.

Note about Patient Encounters 1 and 2 and Randomization:

If the initial preoperative visit (Patient Encounter 1) occurs between Day -30 and Day -15:

- a second preoperative visit (Patient Encounter 2) **is required** between Day -14 and Day -3 to dispense study drug
- randomization will occur between Day -14 and Day -5 during the second preoperative visit, prior to the dispensing of study drug

If the initial preoperative visit (Patient Encounter 1) occurs between Day -14 and Day -5:

- a second preoperative visit (Patient Encounter 2) **is not required** to dispense study drug as study drug can be dispensed during this visit (i.e., Patient Encounters 1 and 2 are combined)
- randomization will occur between Day -14 and Day -5 prior to the dispensing of study drug

Note: It is recommended that Patient Encounter 1 take place **before** Day -5 because in the event of a patient who has already taken warfarin on Day -5 (i.e., in AM), this would render them ineligible for BRIDGE as a minimum of 5 days off warfarin is required before the surgery/procedure on Day 0.

5.7.1.3 Dispensing Study Drug

The BRIDGE trial allows 2 options for dispensing study drug to accommodate potential variability in drug administration capabilities of patients.

Option 1: *Dispensing of **multi-dose vial** containing study drug and unfilled syringes*. During Patient Encounter 1 or 2, patients will receive the required number of multi-dose vials of study drug and unfilled 1.0 cc syringes. Patients (or a caregiver) will be taught how to withdraw the weight-based amount of study drug into the 1.0 cc syringe just prior to subcutaneous administration. After withdrawal from the multi-dose vial, study drug will be administered by the patient (or a caregiver).

Option 2: *Dispensing of **pre-filled syringes** containing study drug*. It is anticipated that for some study patients (e.g., with impaired vision) withdrawal of study drug from a multi-dose

vial, just prior to study drug administration, will not be feasible. For such patients, the BRIDGE trial allows study personnel to pre-fill syringes containing the weight-based dose of study drug in advance of its administration. **Pre-filled syringes containing study drug can be stored at room temperature for up to 14 days prior to study drug administration.** *For example*, if study drug is dispensed within 7 days of the planned surgery/procedure, the BRIDGE trial allows dispensing of study drug for both the pre- *and* post-operative periods, provided that postoperative study drug is administered within 14 days of its dispensation.

A study assessing the sterility of pre-filled 1.0 cc syringes containing active study drug (dalteparin) or placebo (saline) indicated no microbial growth within the syringe contents after 14 days of storage at room temperature [**49**]. Another study assessed the stability of dalteparin after long-term storage in a pre-filled syringe and found no loss of (anticoagulant) drug activity [personal communication, J. Douketis, September 2008]. Taken together, these studies support the safety of dispensing pre-filled syringes containing active study drug (dalteparin) or inactive study (saline) in the BRIDGE trial.

Note about study drug dispensing and administration: During Patient Encounter 1 or 2, when study drug is dispensed, the study patient (or a caregiver) will be taught subcutaneous administration of study drug so that it can be self-administered by the study patient (or a caregiver).

5.7.1.4 Starting study drug

- Study drug administration will start on the morning of Day -3 (twice daily).
- Study drug will be administered until the morning of Day -1 (the day prior to surgery/procedure). The final preoperative dose of study drug will be administered at this time.

5.7.1.5 Monitoring for study outcomes

- Monitoring for efficacy and bleeding outcomes begins on Day -5. All suspected efficacy or bleeding outcomes that are ascertained during a patient encounter will necessitate an unscheduled visit to hospital/clinic for assessment and outcome documentations as required.

5.7.1.6 Patient Encounter 3 (telephone contact: between Day -4 and Day -1)

- Patients will have one scheduled patient telephone contact on Day -1 to assess for study outcomes and to review results of INR testing-see below. (For patients having surgery/procedure on a Monday, Patient Encounter 3 will take place on the Friday preceding the surgery/procedure on Day -3.)

5.7.1.7 INR testing

The BRIDGE trial **recommends** that INR testing before surgery/procedure is done **at least once on Day -1 or Day 0**.

- INR testing will be done preferably on Day -1. (For patients having the surgery/procedure on a Monday, INR testing will be done on Day 0, the day of the surgery/procedure.)
- If the INR >1.8 on Day -1, the patient should receive 1.0-2.5 mg of orally administered vitamin K (derived from a 1.0 mg/mL ampoule or half of a 5.0 mg tablet), while if the INR is 1.5-1.8, it is at the discretion of the treating physician whether or not to give vitamin K. (The provision of vitamin K will be by the Site Investigator **as per usual clinical practice**. Some sites may provide the vitamin K during Patient Encounter 1 or 2 and have the patient self-administer it in the event of an elevated INR on Day -1.)

Note about INR on Day -1:

- It is anticipated that few patients will have an INR >1.8 on Day -1 because in stopping warfarin 5 days prior to surgery/procedure this will provide ample time to eliminate the anticoagulant effect.
- For patients who have INR testing on Day 0 and the INR is ≥1.5, the decision of whether or not to proceed with the surgery/procedure will be at the discretion of the treating surgeon/proceduralist.

5.7.2 Trial Activities and Processes on the Day of the Surgery/Procedure (Day 0)

INR testing on day of the surgery/procedure

- If INR is being done on Day 0 (only required for patients in whom INR testing on Day -1 was not feasible) and the INR is at an acceptable level for the planned surgery/procedure (i.e., typically INR <1.5), the clinician performing the surgery/procedure can proceed.

5.7.2.1 Patient Encounter 4 (visit or telephone contact)

- All patients will undergo a postoperative assessment of hemostasis on the day of surgery/procedure (Day 0). This will consist of a hospital/clinic visit for patients undergoing an in-hospital surgery/procedure (e.g., cholecystotomy, endoscopy), and a telephone contact for patients undergoing an out-of-hospital surgery/procedure (e.g., dental extraction).
- The determination of adequate postoperative hemostasis will be based on the assessment by the Site Investigator and, when appropriate, in conjunction with the surgeon/interventionist.

Study drug dispensation (after surgery/procedure)

- In patients who ***did*** receive study drug for postoperative administration during a preoperative visit, no additional dispensing of study drug will be required. Patients will be given instructions in regard to postoperative administration of study drug.
- In patients who ***did not*** receive study drug for postoperative administration during a preoperative study visit, study drug will be dispensed for the postoperative period. Patients will be given instructions in regard to postoperative study drug administration.

Potential Delay or Cancellation of Surgery/Procedure

It is anticipated that a small proportion of study patients will have their surgery/procedure delayed or cancelled, for example, because of operating room unavailability or an intervening medical illness. In such cases, the following protocol will be followed:

- For patients having the surgery/procedure delayed for ≤3 days ***after*** the originally scheduled surgery/procedure date (i.e., ≤3 days after Day 0), such patients will remain in the study and will continue to have study drug administered according to the study protocol until the morning of the day prior to the rescheduled surgery/procedure. The rescheduled surgery/procedure date will be considered Day 0 for the study. Such patients will continue to be followed through Patient Encounter 9 and efficacy and safety data will be collected.

- For patients having the surgery/procedure delayed for >3 days (or cancelled) ***after*** the originally scheduled surgery/procedure (i.e., >3 days after Day 0), in such patients

study drug will be discontinued and the patient will be managed according to the local investigator's usual practice. Such patients will continue to be followed through Patient Encounter 9 and efficacy and safety data will be collected.

5.7.3 Trial Activities and Processes Following the Day of Surgery/Procedure (Day +1 to Day +37)

5.7.3.1 Resumption of warfarin

- The first dose of warfarin will be given on the evening of Day 0 or on Day +1, provided adequate hemostasis is achieved, and will be determined by the type of surgery/procedure (see below). **The BRIDGE trial recommends that, whenever possible and irrespective of the surgery/procedure, warfarin is resumed on the evening of Day 0.**
- The dose of warfarin that is resumed will be in accordance with the patient's usual dose for that day of the week. *For example*, in a patient who has surgery/procedure on a Monday (Day 0) and usually receives warfarin 7.5 mg on Mondays and Thursdays and 5 mg on the other days of the week, resumption of warfarin will occur on Day 0 with 7.5 mg.

- Resumption of warfarin according to surgery/procedure type:
  - For patients having a ***minor*** surgery/procedure: warfarin will be resumed on the evening of the day of the surgery/procedure (Day 0).
  - For patients having a ***major*** surgery/procedure procedure: warfarin will be resumed when a patient is able to take oral medications, either on the evening of the day of surgery/procedure (Day 0) or the first postoperative day (Day +1).
- In some patients, oral intake of medications may not be possible by the evening of Day +1. In such instances, the first dose of warfarin can be given on Day +2 or Day +3.
- In some patients who are receiving aspirin (ASA) in addition to warfarin, the resumption of ASA will be at the discretion of the Site PI in accordance with local practice. It is strongly encouraged that ASA is resumed on the same day as the resumption of warfarin.

5.7.3.2 Resumption of study drug

Study drug will be administered on a twice-daily regimen.

Resumption of study drug according to procedure or surgery/procedure type:

- *For patients having a minor surgery/procedure*: They will have ***early initiation*** of study drug after the surgery/procedure**. The first dose of study drug will be administered on Day +1**, not earlier than 12 hours after surgery/procedure ***and*** not later than 24 hours after the surgery/procedure, ***and*** when adequate hemostasis has been achieved.
- *For patients having a major surgery/procedure*: They will have ***delayed initiation*** of study drug after the surgery/procedure. **The first dose of study drug will be administered on Day +2 or Day +3**, not earlier than 48 hours after surgery/procedure ***and*** not later than 72 hours after the surgery/procedure, ***and*** when adequate hemostasis has been achieved.
  - In some patients with prolonged inadequate hemostasis, irrespective of the type of surgery/procedure, study drug may be withheld for up to 72 hours after surgery/procedure (Day +3). Withholding study drug for more than 72 hours after surgery/procedure will constitute a protocol deviation.

5.7.3.3 Patient Encounter 5 (hospital /clinic visit or telephone contact: Day +1 to Day +7)

All patients will have at least one scheduled hospital/clinic visit or telephone contact between Day +1 and Day +7 to assess for efficacy and bleeding outcomes. Hospital or clinic visit is to be preferred over telephone contact.

Individual sites that practice remote patient management may use the telephone encounter option. If this approach is used:

- Patient contact must be made directly by study personnel (i.e., not through clinic staff managing the patient).
- The interview must be thorough and cover all symptoms that might be related to efficacy or bleeding outcomes for the study, particularly any non-major bleeding symptoms.

If the patient endorses any symptoms that might represent an efficacy and/or major safety outcome, (Section 5.10 Endpoint Measurements), the research coordinator would need to evaluate the patient in person for this specific patient encounter. Non-major bleeding symptoms will be reviewed with the site P.I. to determine if the patient needs to be evaluated in person*

Any additional patient encounters will be in accordance with usual clinical practice.

5.7.3.4 INR testing

- The BRIDGE trial **recommends** that INR testing after surgery/procedure is done **at least twice between Day +2 and Day +10**.
- In regard to the frequency of INR testing beyond that recommended by the trial protocol, this will be determined by the Site Investigator **as per usual clinical practice.**
- The site and manner of INR testing will be done in accordance with patients' usual practice, which includes testing done at a hospital-based laboratory, a clinic-based laboratory, a free-standing (i.e., private) laboratory, or by a point-of-care (portable) INR measuring device.
- The BRIDGE trial mandates that monitoring of the INR and adjustments of warfarin dose will be done **only by the Site Investigator (or delegate)** during the study period. Monitoring of the INR during the study period will not be allowed by non-study personnel.
- Study drug will be continued until the INR is ≥2.0 (equal to or greater than 2.0) on one occasion.

5.7.3.5 Use of Point-of-Care INR Devices

- When LMWH is co-administered with warfarin, LMWH may prolong the INR independent of the effect of warfarin. When the INR is measured in a laboratory, the potential INR-prolonging effect of LMWH is neutralized by adding a heparinase to the thromboplastin reagents used for INR testing.
- All LMWHs can prolong the INR, with dalteparin demonstrating an intermediate effect compared to other LMWHs. With therapeutic-dose dalteparin, the 3-hour post-dose INR is, on average, 0.72 INR units higher than the pre-dalteparin INR.
- Until recently, it had been difficult to add heparinase to test strips in point-of-care INR measuring devices to neutralize the effect of the heparin, though newer device strips may contain a heparinase.

- If a site (or an individual patient) uses a point-of-care device for INR management, it is recommended that one of the following 2 approaches is used while patients are receiving study drug:
  - If possible, substitute laboratory-based INR testing instead of point-of-care testing during the 1-2 week period when study drug is being administered before and after surgery/procedure.
  - If it is necessary to use a point-of-care INR device during the time when study drug is being administered, schedule INR testing so that the INR is measured **before a scheduled injection** of study drug (e.g., before AM dose of study drug); documentation of the use of a point-of-care INR is required in the electronic data system.

5.7.3.6 Patient Encounters 6, 7, and 8 (telephone contact: Day +8 to Day +29)

- Patients will have weekly telephone contact at Day +8 to Day +14; Day +15 to Day +21; Day +22 to Day +29 to assess for efficacy and bleeding outcomes.

5.7.3.7 Patient Encounter 9 (visit or telephone contact: Day +30 to +37)

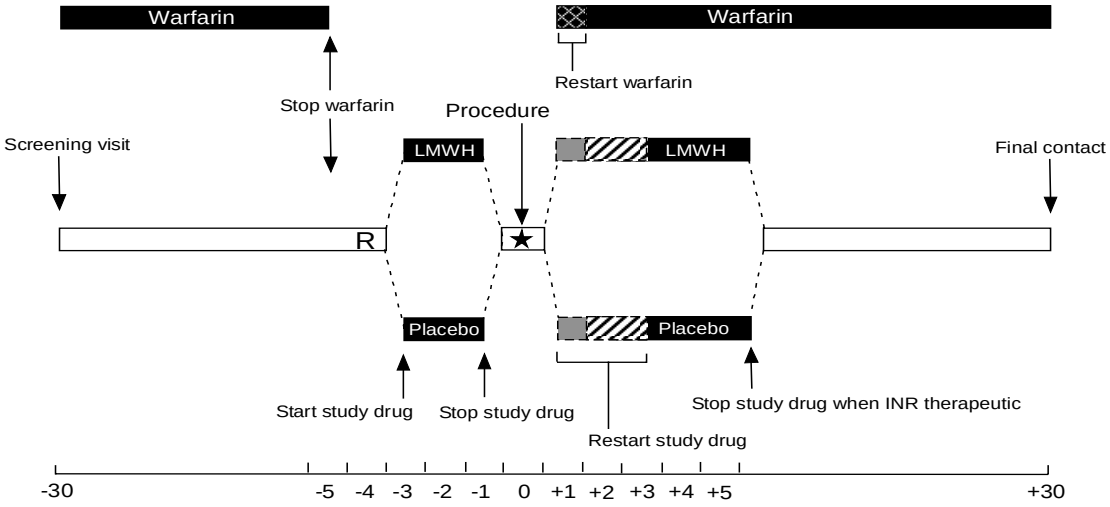
- This patient hospital/clinic visit or telephone contact constitutes the end-of-study patient encounter.
- This encounter will include an assessment of efficacy and bleeding outcomes; other adverse outcomes and to complete and confirm data collection and retrieve unused study medication.
- For patients who are unable to have a hospital/clinic visit, information on study outcomes will be collected by telephone contact, and arrangements will be made for collection of unused study medication through alternative means.

5.8 Non-scheduled Patient Encounters and Final Patient Contact

- In patients who have any suspected or confirmed primary outcome event (ATE, major bleeding) occurring after randomization, this will necessitate documentation of the event in the EDC system within 24 hours after knowledge of the event.
- In patients who have any suspected or confirmed secondary outcome (acute coronary syndrome, venous thromboembolism, non-major bleeding) events after randomization, this will necessitate a non-scheduled patient encounter with a face-to-face hospital/clinic visit within 72 hours after the event.
- The final patient contact will occur on Day +30 to Day +37 to review possible study outcomes and collect any remaining unused study medication.

5.9 Summary of Trial Intervention, Procedures and Patient Follow-up

An overview of the BRIDGE trial flow is outlined above and summarized below:



Preoperative protocol: patients will have an initial screening visit for the trial between Day -30 and Day -15 before the planned surgery/procedure. Eligible patients will be approached for study participation and written informed consent will be obtained.

- Patients will discontinue warfarin on Day -5 (with last dose on Day -6 before surgery/procedure) and will be randomly allocated to receive study drug, defined as either twice-daily dalteparin or twice-daily placebo.
- Study drug will start on Day -3 in the morning and will stop after the morning dose on Day -1. It is recommended that INR testing be done on Day -1 or Day 0 before the surgery/procedure.

Postoperative protocol: an assessment of hemostasis will be done on the day of the procedure (Day 0) and on subsequent days per protocol (depending on inpatient vs. outpatient status). Warfarin may be re-initiated within 24 hrs after surgery/procedure (**dark cross-hatched portion of warfarin bar**). Study drug (dalteparin/placebo) is re-initiated according to a pre-specified classification of procedure-related bleeding risk.

- For patients having a *minor surgery/procedure*, study drug will be initiated within 24 hours after the surgery/procedure when adequate hemostasis has been achieved; the first dose of study drug will be given on Day +1 (**gray portion of study drug/placebo bar**).
- For patients having a *major surgery/procedure*, study drug will be initiated 48-72 hours after the surgery/procedure when adequate hemostasis has been achieved; the first dose of study drug will be given on Day +2 or Day +3 (**hatched portion of study drug/placebo bar**).
- For patients with inadequate postoperative hemostasis, irrespective of the surgery/procedure classification, study drug may be withheld for up to 72 hours after the surgery/procedure (Day +3), after which time continuing to withhold study drug would constitute a protocol deviation. INR testing is recommended at least twice between Day +2 and Day +10. Any additional INR testing during the study period will be as per usual clinical practice. Study drug will be continued until the INR is $\geq$2.0.

Patient follow-up: Patients will be contacted at least weekly after the surgery/procedure to assess for efficacy, bleeding, and other adverse outcomes. Final contact will occur on Day +30 to Day +37 to assess for study outcomes or adverse events and collect any remaining unused study medication. Any suspected efficacy or bleeding outcomes that occur during the study period will necessitate a Patient Encounter (telephone or visit) and, if required, an unscheduled visit with study personnel for further clinical assessment and outcome documentation as required.

5.10 Endpoint Measurements

All endpoints will be analyzed using the modified intent-to-treat population (MITT). This is

defined as all patients who have their warfarin discontinued (Day -5). The patients will be followed for *at least* 36 days (5 days pre-surgery/procedure + 1 day of surgery/procedure + 30 days post-surgery/procedure) *or longer* depending on whether the surgery/procedure was delayed and the date of Patient Encounter 9.

The primary endpoint of this trial (ATE, major bleeding) is defined based on criteria developed by consensus groups. The secondary endpoint of this trial is defined based on criteria developed by consensus groups or by criteria used in previous clinical trials.

- *ATE*, definitions are based on criteria established by the Stroke Council of the American Heart Association-American Stroke Association (stroke) [30], the Transient Ischemic Attack Working Group (TIA) [31], and the American Association for Thoracic Surgery (systemic embolism) [32].
- *Major bleeding*, definition is derived from criteria established by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Hemostasis [33].

5.10.1 Primary efficacy endpoint

The primary efficacy endpoint is *ATE*, defined by one or more of the events listed below.

1) **Ischemic stroke** (*either* criterion must be satisfied) [30]:
   - any new, focal neurologic deficit that persists for >24 hours, *OR*
   - any new, focal neurologic deficit of any duration *and* with evidence of acute infarction on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain
2) **Transient ischemic attack** (*both* criteria must be satisfied) [31]:
   - any brief neurologic deficit caused by focal brain or retinal ischemia, with clinical symptoms lasting, typically, for <1 hour and not for >24 hours
   - no evidence of acute infarction on CT or MRI of the brain
3) **Systemic embolism** (*all three* criteria must be satisfied) [32]:
   - symptomatic embolic episode associated with abrupt arterial insufficiency to the upper extremity, lower extremity or abdominal visceral organ
   - verified by intraoperative or radiologic evidence (*e.g.*, CT angiography) of arterial occlusion
   - occurs in the absence of other likely mechanisms (*e.g.*, atherosclerosis)

5.10.2 Primary bleeding endpoint

The primary bleeding endpoint is *major bleeding*, defined by one or more of the events defined by ISTH.

- All major bleeds must be symptomatic or clinically-overt [33].
- Bleeding that is asymptomatic, such as a small retroperitoneal bleed identified as an incidental finding on computed tomography, would not qualify as a major bleed.
- Similarly, intra-operative bleeding that is expected due to the type of surgical procedure and requires blood transfusion of ≥2 units packed red blood cells would not qualify as a major bleed.
- Furthermore, intra-operative fluid administration that is associated with a decrease in hemoglobin level >20 g/L (>2 g/dL), due to hemodilution, would not qualify as a major bleed.

1) *symptomatic or clinically-overt bleeding that is associated with one or more of*:
   - transfusion of ≥2 units heterologous packed red blood cells or whole blood
   - decrease in hemoglobin level >20 g/L (>2 g/dL).

- need for re-operation or invasive intervention (*e.g.*, evacuation of wound hematoma)

2) *symptomatic or clinically-overt bleeding at a critical anatomic site*

- bleeding that is intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome

3) *fatal bleeding*

- bleeding that directly contributes to death (*e.g.*, intracranial bleed) or causes clinical deterioration leading to death (*e.g.*, bleed associated with sepsis or major organ failure)

5.10.3 Secondary efficacy endpoints

1) **Acute myocardial infarction** *(ST- and non-ST-elevation)* [34]

- typical rise and gradual fall (cardiac troponin) or more rapid rise and fall (creatine kinase-MB) of biochemical markers of myocardial necrosis to at least twice the upper limit of the normal range, with at least one of the following:
  - ischemic symptoms
  - development of pathologic Q-waves on the electrocardiogram (ECG)
  - ECG changes indicative of ischemia (*e.g.*, ST-segment elevation or depression)
  - coronary artery intervention (*e.g.*, coronary angioplasty)

2) **Deep vein thrombosis** (both criteria must be satisfied) [35, 36]:

- symptomatic venous thrombosis (lower or upper limb deep veins, or intra-abdominal veins)
- verified by non-compressibility on venous ultrasound *or* intraluminal filling defect on venography

3) **Pulmonary embolism** (both criteria must be satisfied) [37]:

- symptoms of thrombosis of the pulmonary arteries
- verified by high-probability ventilation-perfusion lung scan *or* intraluminal filling defect on CT angiography, *or* intraluminal filling defect pulmonary angiography *or* a non-diagnostic ventilation-perfusion lung scan with positive testing for deep vein thrombosis as defined above

4) **Death**

- death of any cause based on autopsy findings or other medical records.

5.10.4 Secondary bleeding endpoint

Minor bleeding

- symptomatic or clinically-overt bleeding that does not satisfy the criteria for major bleeding

5.10.5 Procedures and interventions after an efficacy or bleeding outcome

In patients who develop a non-fatal efficacy or bleeding outcome, **standard treatment in accordance with usual clinical practice will be provided.** If the efficacy or bleeding outcome occurs during treatment with study drug, the local investigator can temporarily or permanently discontinue study drug, depending on the patient circumstances, although blinding to treatment allocation will be maintained.

If the efficacy or bleeding outcome requires unblinding to treatment allocation, as this may impact on patient treatment, the local investigator must contact the Principal Investigator (PI) or designee of BRIDGE to discuss the clinical details of the case. The PI or designee will make the ultimate decision to maintain the blind or unblind. If unblinding is determined necessary, the local

investigator will have to utilize the unblinding module in the IXRS randomization system (internet or telephone) to complete the process. Once unblinding has occurred, the patient will not be eligible for further drug assignments. (Refer to Sections 7.0 Potential Co-Interventions)

All patients who develop a non-fatal efficacy or bleeding outcome will complete follow-up until the end-of-study assessment, between Day +30 to Day +37 and any subsequent efficacy and bleeding outcomes will be documented.

5.11 Sample Size Determination and Feasibility

5.11.1 Assumptions for sample size determination

This trial seeks to show that not administering bridging anticoagulation is ***not inferior*** to administering bridging anticoagulation in patients with atrial fibrillation or atrial flutter who require temporary interruption of warfarin. The non-inferiority analysis strategy combines tests for equivalence and for superiority of the placebo arm. Superiority of the placebo arm is plausible as bridging therapy may cause excessive major bleeding that would require prolonged interruption of warfarin therapy and, consequently, an extended period of time at an increased risk for ATE. The power of a given trial design to detect non-inferiority depends on the margin of clinically meaningful difference between the two treatment strategies (bridging vs. no bridging), the sample size of the two arms, and the anticipated rates of ATE in the two arms. The sample size estimates are based on the following assumptions:

- incidence of ATE in bridging group = 1.0% (derived from systematic reviews of patients with atrial fibrillation or atrial flutter who received bridging anticoagulation)
- incidence of ATE in "no bridging" group = 1.0% (derived from linked administrative database and cohort study of patients with atrial fibrillation or atrial flutter who did not receive bridging)
- non-inferiority margin = 1.0% (defined as the outer bound of the 95% CI of an absolute rate of ATE above the bridging group)

5.11.2 Sample size determination

Based on the above assumptions regarding ATE incidence in the bridging and no bridging groups, the non-inferiority margin of 1.0%, power of 80%, and a 2-tailed alpha of 0.05, we will require ***1,641 patients per arm***.

	Non-inferiority Margin			
ATE in LMWH (Bridging) Arm	**0.5%**	**1.0%**	**1.5%**	**2.0%**
0.5%	3308	927	465	307
1.0%	6317	***1641***	772	454
1.5%	9344	2375	1088	625
2.0%	12373	3127	1412	814

We also hypothesize that placebo has ***superior*** bleeding rates compared to LMWH based on the following assumptions: i) incidence of major bleeding in bridging group is 3.0%; and ii) incidence of major bleeding in no bridging group is less than the bridging group. If we assume that the incidence of major bleeding is ~3.0% for the LMWH group, as derived from our background work, 1.0% in the placebo group (as derived from trials where patients received warfarin alone after surgery [27]), and a 2-tailed alpha of 0.05, the proposed trial (with 1,641 patients per arm) has 98.8% power to detect superiority for the bleeding endpoint. The figures represent the required sample size per group, based on a power of 80%, and a 2-tailed alpha of 0.05, to detect differences in various incidences of major bleeding between the bridging group and "no bridging" group.

	Bleeding in Placebo (No Bridging) Arm			
Major Bleeding in LMWH (Bridging) Arm	**0.5%**	**1.0%**	**1.5%**	**2.0%**
2.0%	769	2237	11194	--
2.5%	486	1138	3028	14209
3.0%	344	772	1488	3788
3.5%	262	508	914	1828
4.0%	209	384	640	1113

5.12 Statistical Analysis of Endpoints

The analysis of study endpoints is based on events which occurred between the day of warfarin discontinuation (Day -5) and 30 to 37 days after the day of the surgery/procedure (Day +30 to Day +37).

If a patient has the surgery/procedure delayed for ≤3 days, the final day of follow-up will be 30 to 37 days after the rescheduled surgery/procedure date (i.e., Day +30 to +37 after new Day 0). If a patient has the surgery/procedure delayed for >3 days or cancelled and study drug is no longer administered, the final day of follow-up will be 30 to 37 days after the originally scheduled surgery/procedure date (i.e., Day +30 to +37 after original Day 0). If follow-up data is not available for the specified time points and the patient is alive, the patient will be considered missing for the primary endpoints.

5.12.1 Primary efficacy endpoint analysis

The primary efficacy outcome is ATE, defined by one or more of the following events occurring within the time period specified above:

- ischemic stroke
- transient ischemic attack
- systemic embolism

If the patient dies before day 35 and has not had the primary event, then it will be assumed that the patient would not have had an event had he/she been followed for 35 days.

The primary endpoint analysis is a non-inferiority analysis with an absolute margin of 1.0 percent. For that reason, the statistical test must provide confidence limits for the difference in rates. The two tests available with standard software that provide corresponding confidence limits are the likelihood ratio test and Barnard's test. The likelihood ratio test does not maintain the nominal alpha level for small sample sizes, and so that test will not be used.

There is a proposed an unconditional exact test based on a minimax elimination of the nuisance parameter [38]. The reference set was defined to be the set of all 2 x 2 tables with fixed row margins and all possible column margins. The test and its associated 95 percent confidence limits will be calculated using the StatXact 7 software [39]. If the upper 95 percent confidence limit for the difference in event rates (placebo primary event rate - bridging anticoagulation primary event rate) is less than 0.01, then the primary endpoint will have been met for placebo.

5.12.2 Primary bleeding endpoint analysis

The primary bleeding endpoint is major bleeding, defined by one or more of these events:

- symptomatic or clinically-overt bleeding that is associated with one or more of a) transfusion of ≥2 units heterologous packed red blood cells or whole blood
- decrease in hemoglobin level >20 g/L (>2 g/dL)

- need for re-operation or invasive intervention (e.g., evacuation of wound hematoma)
- symptomatic or clinically-overt bleeding at a critical anatomic site
- fatal bleeding

Because these outcome measures do not require the construction of confidence limits, we will use the simpler Fisher's mid-p test [40] to test significance.

5.12.3 Secondary efficacy endpoint analyses

The following 30 day endpoints will be analyzed using Fisher's mid-p test:

- acute myocardial infarction (ST- and non-ST-elevation)
- deep vein thrombosis
- pulmonary embolism
- death

5.12.4 Secondary bleeding endpoint analyses

Minor bleeding event rates will be analyzed using Fisher's mid-p test.

5.12.5 Interim analyses

Three interim analyses for safety and two interim analyses for efficacy will be performed. The first safety analysis will be performed when safety endpoint information is available for 20 percent of the patients. A second and third safety analysis will be performed when 50 percent and 75 percent of the patients respectively have endpoint information. The first efficacy analysis will be performed when primary endpoint information is available for 50 percent of the patients. A second efficacy analysis will be performed when 75 percent of the patients have endpoint information.

The trial will be stopped for efficacy only for overwhelming evidence in favor of placebo or in favor of bridging anticoagulation. Specifically, the trial will be stopped in favor of placebo if:

- the primary efficacy endpoint significantly favors placebo at the 0.01 level, *and*
- the primary safety endpoint significantly favors placebo at the 0.01 level.

The trial will be stopped in favor of bridging anticoagulation if:

- the primary efficacy endpoint significantly favors bridging anticoagulation at the 0.01 level, **and**
- the primary safety endpoint significantly favors bridging anticoagulation at the 0.01 level.

Because these stopping rules are symmetric, the interim analysis results will be provided to the DSMB in a blinded fashion. The DSMB will take the above rules and guidelines into account when formulating its charter, and has the authority to recommend termination of the trial even if the above guidelines are not met exactly.

The final analysis for efficacy will not require any adjustment for the interim looks, assuming that the trial was not stopped early. Note that the interim analyses are for superiority, but the final analysis is for non-inferiority. The two interim analyses (taking each endpoint separately) spend a total alpha of 0.017. The final analysis spends a total alpha of 0.05. Based on the theory of intersection-union tests, the overall study alpha is the maximum of 0.017 and 0.05. [41,42] Thus the nominal study-wide alpha level for efficacy is 0.05.

5.12.6 Sensitivity analyses

We expect that with good study conduct and an appropriate patient population, the number of patients with missing data will be small. As a sensitivity analysis, we will evaluate the primary and secondary study endpoints based on time to an endpoint event. In the sensitivity analysis, patients who have incomplete follow-up will be censored at the date of last contact. For the primary efficacy outcome of ATE, if a patient dies before day 35 and has not had the primary event, then the patient will be censored on the date of death.

This is a sensitivity analysis because the evidence used to estimate the anticipated event frequency and define the non-inferiority margin (section 5.11) is expressed as an event rate at a fixed time (35 days), as opposed to a hazard function. Although it is possible to assess non-inferiority using censored data, analysis of binary outcomes remains appropriate for instances where the amount of censoring is very low. [43]

To evaluate the properties of the two analysis strategies, consider an exponential distribution censored so that the overall event rate approximates 1 percent. Based upon 1,000,000 simulations assuming 1641 patients per arm and no losses to follow-up, the observed alpha level for the log-rank test is approximately 0.0452, and the alpha level for Fisher's mid-p is approximately 0.0481 (for a nominal alpha level of 0.05). Both tests are affected by the small number of events, but the log-rank test is affected slightly more. Assuming a hazard ratio of 0.5 and testing for superiority, the power for the log-rank test was 51.98 percent whereas the mid-p test has a power of 52.76 percent. Although it is difficult to generalize from these two simulations, we anticipate that the log-rank test is, if anything, conservative for small numbers of events. Further, the log-rank test has slightly less power to detect differences than Fisher's mid-p test (because of its conservativeness), but the difference in power shrinks as the fraction of patients with partial follow-up expands.

6.0 ACTIVE STUDY DRUG and PLACEBO

6.1 Provision, Storage and Dispensation of Active Study Drug and Placebo

Active study drug (dalteparin) will be provided in multi-dose vials containing 95,000 units/3.8cc of drug at a concentration of 25,000 units/cc. Matching placebo will be provided in identical multi-dose vials containing 3.8cc of saline solution and 14mg of benzyl alcohol per mL as a preservative. Active study drug and placebo will be stored at room temperature in a secure and locked location, with access limited to the BRIDGE study personnel.

6.2 Dose Regimen for Active Study Drug (dalteparin) and Placebo

Study drug will be administered as approximately 100 units/kg actual body weight twice daily. The dose administered will be closest to the nearest weight (kg) or 0.01 cc of study drug. This increment corresponds with the gradation of the tuberculin syringe.

6.3 Potential Adverse Reactions related to Study Drug Administration

6.3.1 Dalteparin

The main adverse reaction associated with administration of dalteparin, as with other parenteral anticoagulants, is bleeding. In the context of the BRIDGE trial, bleeding if it occurs is likely (in approximately 80-90% of cases) to occur at the site of the surgery/procedure. Major bleeding, which is a more serious form of bleeding that may require blood transfusion, re-operation or other medical treatment, is an outcome that may occur in approximately 3% of patients. The BRIDGE trial will closely monitor patients for this outcome and if it occurs, patients will receive

prompt medical treatment. Other adverse reactions associated with the administration of dalteparin are listed below as are the approximate risk for these adverse outcomes:

6.3.1.2 *Possible* (≥10%)

- bruising or bleeding at injection site
- discomfort or pain at injection site

6.3.1.3 *Unlikely* (<10%)

- elevation in liver enzymes (typically resolves after stopping LMWH, including dalteparin)
- mild allergic reaction (skin rash)
- infection at injection site

6.3.1.4 *Rare* (≤1%)

- heparin induced thrombocytopenia (associated with stroke, myocardial infarction, venous thromboembolism, limb gangrene, amputation or death)
- epidural hematoma with possible paralysis in patients receiving dalteparin *during* spinal anesthesia
- severe allergic reaction (angioedema, anaphylaxis)

6.3.2 Saline Solution

Adverse reactions associated with administration of saline solution are limited to the effects of the injection.

6.3.2.1 *Possible* (≥10%)

- bruising or bleeding at injection site
- discomfort or pain at injection site

7.0 Potential Co-Interventions

7.1 Concomitant Antiplatelet Therapy

A considerable proportion of patients who are screened for this trial use concomitant antiplatelet therapy with warfarin. For example, low-dose aspirin (≤100 mg per day) is used by approximately 25% of patients with chronic atrial fibrillation who, typically, have concomitant coronary artery disease or other arterial vascular disease [38]. Antiplatelet drugs are also standard of care for some procedures, such as percutaneous coronary interventions, and mandating interruption of antiplatelet therapy in these settings would make the Trial results less applicable to "real world" clinical practice. Specifying separate protocols for periprocedural interruption of aspirin, clopidogrel and/or other antiplatelet drugs would also add complexity, impair study feasibility, and increase the potential for protocol violations.

Power calculations usually assume that events occur homogeneously across an entire group (either treated or placebo). However, it is possible that patients on aspirin or other antiplatelet drugs could have higher expected bleeding rates than the rest of the study population. Although these patients will be randomized to bridging anticoagulation or placebo, the potential exists for the antiplatelet subjects to be assigned unequally between the two arms by play of chance. To address this concern, we have conducted statistical simulations of the effect of antiplatelet therapy on the proposed trial design, demonstrating that concomitant antiplatelet therapy will not significantly alter the statistical power of the trial or its alpha level Consequently, for this trial, *the management of perioperative antiplatelet drug therapy will be left to the discretion of the treating clinician.*

7.2 Antithrombotic Prophylaxis against Postoperative Deep Vein Thrombosis (DVT)

The use of additional anticoagulants for prophylaxis against DVT, such as low-dose UFH (***e.g.,*** UFH, 5000 units twice-daily) and low-dose LMWH (e.g., enoxaparin, 30 mg twice-daily), will be

considered a protocol violation, as all patients will receive warfarin after surgery for prophylaxis against postoperative DVT.

In the 2008 ACCP Antithrombotic Consensus Guidelines, warfarin therapy (INR range: 2.0-3.0) was deemed effective in preventing DVT after hip or knee replacement and is given a Level 1A recommendation for use as DVT prophylaxis in these high-risk patients [27]. It is likely, therefore, that warfarin will also be effective in preventing DVT in lower-risk patients who are participating in this trial and are undergoing other types of surgery.

The use of mechanical devices for prophylaxis against DVT such as anti-embolic stockings or intermittent pneumatic compression devices will be allowed as this will not impact on the primary trial efficacy and bleeding outcomes (ATE, major bleeding). 7.3 Clinical Indication for Therapeutic Anticoagulation

Patients who are randomized to study drug and subsequently develop a need for therapeutic-dose anticoagulant therapy (e.g., acute coronary syndrome) will have study drug discontinued, and will receive therapeutic-dose anticoagulation as clinically indicated.

7.3 Antithrombotic Treatment for Suspected/Confirmed Heparin-induced Thrombocytopenia

Patients who are found to have thrombocytopenia during scheduled or unscheduled laboratory testing and have suspected or serologically proven heparin-induced thrombocytopenia will have study drug discontinued. Subsequent patient management and standard treatment will be at the discretion of the treating clinician [39].

7.4 Use of other Drugs that Affect Hemostasis

The use of other drugs that may have antithrombotic properties (e.g., aspirin, non-selective NSAIDs, COX-2 selective NSAIDs, pentoxyphylline, cilostozol) will be allowed, but documented, given the size of this trial and the widespread use of such medications. In the perioperative period, management of study patients who are taking these drugs with antithrombotic properties will be as per usual clinical practice..

8.0 STUDY TIMELINE

The BRIDGE trial timeline is summarized in **Figure 1** below. Initial study start-up period is anticipated to be 6 months, including site selection and start-up, which will include site evaluation, contracting, assistance with institutional review board (IRB) and regulatory issues, project-specific training, development and distribution of study materials, subcontracting for the manufacture and purchase of placebo and study drug and it's distribution and assessment of sites' readiness to commence enrollment.

An enrollment period of 44 months is projected, with an approximate 30 to 37 day after surgery/procedure follow-up period for each enrolled patient. Site and study closeout activities including closing all study sites, reconciling safety and other databases, locking of the database, archiving documents and data, performing statistical analyses, and preparing the final study report, presentations, and publications of the study data will occur during the final 9 months of the study.

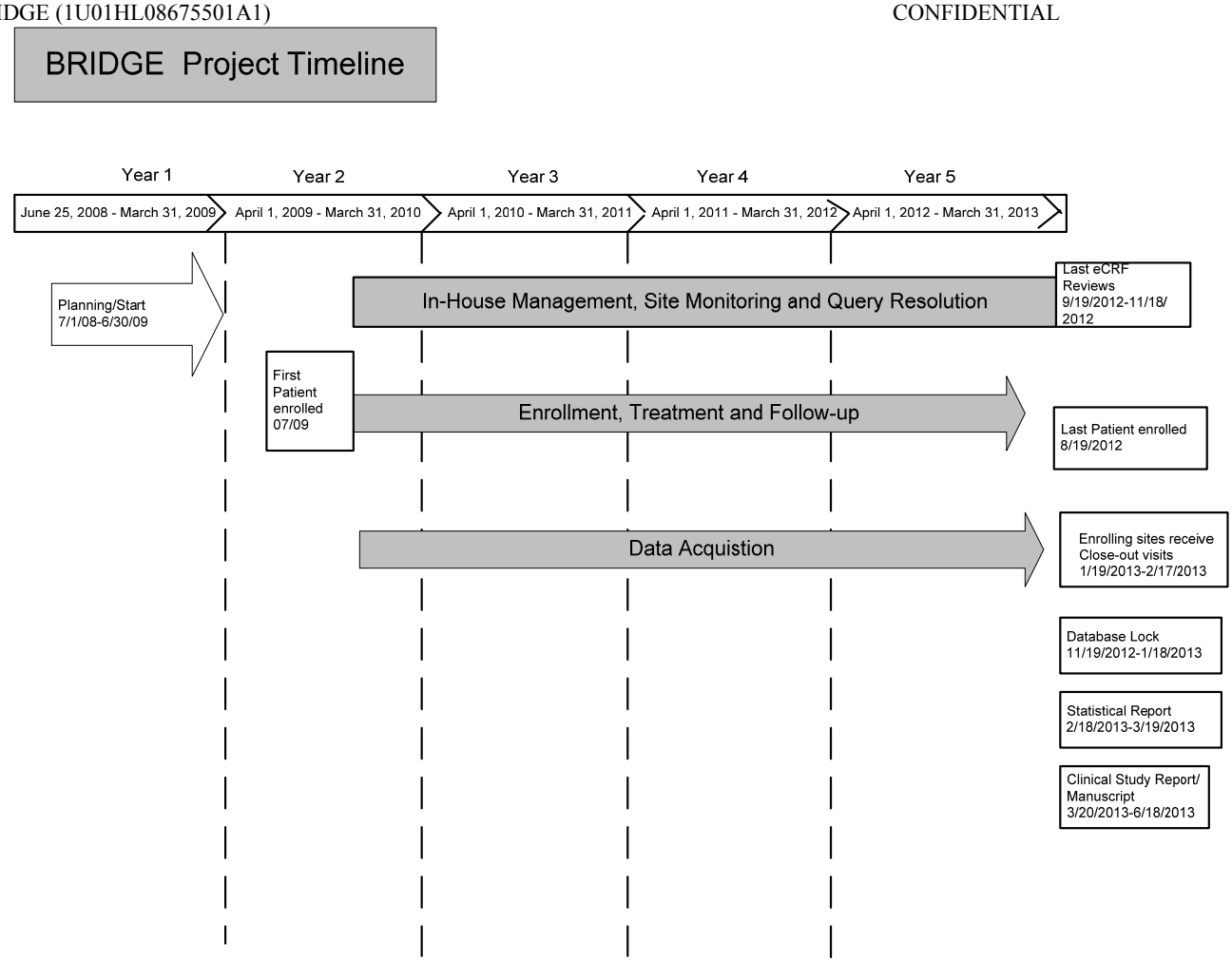


Figure 1. Timeline for the BRIDGE Trial

9.0 TRIAL ORGANIZATION and OPERATIONS

The DCRI functional groups are separate and distinct units and will be following their PI leadership: Dr. Ortel as the CCC PI, and Dr. Hasselblad as the SDCC PI. The Project Leader at the DCRI will be the point of contact for communication and issue resolution among the various operational groups under each component of the grant application. Effective and efficient communication between the CCC and the SDCC will be achieved by conference calls and/or meetings and with routine correspondence as needed while still keeping the data separate. Standard reports will be shared among the coordinating centers.

The organization of the **BRIDGE** trial and inter-relationships between the NHLBI, the Clinical Coordinating Center, the Statistical and Data Coordinating Center, the various committees, and the potential sites is outlined in **Figure 2**.

9.1 National Heart, Lung and Blood Institute (NHLBI)

The Project Officer will participate in monitoring study progress, which will include regular communications with the P.I. and staff, as well as attendance at steering committee meetings, data and safety monitoring committee, and related meetings. If, at any time, recruitment falls significantly below the projected milestones for recruitment, the NHLBI has the right to consider

ending support and negotiating a phase-out of the award. The NHLBI retains, as an option, periodic external peer review of progress.

9.2 Clinical Coordinating Center (CCC)

Dr. Ortel, Principal Investigator for the CCC, will be pivotal in all strategy and decision-making efforts for the CCC. . Dr. Ortel will work closely with Dr. Becker, Co-investigator, in the management of the study. He will also provide thought leadership and clinical expertise while developing and maintaining relationships with the site investigators and act in a scientific and medical role for this study. Dr. Ortel will work closely with the Clinical Operations Team to help meet enrollment goals and with the BRIDGE Steering Committee to see that the study is completed as planned.

Critical functional groups within the CCC are outlined in **Figure 2**.

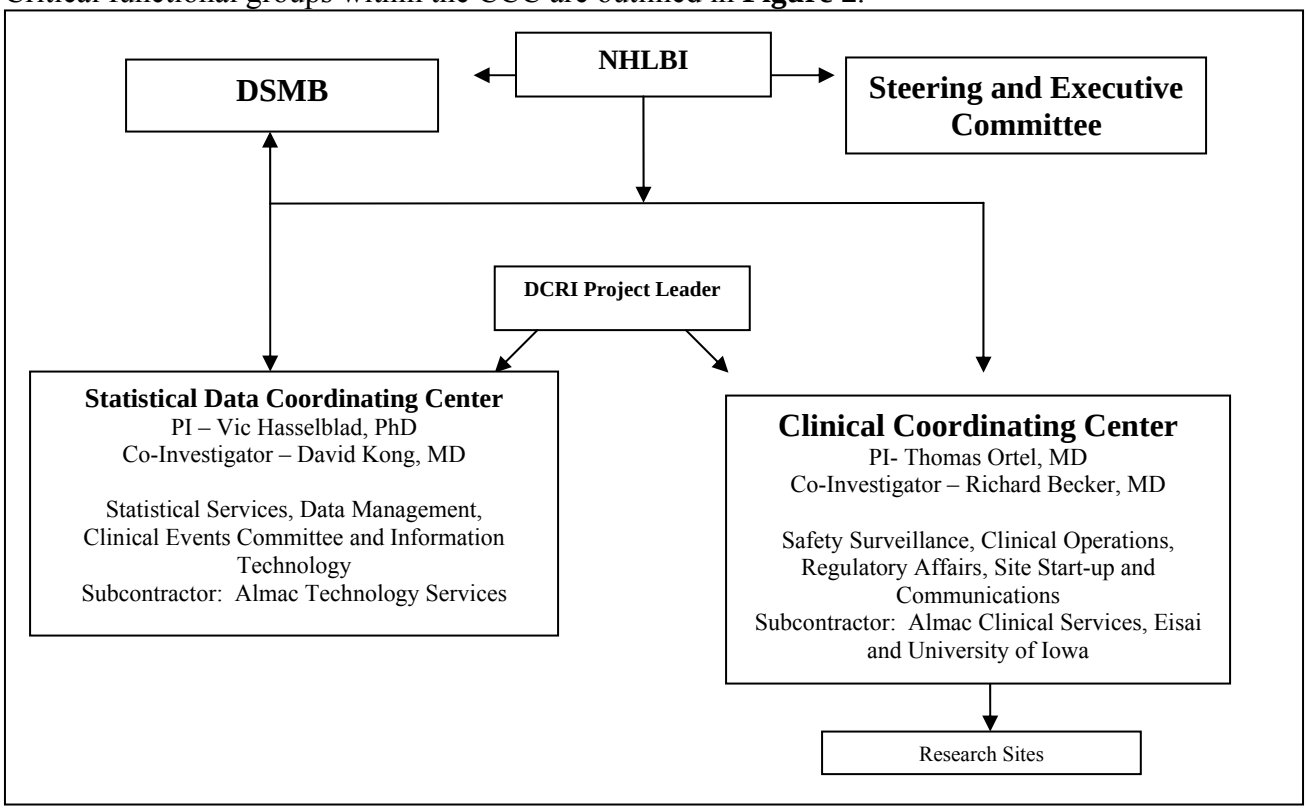


Figure 2. BRIDGE Operational Structure

9.3 Statistical Data Coordinating Center (SDCC)

Victor Hasselblad Ph.D. will be ultimately responsible for the SDCC strategy and decision-making efforts. He will work closely with Dr. Kong, Co-Investigator, in the management of the study. As the SDCC PI, Dr. Hasselblad will provide leadership and expertise to the functional groups of the SDCC. Critical functional groups within the SDCC are outlined in **Figure 2**.

9.4 BRIDGE Steering Committee (BSC)

The BSC consists of the Bridging Anticoagulation Collaborative Group, a consortium of university-based, clinician-scientists **(Figure 3).** The BSC will have overall responsibility for trial design, operational oversight of the other committees and will review all analyses, publications, and plans for dissemination of trial results. The BSC will have regular investigator teleconferences and

meetings to allow discussion of education and training to promote compliance with the study protocol and maintaining study integrity.

Membership	Associated Institution
Joe Caprini, M.D.	Northwestern University
James Douketis, M.D.	McMaster University
Scott Kaatz, D.O.	Henry Ford Health System
Andrew Dunn, M.D.	Mount Sinai School of Medicine
David Garcia, M.D.	University. of New Mexico
Alan Jacobson, M.D.	University. of California, Loma Linda
Amir Jaffer, M.D.	University of Miami
Sam Schulman, M.D.	McMaster University
Alex Spyropoulos, M.D.	McMaster University
Alexander Turpie, M.B.	McMaster University

Figure 3. Bridging Anticoagulation Collaborative Group

9.5 BRIDGE Executive Committee (BEC)

The Executive Committee will be chaired by Dr. Ortel and will include the following members: Dr Hasselblad, Co-Investigators Becker and Kong and the BSC member, Jim Douketis (or delegate), the NHLBI Project Officer, the Project Leader, two site investigators, one site clinical research coordinator, and any additional members that the NHLBI feels are appropriate. The BEC will review and give final sign-off on the BRIDGE Protocol, the Manual of Procedures (MOP), the monitoring plan, the case report form (eCRF), and all site materials, the data management plan and the statistical plan. The BEC will also review any potential ancillary sub-studies and all publications, and is responsible for dissemination of trial results. The BEC will meet monthly via a teleconference during trial start-up and bi-monthly thereafter.

9.6 Clinical Event Classification (CEC) Committee

The CEC Committee will be an independent committee with no direct involvement in the day-to-day undertaking of the trial. The overall responsibility of the CEC Committee is to provide an independent and blinded adjudication of the primary efficacy and safety outcomes as well as all cause deaths.

9.7 Data and Safety Monitoring Board (DSMB)

The National Heart, Lung and Blood Institute DSMB adheres to all National Institutes of Health (NIH) regulations and policies including the Data and Safety Monitoring Policy found on the website at http://www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm.
The objectives of the Board are to periodically review the trial data to assess the safety of bridging using delteparin in this patient population and to assure the integrity and proper conduct of the trial. The DSMB may recommend discontinuation of the trial, or modifications of the study protocol for safety reasons.

9.8 Investigative Clinical Sites

The site investigator will be responsible for on-site clinical and administrative management of the protocol. The site investigators will have experience in the treatment and management of patients that require the temporary interruption of warfarin therapy for an elective surgical or invasive procedure.

9.8.1 Clinical Site Requirements

Each clinical site should have the ability to:

- Assign personnel to participation in all study training
- High speed internet access for randomization and electronic data capture
- Medically manage and communicate with enrolled patients in the administration of study drug and processes

9.8.2 Site Monitoring Visits

- A Clinical Research Associate (CRA) in the Clinical Operations group will conduct an on-site evaluation/initiation visit for each investigative site. The purpose of these visits are:
  - become familiar with the staff and resources of each site
  - further review the protocol and project procedures
  - answer questions and confirm that the site has completed all project required training
  - site is ready to begin enrolling subjects.
- Only after all project training has been completed will a site be able to begin patient enrollment into the study.
- Evaluation/initiation visits will occur after the investigator teleconferences and before enrollment
- After this initial visit, the CRA will visit the each site annually (interim visits) to verify that the research is being conducted in compliance with good clinical practice (GCP) and protocol requirements.
- At the end of the trial each site will receive a close-out visit as needed. Monitoring activities at this visit will include
  - inventory, collection of any outstanding data
  - disposal of unused supplies
  - archival requirements of study files
  - final review and resolution of any outstanding action items
- The close out summary letter will outline pertinent details discussed and agreed upon action to the investigator.

9.8.3 Clinical Operations (Site Management and Monitoring)

- The Clinical Operations Team will be the primary day-to-day contact with sites and will coordinate site start up and training activities for the protocol and electronic data capture (EDC) system. This training will be organized in the Manual of Procedures (MOP) and conducted in the form of web based teleconferences and on-site visits.
- The members of the Clinical Operations Team will coordinate on-going education of the sites on:
  - study procedures, assuring that regulatory and GCP requirements are being followed

- monitoring study progress in terms of patient recruitment, retention, and data quality
- assisting the trial sites in obtaining IRB yearly renewals
- providing support to complete all activities and deliverables in accordance with expected study timelines and project plans.

10.0 SAFETY and ETHICAL CONSIDERATIONS

10.1 Protection of Human Subjects

10.1.1 Risks to the subjects

10.1.1.1 Human subjects involvement and characteristics

All human adult subjects who meet inclusion criteria and who do not meet any of the exclusionary criteria will be considered eligible for this trial. Patients will be on chronic warfarin therapy for atrial fibrillation or atrial flutter. As stated in the eligibility criteria, patients will be excluded from the trial if they are deemed to be at risk for hemorrhagic complications related to the administration of bridging anticoagulation. It is estimated that atrial fibrillation affects 2.2 million adults in the U.S., and that the median age of people with atrial fibrillation is 75 years [40]. Given the older age range of this population, it is anticipated that these patients will likely have other common medical conditions.

Special or vulnerable populations will not be included in the **BRIDGE** trial. This study aims to examine the research question in adults only. Prisoners will not be targeted for inclusion. However, if an incarcerated individual is somehow a candidate for inclusion in the trial, they will not be excluded solely on the basis of their prisoner status. All ethical issues and institutional review board policies will be applied to determine the eligibility of prisoners in this study.

10.1.1.2 Sources of material.

- Data for this study will be collected locally at each of the investigative sites and entered into the electronic data capture forms for transfer to the SDCC.
- Clinical and laboratory data will be collected from the medical record at each institution. In addition, some of the information collected may be from another hospital or institution and released by the patient for inclusion into the trial.
- Patients will be assigned an unique identification number (PIN) for data transfer in the EDC system Personal identifying information, such as name, address, driver's permit, Social Security Number, etc., will not be entered into the database.
- The control of access to databases will be managed centrally by the DCRI through user passwords linked to appropriate access privileges.

10.1.1.3 Potential risks.

- Protocol-specific risks associated with the **BRIDGE** trial include local bruising or pain at injection sites
- Patients will be carefully instructed on how to self-administer the study drug, and their ability to correctly perform self-injection will be confirmed by the study personnel.
- Rarely, some patients receiving LMWH develop an allergic reaction to the medication, in which case the study drug will be discontinued and, depending on the severity of the allergic reaction, the patient's treatment strategy unblinded.

10.1.2 Adequacy of protection against risks

10.1.2.1 *Recruitment and informed consent*.

The DCRI Clinical Operations Group will be responsible for:

- verifying that the appropriate assurances and certification of training in the protection of human subjects are in place prior to the initiation of any protocol.
- providing educational guidance to all site personnel regarding the conduct of clinical studies according to good clinical practices
- verifying that informed consent has been obtained from each patient. These records will be verified during the monitoring visits
- working with each site in the review of their site specific informed consent document prior to submission to the IRB.
- working to ensure that no subject will be recruited into the study until a copy of the Institutional Review Board (IRB) approval (and any renewal requirements) has been filed at the site and Clinical Coordinating Center (DCRI)
- maintaining the current version of the protocol, and any revisions will be made available for follow-up submissions to site IRB/EC's.

10.1.3 Standard data management practices.

- Electronic Data Capture (EDC) will be used for this study. The majority of the study data will be transcribed by study personnel from the source documents onto an eCRF and transmitted in a secure manner to the SDCC
- All data relating to the study must be recorded in eCRFs prepared by DCRI and approved by the BSC.
- Data must be entered into eCRFs in English.
- The investigator's electronic signature is recorded in the database as verification that all data are complete and accurate.
- The investigator will receive a Compact Disc (CD) containing the site eCRF data after completion of the study.

10.1.4 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include

- the selection of qualified investigators and appropriate study centers
- review of protocol procedures with the investigator and associated personnel before the study
- periodic monitoring visits by the sponsor
- Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples.
- Electronic CRF completion guidelines will be provided and reviewed with study personnel before the start of the study.
- The DCRI CRA will review eCRFs for accuracy and completeness during on-site monitoring visits; any discrepancies will be resolved with the investigator or designee, as appropriate.

10.1.4.1 Standard site management practices

The Clinical Operations Team will be responsible for

- verifying that the appropriate assurances and certification of training in the protection of human subjects are in place prior to the initiation of any protocol.
- providing education to all site staff regarding the conduct of clinical studies according to good clinical practices
- assisting sites in the development of informed consent templates to make sure that they contain appropriate elements

- ensuring that the CRA visits each site approximately once a year unless a protocol requires more stringent oversight for safety and regulatory reasons, in which case the monitoring may occur more frequently.
- Assuring during the initial visit that the site has adequate facilities/staff integral to the successful operation of the study. The site visit may also be utilized to conduct training regarding regulatory compliance or individual protocol procedures.
- On-site visits that will be supplemented with in-house coordination (activities that can be handled via phone/fax communication/internet data base)
- Other activities that may be performed by Clinical Operations Team are:
  - tracking recruitment of patients entered
  - updating relevant trial information on the trial web site

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11.0 Adverse Event Reporting and Follow-up

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product; it does not necessarily have to have a causal relationship with this treatment.

The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All adverse events should be documented in the patient's medical record. All adverse events should be monitored until stabilization or resolution. BRIDGE will not be collecting non-serious adverse events in the EDC system

11.1 Serious Adverse Events

A Serious Adverse Event (SAE) is any adverse event that, at any dose:

Results in death.

- Is life threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of an existing hospitalization.
  - The following hospitalizations will **not** be considered serious:
    - Preplanned (before study) hospital admissions, unless the hospitalization is prolonged.
    - Planned admissions (as part of the study, e.g. routine biopsies).
    - Re-hospitalizations lasting less than 24 hours.
    - Emergency room visits.
    - Hospitalizations for elective surgery for a pre-existing condition. If untoward event occurs during an elective procedure, its occurrence must be reported as an AE, either serious or non-serious, according to the usual criteria.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.

- Any medically significant events that may require medical or surgical intervention to prevent one of the outcomes listed above.

11.1.1 Serious adverse event collection and reporting

It is the Investigators responsibility to report all SAEs (including all secondary efficacy outcomes) that occur from signing of informed consent and randomization through Day +37 by entering serious adverse events data into the Inform™ EDC system within 24 hours of becoming aware of the SAE; the SAE must be followed through resolution or stabilization.

- Consented patients that withdraw from the study **prior** to randomization and experiences an SAE, the event must be followed (data collection) through the completion of the screening Encounter 1 or 2 and the completion of the screening eligibility eCRF.

11.1.2 Lack of Efficacy

Lack of efficacy **will not** be reported as study drug related. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported only if they fulfill the SAE definitions.

11.1.3 Clinical or Laboratory Abnormalities

Abnormal laboratory findings or other abnormal assessments that are judged by the investigator as clinically significant will be recorded as SAEs if they meet the definition. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as SAE.

11.1.4 Assessment of Causality

- Drug-related means that there is a reasonable possibility that the adverse event may have been caused by the test agent.
- The investigator is obligated to assess the relationship between investigational product and the occurrence of each SAE.
- Causality will be assessed as
  - Unlikely related: An event for which an alternative explanation is more likely - e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
  - Likely related: An event that might be due to the use of the drug. An alternative explanation is less likely - e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive (e.g., confirmed by dechallenge).

The Investigator should use clinical judgment to determine the relationship. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The degree of certainty with which an event is attributed to investigational product will be determined by how well the event can be understood in terms of one or more of the following:

- known pharmacology (including half life) of the study drug.
- any reaction of a similar nature previously observed with this drug or class of drugs.
- reports in the literature of the experience as related to this drug or class of drugs.

- the temporal relationship of the experience with drug infusion, termination of the event with withdraw of the drug, or reproduction of the event on repeat challenge with the drug.

11.1.5 Unexpected Adverse Events are those that have not been listed in the:

- Package insert for a given drug or investigator's brochure (for FDA investigational agents);
- Protocol; or
- Informed consent document.

Note: that expected events listed in the protocol are based on participant characteristics, take into account the nature of the intervention (if any), and include events that might reasonably be expected to occur in the study population but do not bear on the safety of the study.

11.1.6 Unanticipated Problem: According to OHRP (Office for Human Research Protections), unanticipated problems generally include any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.1.7 Follow-up of SAEs

- All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the D +37 follow-up visit, whichever occurs first.
- As additional information pertaining to an SAE becomes available, the eSAE form should be updated and resubmitted within 1 business day of knowledge of the information.

11.1.8 DCRI Safety Surveillance and Medical Monitor:

- DCRI Safety Surveillance will be notified of SAEs via email and will print the SAE form from the electronic data capturing system.
- DCRI Safety Surveillance will perform a clinical review of all SAE reports to verify that all sections are complete and consistent.
- DCRI Safety Surveillance will query for incomplete information, data clarification, and/or follow-up information within the Inform database.
- DCRI Safety Surveillance will write a clinical narrative of the event, enter the data into the Clintrace safety database and code the event using the current MedDRA dictionary.
- The DCRI Medical Monitor will review all SAEs, the MedDRA coding and assess the event for “expectedness” per the dalteparin product label.
- DCRI Safety Surveillance will forward the SAE report, a copy of the narrative, a copy of any queries sent to the site, and the Medical Monitor’s assessment to Dr. Ortel, and the DSMB chair within 1-2 business days of initial receipt. A copy of the above documents

will be forwarded to Eisai for SAEs assessed by the site investigator as "likely related" to study drug.

- SAEs will be reported to NHLBI according to current NHLBI Adverse Event and Unanticipated Problem Reporting Policy. The NHLBI Project Officer will be provided with a copy of the SAE report for all fatal, life-threatening, or unexpected serious adverse events that are likely related to study participation within 7 calendar days. All unanticipated problems will be reported to NHLBI within 30 calendar days.

11.1.9 Regulatory Reporting

All SAEs which are assessed as unexpected by the Medical Monitor and associated with the use of the study drug (likely related) by the Site Investigator require expedited reporting to the FDA and/or Health Canada. For these events, DCRI Safety Surveillance will generate CIOMS forms and forward them to Dr. Ortel for review and to DCRI Regulatory Services for submission. DCRI Safety Surveillance and Medical Monitor will provide an Investigator Alert packet for distribution to investigative sites.

12.0 Relationship to Institutional Policies on Conflict of Interest

Since existing polices on conflict of interest may vary between participating institutions, it is expected that site investigators will comply with the policies on conflict of interest, which exist within their individual participating institutions. This is the responsibility of each individual investigator.

13.0 Prototype of Informed Consent *(see appendix A)*

13.1 Patient Withdrawal from the BRIDGE Trial

A patient may be withdrawn from the trial at any time during the study and without prejudice to their subsequent care if the patient, site investigator, or another treating clinician believes it is not in the patient's best interest to continue participation in this trial.

14.0 Regulatory Affairs

The DCRI Regulatory Services group will review the patient education and enrollment materials and the SAE plan. Since this trial will be conducted at Canadian sites, the Regulatory Services group will interact with Health Canada on behalf of the **BRIDGE** trial, and will provide ongoing regulatory guidance to the project team.

15.0 Scientific Reporting and Publication

The results of this trial will have a major impact on patient care, given that up to 400,000 patients are assessed for bridging therapy annually in North America. In accordance with NIH policy, the Executive Committee will be responsible for the scientific reporting, publishing and/or presentation of the trial results. Several strategies will be implemented to broadly disseminate the study results. First, our primary audience will include physicians and other healthcare providers (e.g., pharmacists, nurses) involved in the management of patients on chronic anticoagulant therapy. Providers will be targeted through several organizations, including the Anticoagulation Forum in the U.S. and the Thrombosis Interest Group of Canada.

During the last year of the study, the Executive Committee will hold monthly teleconferences to review upcoming national and international meetings to implement broad dissemination of the study results. It is anticipated that these results will be presented at a Late-Breaking Clinical Trials session at an international scientific meeting (e.g., American Heart Association, American Society of

Hematology) and undergo fast-track publication in a major journal. If judged appropriate by the BRIDGE Steering Committee and NIH program staff, a Clinical Alert may be sent to the relevant specialists in internal medicine, hematology, and cardiovascular diseases, as noted above. If the trial results are highly significant, we will work with the NIH to generate a press release to the public concerning the results. The Executive Committee will also seek to promote rapid inclusion of the trial results into consensus reports, such as the ACCP Guidelines for Antithrombotic and Fibrinolytic Therapy, to promote broad dissemination of the results.

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Appendix A

Consent for Participation in a Clinical Research Study

Title: *B*ridging Anticoagulation in Patients who *R*equire Temporary *I*nterruption of Warfarin Therapy for an Elective Invasive Proce*d*ure or Sur*ge*ry ("BRIDGE")

Protocol Number: 1U01-HL-086755-01A1

Sponsor: National Institutes of Health
National Heart, Lung, and Blood Institute

This clinical research study is being sponsored by a grant from the National Institute of Health. Portions of ***(insert PI's name and address)*** and his/her research team's salaries are being paid by this grant.

WHAT IS CLINICAL RESEARCH AND INFORMED CONSENT?

You are being asked to take part in a clinical research study. Clinical research is the scientific method used to improve medical practice and patient care. Your doctors, in collaboration with the National Institutes of Health, are trying to improve the care of patients who require interruption of warfarin because of a planned surgery or other invasive procedure.

Your participation is voluntary and if you choose not to participate in this study, your care will not be affected in any way. Prior to deciding if you should participate in this study, you should understand enough about the risks and benefits to make an informed decision. This process is called informed consent.

This consent form contains detailed information about this research study. The purpose of the consent form is to explain all the procedures involved in this study before you decide whether or not to participate. You should read this consent form carefully and you may ask your study doctor or the study staff questions about anything that is not clear to you.

BACKGROUND INFORMATION FOR THIS RESEARCH STUDY

A brief overview of information that will help you to better understand the reason for doing this research study is provided below. Please feel free to ask additional questions about the information.

1) *What is atrial fibrillation or atrial flutter*? Atrial fibrillation or atrial flutter is an irregular heart beat that can cause blood clots to form in the heart. Atrial fibrillation or atrial flutter can cause palpitations, dizziness and, in severe cases, loss of consciousness. Medications, such as warfarin, decrease the risk for strokes, as well as other complications due to emboli, by decreasing the likelihood of forming a blood clot in the heart.

2) *What is warfarin*? Warfarin is a blood thinner used by over 2 million people in North America for the prevention of stroke, heart attack and other blood clots.

3) *Why am I receiving warfarin therapy for atrial fibrillation or atrial flutter?* Blood thinners prevent the formation of blood clots in the chambers of the heart (atrium). These blood clots, if allowed to form, can break off into the circulation, travel to the brain and cause a stroke. These clots may also travel to the extremities and cause a painful clot in an arm or leg. Warfarin is an effective medication that prevents the formation of blood clots. If warfarin is not given to a person with atrial fibrillation or atrial flutter, their risk for having a stroke is about 5-6% per year. With warfarin therapy, this risk is reduced to 1-2% per year.

4) *What is the usual care for people who are receiving warfarin therapy and need surgery or a procedure?* People, who require an interruption of their warfarin therapy because of surgery or a procedure, usually stop taking warfarin about 5 days before the surgery. This is done because it takes about 5 days for the blood thinning effect of warfarin to wear off and be eliminated from the body. Warfarin needs to be stopped in order to prevent too much bleeding from occurring during and after surgery.

When warfarin is re-started after surgery, it takes about 5-7 days for the blood thinning effect to return. As a result, during this time period the blood thinning effect of warfarin is less than desired.

Since interrupting warfarin before and after surgery reduces the blood thinning effect and may increase the risk for blood clots, some doctors choose to administer a blood thinner that works quickly but also wears off quickly. Use of this short acting blood thinner is referred to as "*bridging anticoagulation*". At this time, there is no agreement among experts and practicing physicians regarding whether bridging anticoagulation should be used. Some doctors give bridging anticoagulation to prevent the formation of blood clots during interruption of warfarin, however some doctors do not give bridging anticoagulation because it might cause bleeding during (or after) surgery.

What is the purpose of this research study?
This research study aims to determine the effectiveness and safety of giving a low molecular weight heparin (LMWH) called dalteparin (Fragmin®) as bridging anticoagulation to people with atrial fibrillation or atrial flutter who require temporary interruption of warfarin because of surgery or another procedure.

Why is this research study being done?
It is not known whether bridging anticoagulation is helpful to patients who require temporary interruption of warfarin. On the one hand, bridging anticoagulation minimizes the time patients are not receiving blood thinning treatment prior to and after surgery and therefore may reduce their risk for developing a stroke or other types of blood clots. On the other hand, giving bridging anticoagulation may increase the risk for bleeding, which may be harmful. Such bleeding may require medical attention and may lead to other health problems. Overall, there is uncertainty about the benefit and harm of bridging anticoagulation. This research study will determine the possible benefits and harms of bridging anticoagulation and will inform doctors about the best way to care for patients like you in the future.

Why am I being asked to participate in this research study?

You are being asked to participate in this research study because you are currently receiving treatment with warfarin for a condition called atrial fibrillation or atrial flutter and because of a planned surgery or procedure you are required to temporarily stop your warfarin therapy. About 3,626 subjects in the United States and Canada will be asked to participate in this study at about 45 clinics or hospitals.

What will happen if I do not agree to participate in this research study?

If you do not agree to participate in this research study, the management of warfarin and whether to use bridging anticoagulation will be determined by your primary care physician.There will be no penalty if you choose not to participate.

What will happen if I agree to participate in this research study?

If you agree to participate in this research study, your involvement *will last for up to but no longer than 67 days* (up to 1 month before your planned surgery or procedure until 37 days after your surgery or procedure). Overall, the following things will happen:

- You will self administer subcutaneous (just under the skin) injections of the study drug, which will consist of a blood thinner (dalteparin (Fragmin®)) or an inactive substance (placebo).
- You will have approximately 9 study encounters during this time period, consisting of at least 2 visits to the hospital/clinic and 5-7 telephone calls from the study nurse/coordinator.
- You will be asked to provide at least 3 International Normalization Ratio (INR) testing results as part of the routine care by your primary physician. If the test is done at a laboratory, approximately 6 teaspoons of blood will be needed for each test. If a Point-of-Care device for INR testing is used, only a few drops of blood will be needed for each test. The INR test measures how thin your blood is and will be reviewed by your study doctor who will determine if you need to adjust your dose of warfarin. As part of your routine care, your primary care physician will complete at least one INR test before surgery, and two INR tests sometime between 2 and 10 days after you receive your surgery or procedure.
- You will be required to answer some questions about your health during 5-7 (five-minute) telephone calls from the study nurse/coordinator.

Patient Encounter 1: Visit for Screening and Consent

This will occur approximately 15 to 30 days before your planned surgery or procedure.

- You will be asked to review the consent form and, if you are satisfied that all your questions have been answered, to provide written informed consent.
- Your medical record will be reviewed and if you are eligible for this study you will be asked to participate.

Patient Encounter 2: Visit for Randomization

This will occur 5 to 14 days before your planned surgery or procedure. Patient encounters 1 and 2 may be combined if the initial visit occurs 5 to 14 days before your planned surgery. During this visit, the following procedures will be done:

You will be randomly assigned (like a flip of a coin) to Group A or Group B. Participants in Group A will receive anticoagulant bridging therapy, participants in Group B will receive

placebo. A placebo is an inactive substance that cannot hurt or help you; it will be administered using the same method as the anticoagulant bridging therapy. You have an equal chance of being assigned to receive the anticoagulant bridging therapy or placebo. This study is blinded, this means neither you nor your doctor will know whether you have been assigned to Group A or Group B until the end of the study.

If you are assigned to

Group A, you will stop taking warfarin 5 days before surgery or procedure and will receive bridging anticoagulation with the LMWH called dalteparin (Fragmin®). You will self administer an injection of the LMWH twice-a-day beginning approximately 3 days before the surgery or procedure; you will stop after giving yourself your morning injection the day before surgery. Your study doctor will let you know when to restart study drug after your surgery. You will continue to self administer study drug twice a day until approximately 6 days after the surgery or procedure.

Group B, you will stop taking warfarin 5 days before surgery or procedure and will not receive bridging anticoagulation. Instead you will receive an inactive substance (placebo) that appears identical to the active study drug. You will self administer an injection of the placebo twice-a-day beginning approximately 3 days before the surgery or procedure; you will stop after giving yourself your morning injection the day before surgery. Your study doctor will let you know when to restart study drug after your surgery. You will continue to self administer study drug twice a day until approximately 6 days after the surgery or procedure.

- Study drug (dalteparin or placebo) will be dispensed in a kit containing glass vials and other supplies, i.e. alcohol preps, syringes. You will be given a container for disposal of the used syringes. You will be shown how to withdraw the study drug from the vial and how to self-administer the study drug by injection. The process is similar to the one a person with diabetes uses to draw up and give themselves insulin. If you are unable to withdraw the study drug from the glass vial because of impaired vision or another reason, you will have the option of having the study drug drawn up for you by the study personnel. Pre-filled disposable syringes can be stored at room temperature for up to 14 days prior to administration of study drug.
- You will be shown how to withdraw the study drug from the vial and how to self-administer the study drug by injection. The process is similar to how a person with diabetes draws up and gives themselves insulin
- You will be given a study diary and asked to record the dates and times you take warfarin and administer study drug. You will be given written and detailed instructions about the study.

Patient Encounter 3: Telephone Contact

- This will occur 1 day before your planned surgery. You will be asked about any new symptoms or other health problems since your last contact and about the injections of the study drug.

Patient Encounter 4: Visit or Telephone Contact

- This will take place on the day of your surgery or procedure and will consist of either a visit or telephone contact depending on the type of surgery or procedure you have had and the location where it took place (hospital or out-of-hospital clinic).
- You will be assessed for possible bleeding from the surgery and about any new symptoms or other health problems.
- You will be given instruction about when to restart warfarin and the study drug injections.
- You will receive additional study drug to use after your operation or procedure if you did not receive it during Patient Encounter 2.

Patient Encounter 5: Clinic/Hospital Visit or Telephone Contact

- This will take place between 1 and 7 days after surgery or procedure. You will be assessed for possible bleeding from the surgery or procedure and about any new symptoms or other health problems.
- Your INR will be measured at least twice during the period between 2 and 10 days after your surgery or procedure. Your INR lab results will be reviewed and your study doctor may adjust your warfarin dose.

Patient Encounters 6, 7 and 8: Telephone Contact

- These telephone contacts will take place between 8 and 29 days after surgery or procedure, with the first contact 8 to 14 days after surgery, the second contact 15 to 21 days after surgery and the third contact 22 to 29 days after surgery. You will be assessed for possible bleeding from the surgery or procedure and about any new symptoms or other health problems.

Patient Encounter 9: Visit or Telephone Contact

- This will take place approximately 30 to 37 days after surgery or procedure. You will be assessed for possible bleeding from the surgery or procedure and about any new symptoms or other health problems. You will return your study diary and the study drug kit with any unused items. You will be instructed on how to dispose of the used needle and syringe container by your study doctor or nurse. This encounter will constitute the end of the study.

What are my responsibilities if I participate in this study? It is important for you to notify your health care team (study doctor or nurse/coordinator) about any new symptoms of bleeding, symptoms that may suggest a stroke or any other new health problems so that you can receive prompt medical attention if required.

- It is important for you to attend each of the scheduled study visits and to participate in the study telephone contacts so your health care team can monitor your blood thinning therapy and the administration of the study drug, and discuss any new health problems.
- You should store your study drug medication kit at room temperature in a safe place out of reach from children. After the study drug is used, place the used needle and syringe into the sharp objects container that will be given to you.
- You should be available (by a home telephone or cell phone) for the designated contacts from the study nurse/coordinator.

- You will record the dates and times you take warfarin and study drug in the study diary
- You will return all unused study drug to your study doctor or nurse at Patient Encounter 9.

What are the possible risks if I participate in this study?
Dalteparin, like all medications, may cause side effects. You may experience none, some or all of the symptoms listed below. Please advise the study doctor immediately of any unusual symptom(s) that you might experience. You should tell the person obtaining your consent about any other medical research studies you are involved in right now. While you are in the study, you are at risk for the following side effects:

- *Likely*: discomfort and bruising at study drug injection sites.
- *Less likely*: bleeding which can occur at any site on your body, and can be internal and/or external, (e.g. blood in your urine or bowel movements, nose-bleeds, bleeding-gums, bruising). Also you may experience small bruising in areas following injection.

- *Rare but serious*: Changes in liver function tests can occur with dalteparin therapy. As with any blood thinner, bleeding associated with dalteparin (Fragmin®) therapy may cause anemia, or a decrease in red blood cells, which could result in fatigue. Bleeding may also be life threatening and require a blood transfusion. Although dalteparin (Fragmin®) has been proven effective in other clinical situations to prevent blood clots, you may develop a blood clot during dalteparin therapy. This is due to a rare condition called heparin induced thrombocytopenia (HIT) which occurs in a very small percentage of people after exposure to drugs like dalteparin and increases their risk of developing a life threatening blood clot.

There may be risks or discomforts that are not known at this time. You will be told of any significant new findings that become available during the course of this study that may relate to your willingness to continue your participation.

Risks for Women of Childbearing Potential
The effects of dalteparin on an unborn child are not known, and it is not known whether receiving dalteparin now can have effects on unborn children in the future. Therefore, pregnant women are not allowed to participate in this trial. Please notify the physician immediately if this pertains to you.

What are the possible benefits if I participate in this study?
You may not directly benefit from this research study. However, your participation in this study and the knowledge gained from this study may benefit future patients with atrial fibrillation or atrial flutter who require interruption of warfarin therapy.

Do I have to participate in this study?
No, your participation in this research study is voluntary. If you decide to participate, you can stop your participation at any time. If you decide to withdraw from the study we ask that you contact ***(insert site PI name here)*** in writing to the address listed on the first page of this form. You should let him/her know that you are withdrawing from the study. You

may be asked to return for a visit for safety reasons. If you decide not to participate your medical care will be determined by your primary physician. This may or may not include bridging anticoagulation.

There will be no penalties or loss of benefits to which you would otherwise be entitled if you choose not to participate or if you choose to stop your participation once you have started. You will be told about any significant information that is discovered that could reasonably affect your willingness to continue being in the study.

Who else can stop my participation?
Your study doctor or primary care doctor may decide to take you off this study if your study doctor determines that it is no longer in your best interest to continue. The study will be stopped if data indicate overwhelming evidence in favor of either the anticoagulant bridging therapy or placebo. The study's principal investigator or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and you may be asked to return for a visit for safety reasons.

Will it cost anything to participate?
The study drug and tests specific to this study will be provided to you at no charge. We do not expect there to be any additional costs to you if you participate in this study. Items related to the routine medical care that you would receive even if you did not participate in this study will be billed to you or your insurance company.

Will I be paid to participate?
You may receive financial reimbursement for your time and travel expenses, including parking costs. This should be discussed with your study doctor or nurse/coordinator.

Will I receive medical treatment in the case of illness or injury?
In the event of a medical illness or injury related directly or indirectly to your participation in this study, you will receive all appropriate medical treatments. If you develop a health problem that requires medical attention, you should contact your doctor as soon as possible.

(U.S. only: There is no federal, state, or other program that will compensate you or pay for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.)

Will my personal information be kept confidential?
By signing this consent form, you agree that we may collect, use and release your personal and health information for the purpose of this research study. Your name and personal information will never be made available to anyone who is not involved in this research study. The results of this study may be published in the medical literature, but your name and personal information will not be revealed.

The National Heart, Lung and Blood Institute (NHLBI) will have access to your study-related records, as will the, ***(insert IRB or REB Name***), the Statistical Data Coordinating Center and Clinical Coordinating Center at Duke Clinical Research Institute. Following

completion of the study, medical information that is obtained from you for study purposes will be kept for at least six years after the study is completed.

We may collect and use:

- Your existing medical records.
- New health information created during this study.
- Health insurance and other billing information.

We may release this information to the following people:

- The Principal Investigator and his/her associates who work on, or oversee the research activities.
- Government agencies who oversee research (e.g., Food and Drug Administration, Health Canada)
- Your insurance company or others responsible for paying your medical bills.
- Duke Clinical Research Institute
- Institutional Review Boards or Ethics Committees.

This consent form, test results, medical reports and other information about you associated with this study may be placed into your medical record. Generally, you are allowed to look at your medical record. During the research study, you will be allowed to look at your research study information that is not in your medical record.

The BRIDGE Executive Committee on behalf of the National Heart, Lung and Blood Institute (NHLBI) or others will publish the results of this study. No names, identifying pictures or other direct identifiers will be used in any public presentation or publication about this study unless you sign a separate consent allowing that use.

If you decide not to sign this consent or withdraw your consent, you cannot participate in this study. If you notify us that you wish to stop participating in this study, we may continue to use and release the information that has already been collected. You do not waive any of your legal rights by signing this informed consent.

Whom can I contact if I have questions about this study?

If you desire or want any further information about this study, or information regarding this research, or in the event of a research-related injury, you may contact the study physician, ***(insert site specific information and local IRB)***

***B*ridging Anticoagulation in Patients who *R*equire Temporary *I*nterruption of Warfarin Therapy for an Elective Invasive Proce*d*ure or Sur*ge*ry ("BRIDGE")**

STATEMENT OF INFORMED CONSENT

I have read the above information. I have received answers to any questions I may have had. By signing this consent form, I will not waive any of my legal rights. I will receive a signed and dated copy of this Consent Form.

I voluntarily consent to participate in this research study and I understand that I may withdraw my consent at any time without penalty or prejudice to my subsequent care.

Name of patient (print)	signature	date
Alternate decision maker (print)	signature	date
Name of person obtaining consent (print)	signature	date
Name of Principal Investigator (print)	signature	date