DGIM Project Summary

Name of Project: Clarification of Optimal Anticoagulation Through Genetics (COAG)

Investigator(s). (Include phone numbers and email address, indicate PI and primary contact):
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Research question(s):
Does the use of genetic and clinical information for selecting the dose of warfarin during the initial dosing period lead to improvement in stability of anticoagulation relative to a strategy that incorporates only clinical information (without genetics) for initial dosing?

Brief Background/Significance:
Warfarin sodium is one of the top 20 medications used in the US. Warfarin is highly efficacious at preventing thromboembolism, a condition associated with substantial morbidity and mortality. However, warfarin must be dosed properly to avoid life-threatening complications (from overdosing) and lost efficacy (from underdosing).

Warfarin dose requirements vary widely among patients and warfarin dosing is typically initiated empirically and adjusted through trial and error, putting patients at risk. The practice of empiric dosing results in improper dosing in a large number of individuals, and out-of-range INRs are extremely common early in therapy. Variability in warfarin dose-response is related to both clinical and genetic factors. Dosing algorithms to date using only clinical factors have had limited success. Because of the difficulties of dosing warfarin and the multifactorial nature of warfarin response, the concept of dosing algorithms that use both clinical and genetic variables to improve anticoagulant management, reduce complications, and enhance efficacy has real potential.

This proof-of-concept trial is important because formal testing of the utility of a genetic-guided dosing strategy among a large, diverse group of patients using warfarin has not been rigorously performed. There is clearly a need to improve warfarin management.

Inclusion/exclusion criteria (list):
1. Age ≥ 18 years
2. Willingness and ability to sign informed consent
3. Able to be followed in outpatient anticoagulation-management clinic
4. Expected duration of warfarin therapy of at least 3 months
5. Anticoagulation management for the patient will be performed in-hospital and as an outpatient by clinicians that will adhere to the study dosing algorithms and dose titration plans
6. Target INR 2-3

Method of contact/recruitment (be specific):
Study investigators recruit their own patients directly and/or nurses or staff working with researchers approach patients. Study investigators will ask colleagues for referrals. Study investigators will also use UCare to review charts to identify prospective subjects.

Once potential subjects are identified and deemed eligible, study staff will meet with the patient to explain the study and obtain informed consent. We anticipate that most eligible subjects will be approached during a hospitalization and interviews conducted in their private hospital room. Subjects identified in the outpatient setting will be approached during usual clinic hours during a scheduled clinic visit.

**Benefits/burden for participants (clearly identify potential for harm):**

*Warfarin Risks*
Warfarin has known risks even within the therapeutic range, including minor bleeding (10% per year), major bleeding (3% per year), blood clot returning, and less commonly, hair loss, skin rashes, or death from bleeding (<1% per year). Warfarin is also a known teratogen. Because all subjects recruited for this study have all already been prescribed warfarin, we do not anticipate any additional adverse consequences associated with exposure to warfarin related to being in the study.

*Research Risks (risks that can occur from study participation.):*
Risks of the Study Dosing: Study dosing methods may conceivably lead to a higher or lower dose of warfarin than determined by clinicians. The degree of anticoagulation will be monitored through measuring the INR regularly, which will then guide adjustment in warfarin dose. There may be a risk of under-dosing based on the genotype-guided method.

There are also always risks associated with drawing blood. Another possible risk is the loss of confidentiality about subject medical information. Lastly there is the unlikely risk that if people other than the researchers gained access to genetic information they could misuse it.

**Any benefits or burden to DGIM practitioners?**

**Timeline for recruitment (projected start and stop dates):**
2/1/2010 – 2/1/2012

**Funding source:**
National Institute of Health / National Heart Lung and Blood Institute

**Potential for DGIM collaborators? (We encourage DGIM resident and fellow involvement in particular):**

Do you agree to notify us when recruitment is completed?
Yes

**Date form completed:**
01/27/2010