What Does the DMC Really Need to Know?

Stephen E. Kimmel, MD, MSCE
Professor of Medicine and Epidemiology
Director, Epidemiology Division
Director, Center for Therapeutic Effectiveness Research
The Bottom Line

• Talk to your DMC
  – Openly
  – Up-front
  – Often

• Useful exercise
  – Ask yourself what you would want to know to ensure the protection of participants
  • Safety
  • Success
Data and Safety Monitoring Board
Briefing Book
1 March 2013

Clarification of Optimal Anticoagulation Through Genetics:
A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy
in the Use of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation
and Improve Anticoagulation Control for Patients

Sponsored by:
National Heart, Lung, and Blood Institute (NHLBI)
National Human Genome Research Institute (NHGRI)
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Attachments

Overall tables and figures, through 25 January 2013, including descriptions
By-arm tables and figures, through 25 January 2013, including descriptions
DSMB charter
DSMB minutes (17 August 2012)
Current protocol and current informed consent
# COAG Protocol Summary

<table>
<thead>
<tr>
<th>Study Title &amp; Description</th>
<th>Clarification of Optimal Anticoagulation Through Genetics (COAG): A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy in the Use of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation and Improve Anticoagulation Control for Patients</th>
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<tr>
<td>Sponsor</td>
<td>National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), National Human Genome Research Institute (NHGRI)</td>
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<tr>
<td>Pharmaceutical and Other Collaborators</td>
<td>Bristol-Myers Squibb, The Critical Path Institute, Osmetech, AutoGenomics, Inc.</td>
</tr>
<tr>
<td>Agent</td>
<td>Warfarin (Coumadin®)</td>
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| Design & Sample Size      | 2-arm randomized clinical trial design – initial dosing guided by genetic and clinical information (genotype-guided dosing) OR initial dosing guided by clinical information only (clinical-guided dosing)  
1022 patients - 511 genotype guided dosing / 511 clinical guided dosing  
Sample size estimates assume estimated drop-out rate of 10% after randomization  
Analysis of the primary outcome will be by intention-to-treat |
| Power & Effect Size       | The sample size of 1022 will provide 90% power to detect a difference of 5.5% from the expected PTTR of 65.6% among those in the clinical-dosing arm; the computations assumed that the standard deviation for PTTR will be approximately 25%, and that approximately 40% would not be expected to benefit from genetic-guided dosing based on their genetic variants |
| Population                | Patients starting anticoagulation therapy for the first time at in-patient and out-patient levels of care |
| Inclusion Criteria        | Age ≥18 years, Expected duration warfarin therapy at least 1 month, Target INR 2-3 |
| Dose Regimen              | Dose day 1-3 according to dose initiation algorithm; dose day 4-5 according to dose revision algorithm and INR, after 5 day, dose titrated according to INR |
| Treatment Duration        | 4 weeks blinded study phase and 20 weeks follow-up period |
| Primary Endpoint          | Percentage of time participants spend within the therapeutic INR (PTTR) during the first four weeks of therapy |
| Primary Objective         | Compare efficacy of two dosing strategies with respect to the time spent within the therapeutic INR range (PTTR) during the first 4 weeks of therapy |
| Interim Analysis          | Upon recommendation of the DSMB |
| Target Accrual            | 1022 participants |
| Rate of Accrual           | Three (3) participants per center per month |
| Total Clinical Centers    | 18 (U.S.A.) |
| Trial Initiation Date     | September 2009 |
| Accrual Completion        | 30 April 2013 |
| ClinicalTrials.gov Registration Number, Title, & Link |  
- http://www.clinicaltrials.gov  
- NCT00839657 – Clarification of Optimal Anticoagulation Through Genetics  
- http://coagstudy.org |
Some Specifics To Consider

- Study Success
  - Eligibility Status by Enrollment
  - Randomized vs Target
  - Gender, Race, Baseline Characteristics
  - Withdrawals, Cross-overs, Protocol Violations, Completed Visits, Unblinding
  - Data completeness
  - Protocol fidelity
Some Specifics **To Consider**

- **Safety**
  - **Serious Adverse Events**
    - **How specific?**
  - **Unanticipated Problems**
    - "The phrase ‘unanticipated problems involving risks to subjects or others’ is found but not defined in the HHS regulations at 45 CFR part 46.” But, includes **all** of the below:
      - *unexpected* 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; and
      - suggests that the research places subjects or others at a **greater risk of harm** than was previously known or recognized.

- **DMC-Focused Events**
  