What Does the DMC Really Need to Know?

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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

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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

Study Title & Description	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
Sponsor	National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), National Human Genome Research Institute (NHGRI)
Pharmaceutical and Other Collaborators	Bristol-Myers Squibb, The Critical Path Institute, Osmetech, AutoGenomics, Inc.
Agent	Warfarin (Coumadin®)
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 65.8% 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

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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

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/