Reviewer's report

Title: Statistical design of personalized medicine interventions: The Clarification of Optimal Anticoagulation through Genetics (COAG) trial

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Reviewer: Anke Hilse Maitland-van der Zee

Reviewer's report:

This is a well written manuscript on the statistical design issues in a pharmacogenetics trial.

There are no major compulsory or minor essential revisions.

Discretionary revisions
* The authors state that they will genotype before first dosage. How will they make that happen. In clinical practice nowadays that will be quite complicated to achieve.

* The authors state that the proportion of patients that is included in the trial with the different genotypes needs to be monitored. This because this will influence the detectable difference. I wonder whether that would be really necessary given:
  - the fact that the percentage of patients with a certain genotype in a population is known and the large sample size leads to a good pre-study prediction of the amount of subjects that will be included
  - the fact that in the analysis phase the analyses will be stratified by genotype.

Maybe the authors can add some explanation why they still think it should be monitored.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests