Author’s response to reviews

Title: Implementation of genotype-guided dosing of warfarin with point-of-care genetic testing in three UK clinics: a matched-cohort study

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Author’s response to reviews:

Dear Editors

RE: Manuscript Number BMED-D-19-00177

Sincere thanks for your response and reviewers’ comments. We have addressed the insightful reviewer comments and have uploaded an updated manuscript to reflect these, with changes tracked. We have also provided a response to each reviewer and editorial comment below (this is also summarised in our rebuttal letter, uploaded). We hope that you will be able to consider our manuscript further for publication in your journal, and look forward to hearing from you soon.
Reviewer 1

1. To change GGD letters because it did not indicate point-of-care genotyping information.

We thank the reviewer for this suggestion, and have changed the acronym used to describe the point-of-care genotype guided dosing approach from ‘GGD’ to ‘POCT-GGD’ throughout the manuscript, to reflect the point-of-care testing nature of the approach.

2. In the Results from Abstract: to show values for 2 groups and not only the difference.

We thank the reviewer for this observation and agree that for completion the mean time in range should also be stated for each of the two groups separately. These values have been added (page 2, lines 32-33, Abstract).

3. Discussion: statistical power was calculated before; but number of patients was small, thus, this limitation can be included in the Discussion too. Maybe, as limitation, some used questions are not validated, previously.

As stated in the ‘Outcomes assessed and statistical analysis’ subsection of the Methods section (lines 172-176), a sample size calculation was undertaken in advance, based on our primary outcome of time in target INR range. However, due to recruitment rates falling below target we made the decision to utilise the anonymised dashboard data to increase sample size, and at this point undertook revised power calculations (lines 177-185). These showed that our revised sample size provided us with sufficient power to detect a clinically significant difference in the primary outcome. As our study was adequately powered, we feel that these explanations in the Methods section are sufficient to reassure the reader that we had sufficient power to test our primary hypothesis. However, in light of the reviewer’s comments we have added a sentence to the Discussion section (page 13; lines 319-323) to highlight recruitment problems as a limitation of our study, and how this was addressed.

In terms of the secondary outcome capturing bleeding events, we appreciate that given the rarity of this outcome we did not have sufficient power to test for a difference between groups, and have already listed this as a limitation in the Discussion section (lines 306-315).
Further, we have acknowledged our lack of validating the staff and patient questionnaires as a further limitation (page 13, lines 327-330, Discussion section), and thank the reviewer for this suggestion.

4. Table 1: p values must be reported, comparing 2 groups.

We thank the reviewer for this suggestion, however we do not believe it is necessary to test the difference in baseline characteristics between the two groups since these are not hypotheses we set out to address in our study. Whilst our study is not a randomised controlled trial, we agree with the guidelines provided by CONSORT 10 (https://doi.org/10.1136/bmj.c869) and supporting documentation) which state that doing so is unnecessary and can be misleading, and believe that the same applies in our study.

Reviewer 2

1. Methods, page 6 lines 4-6. Please show in brackets the eGFR cut-offs for stage 4 and 5 CKD.

The eGFR cut-offs were as follows and are now included (page 6, lines 106-107): stage 4 CKD (15-29mL/min), stage 5 CKD (<15mL/min)

2. Results, page 9, line 47. Start the sentence with the number 222 written-out.

We thank the reviewer for this suggestion and have made the change accordingly (page 9, line 216, Results section).

3. Table 1, page 21 Baseline characteristics and page 6 lines 15-16. I am confused about where these patients have been referred from - directly from hospital, from the GP, or cardiologist? The baseline INRs in the table show that they are already anti-coagulated, but the referrals are for commencement of warfarin. Also, some patients have had DVTs and PEs, so their clinical journey to the anti-coagulant clinic is expected to be different to those newly diagnosed with AF
i.e., they will have been treated in hospital I presume. Since the baseline INRs in table 1 show that patients were already anti-coagulated, some extra information on these points would be appreciated.

We would like to thank the reviewer for these observations. In terms of table 1, we realise that the label ‘INR range’ was rather misleading, where in fact the values represent the patients’ target INR range. We apologise for the confusion this has caused and have now amended the table accordingly to make this clear (page 21, Table 1).

The pathway is indeed different for VTE patients – they would have been diagnosed with the condition, and would have been put on subcutaneous low molecular weight heparin, and then referred to the anticoagulant clinic for commencement of oral anticoagulation, where they would have recruited. Patients with VTE are treated as outpatients unless they have a complicated or severe disease process.

4. Methods, how many patients had previously been on a DOAC before the clinical decision was made to change to warfarin?

No patients had previously been on a DOAC.

5. Results, page 12. Please define LGC.

We thank the reviewer for this observation. LGC stands for Laboratory of the Government Chemist – it is the name of the company. We have changed the wording to ‘LGC Limited’, included the full name the first time LGC is mentioned, and added the web address of the company for clarity (page 7, line 149, Methods section; page 12, line 285, Results section; page 16, line 411, Authors’ contributions section and page 17, line 432, Acknowledgements section).

6. Discussion - although the title and majority of the manuscript uses GGD, which I am happy to be left alone, the discussion would benefit from highlighting to readers that CYP2C9 and VKORC genotype are only two covariants used in the dosing algorithm to guide dosing. What are the contributions of genetic vs. non-genetic covariants to the overall benefits i.e., if only on the non-genetic covariants were considered, how would this perform? This paper seems like a
nice example of model-informed precision dosing because all the important covariants that influence warfarin PK/PD are used, so the branding as simply 'genotype-guided dosing' could be considered a little misleading. Please comment.

We thank the reviewer for these observations, and agree that it is a very important point to consider. We have therefore highlighted in the discussion section, as a reminder to readers, what information the GGD algorithm includes as covariates (page 12, lines 293-294). It is important to appreciate that this is an implementation study, and so the aim was to change from the current standard practice, which does not take into account any non-genetic covariates (apart from age) to the use of our algorithm, which we had previously tested in EU-PACT.

We had similar concerns when conducting our previous EU-PACT trial which compared the GGD approach to standard clinical care in an RCT setting, and feared being criticised for not also comparing to an algorithm including non-genetic covariates only. To address these concerns in EU-PACT, we compared percentage time in target INR in our trial’s control arm to that in previous studies and found that it was either equivalent or greater than for previous studies, which reassured us that our control arm was not underestimating time spent in target INR range.

7. Discussion page 13, lines 41-45. This sentence on a future paper should be deleted since the paper is not accepted for publication.

We thank the reviewer for this suggestion, and have deleted the sentence accordingly (page 13, Lines 336-338, Discussion section).

8. Discussion page 14, lines 32-34. Again, please delete the last sentence on a possible future publication.

We thank the reviewer for this observation, and have deleted the sentence accordingly (page 14, lines 362-363, Discussion section).

9. Reference 12 is not a proper reference. Please delete or provide the full citation.
We have now deleted this reference (References section).

Editorial comments

1. Each file (whether main or Additional) should be mentioned in the main manuscript text in order. At the moment, supplemental files are not cited in ascending order within the main body of text.

We have now changed the order in which supplementary files are included, and ensured they are cited in ascending order within the main manuscript.

2. You should upload your figures as separate files. Figures should be uploaded as high-resolution files in the appropriate format (e.g. TIFF, PDF, JPEG, EPS). Note that Figures must be <20Mb in size

Figures have now been uploaded as separate files in the required format.

3. Additional files should be uploaded as a “Supplementary” file type in the system

This has now been done.

4. Please provide a subsection just after the main file legends listing all the additional files and include: file name (e.g. Additional File 1), title and short description of data, file format including the correct file extension (for example .pdf, .xls, .txt, .ppt). I would suggest you add this information after Figure Legends.

We have now included this information for all additional files.
5. You should include a “Declarations” section, consisting of the following sub-sections: Acknowledgments; Funding; Availability of Data and Materials; Authors’ Contributions; Competing interests; Ethics Approval and Consent to Participate. All of these subsections MUST be present.

Please change DECLARATIONS OF INTEREST to Competing interests. Please include Disclaimer statement within Competing interests subsection

We have now changed the ‘Declarations of Interest’ to ‘Competing interests’ and incorporated the Disclaimer statement into that subsection.

Thank you again for considering our manuscript.

Sincerely,

Professor Andrea Jorgensen