Author's response to reviews

Title: AUtomated Risk Assessment for Stroke in Atrial Fibrillation (AURAS-AF), an automated software system to promote anticoagulation and reduce stroke risk: study protocol for a cluster randomised controlled trial

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Author's response to reviews:

Dear Editors,

We are grateful to the reviewer for useful comments that will improve this paper. As discussed below we initially wished to publish the unmodified protocol approved by the ethics committee but as the reviewer points out this is very long and wordy for journal readers. We have therefore shortened and modified it very significantly, and are therefore not submitting a 'tracked changes' version.

Our responses to the points raised are given below.

Yours sincerely,

Tim Holt

Major compulsory revisions

1. The Journal requests that protocols be reported in line with the CONSORT statement and then sets out a long list of sections to include. The CONSORT statement is not referenced, the journal order is largely ignored and, for the purposes of this Journal, the document is both repetitive and wordy. As an example, the Journal refers to a list of “Tips for preparing your manuscript” which suggests two paragraphs on “why you started” http://www.biomedcentral.com/authors/report. The submitted document contains 16 paragraphs under background and rationale. Similarly, I think the 24
paragraphs on ethical issues could be dramatically reduced. The authors might want to rephrase the suggestion that an ethical risk of the trial is "reducing patient autonomy". Patient autonomy can only be properly exercised in knowledge of benefits and risks - not offering therapy to patients is not a way to protect patient autonomy.

Our response: We have considerably revised the manuscript, shortening it (especially the background and ‘ethics’ sections mentioned), and have reordered it to fit better with the journal’s guidance and other published protocols. We hope this summary of the protocol is now less repetitive. Due to the request for substantial revision of format we have not highlighted individual changes. We were following suggestions in the recent SPIRIT guidelines that one version of the protocol should be maintained, therefore had included all elements of the REC approved protocol. We hoped to publish this unmodified, approved protocol but recognise that this is indeed wordy and that the format requires substantial revision for publication in the Journal. We designed the trial with the CONSORT cRCT extension in mind and now reference this (page 15, paragraph 2).

When we mentioned patient autonomy, we did not intend to suggest that this would be greater when a patient does not know about a treatment. The ethical issue is a general one that concerns the potential for opportunistic screen reminders to ‘take over’ the consultation and the patient's own planned agenda for that consultation. We hope that we have clarified this on page 4, paragraph 1.

Minor essential revisions

2. The document repeatedly refers to “eligible” patients with AF but we are not told that the NICE criteria will be used until section 7.2 and not told what the NICE criteria are until Box 1 under section 7.3.2.

Our response: With the revised order (see point 1), we hope that the eligibility criteria for our trial are now clearer, as they are introduced earlier (in the aim on page 4). They are based on the most up to date guideline at the time of the Ethics application, and were defined on the advice of the AURAS-AF Trial Steering Committee. In the Background section, the definition of ‘eligibility’ varies between the studies discussed. We have stated that these are dependent on the national clinical guideline at the time of the study (page 3, paragraph 2).

3. Overall I think potential harms of oral anticoagulation are not sufficiently mentioned. For example, in Background, the comment about “concern over the QOF’s current stance” and related text in the same and the following paragraph seem to imply that the authors consider that all patients with AF should be on warfarin (Dabigatran is probably not sufficiently mentioned in this document). Similarly, the authors seem much more concerned about inappropriate under-prescribing than they are about inappropriate over-prescribing.

Our response: We have added a sentence on the harms of OACs (especially
haemorrhage) on page 3, paragraph 2. In keeping with current guidelines, we do not consider that all patients with AF should be offered an OAC, and hope this addition clarifies this. Neither do we mean to focus solely on warfarin (or any individual OAC – although warfarin is still the most commonly used); the revised background section is now less focused on any one OAC. We have now stated in the background that we do not specify any type of OAC to be prescribed (page 4, paragraph 2) We recognise the potential harms of OAC therapy in AF but the trial intervention is designed to safely increase the level of uptake of OAC therapy in the eligible population (those whose risk of stroke justifies its consideration). Under-prescribing in this group and the resulting rate of preventable thromboembolic stroke have been identified as a serious public health problem. The majority of the population with AF should be offered an oral anticoagulant as the proportion at truly low stroke risk is less than 20% and even in the frailer patients with comorbidities (at higher risk of haemorrhage), risk of thrombo-embolic stroke usually justifies that this treatment should at least be considered and the pros and cons discussed with the patient where possible. Situations where risk of OACs genuinely outweighs benefit are in fact much less common than is generally perceived. The AURAS-AF software tool is designed to overcome this barrier to prescribing during routine care but requires rigorous testing to confirm both effectiveness and safety.

4. It would be helpful to list the clinical codes (Read or alternative) that will be used to automatically extract data on eligibility and outcomes. Similarly, it would be helpful to confirm which of the NICE eligibility criteria well coded in the GP notes – I would not expect NYHA class, LVEF and falls risk to be well coded. This may raise issues over the accuracy of the denominator for calculation of percentage of appropriate prescribing.

Our response: We have added the clinical codes as an online appendix. The reviewer is correct that some areas may be coded more or less well. The tool has a system to identify ‘suspected’ diagnoses, based on other elements of the medical records. This will hopefully overcome the reviewer’s concern. If there is a suspected diagnosis and this would make a difference to eligibility, the clinical must confirm or reject the diagnosis before they can proceed with the tool. This is now stated on page 7, paragraph 1 (using heart failure as an example) and in the appendix. To be conservative, the denominator for the primary outcome is the group that does not assume suspected but unconfirmed diagnoses, as the effectiveness of the more inclusive approach to case identification has not been confirmed. We will therefore also measure the number of patients during the study whose suspected diagnosis is confirmed. We see this as a secondary benefit of using the tool as it should result in the eligible population becoming more visible over time on the basis of their electronically recorded information.

5. It would be useful to concisely give more detail on the qualitative data collection. It would be useful and interesting to know what the investigators suspect or expect the results to be, and why, as these prior assumptions will shape the questions asked, the spontaneous additional questions used as
probes, and the interpretation of the interviews. They have already conducted a systematic review and no doubt will already have clear ideas on what to expect.

Our response: The systematic review of reminder interventions was a quantitative synthesis, but the included studies also threw considerable light on qualitative issues relevant to the current study. However, one of its conclusions was that response to such interventions is difficult to predict and may be influenced by the particular clinical area. In the case of OAC therapy in atrial fibrillation, there are many issues influencing both patient choice and clinician behaviour. Many of these have already been explored and published (for instance, concerns over haemorrhage highlighted earlier by the reviewer). In this study we are exploring more specifically the potential for a novel software tool to overcome barriers to safe OAC prescribing. This approach has not been used before in this setting and the qualitative data will therefore be very important and novel.

Similarly I suggest identifying criteria for purposive selection of patients and staff – this should probably be for maximum variability across age/gender/medical condition/ethnicity/deprivation for patient, and age/gender/practice size/locality amongst GPs. Having providers nominate patients is not ideal, although asking providers to veto the list (e.g. to eliminate dying people) is essential. It would be appropriate to nominate a specific qualitative methodology (perhaps general inductive theory or qualitative description). And it would be helpful to see the interview guides.

Our response: We will select GPs to get a spread across list size and region (page 13, paragraphs 2 and 3). We have no prior expectation of how patient characteristics will impact the experience of the tool, therefore have not chosen any maximum variability criteria for recruitment. We therefore use a convenience sampling strategy. Having the general practices identify interview patients has made the ethical application a lot more straightforward (because less researcher access of patient notes is needed). Although we acknowledge this as a slight weakness, we do not foresee too much bias – especially given that we were not employing any maximum variability criteria. We have details of the qualitative analyses on page 14, paragraph 1. We now attach the interview topic guides (Clinician and Patient) to go into the web appendix.

Discretionary revisions

6. The authors distinguish between “systematic” and “opportunistic” screening, where the first refers to sending out invite letters based on a list, and the second refers to screening in response to a reminder generated in real time when the patient attends the practice. As a suggestion, I think the that “opportunistic” is best applied to non-systematic care provided if-or-when the provider thinks of it, and what the authors describe here is more accurately termed “systematic opportunistic” screening i.e. the opportunity has been systematically planned or created.
Our response: Thank you for the suggestion – however we feel that this is not crucial to the manuscript. We feel that “systematic opportunistic” would confuse the matter, and the current dichotomy is clearer. It is also the wording approved by the Ethics committee and we would prefer therefore to keep it as it is.

7. 7.2.1.IIc As well as planning to record stroke rates after 1y, it would be also be useful to repeat remote collection of % appropriate oral anticoagulant therapy because even if the reminders are effective the literature suggests that when they are removed at 6 months the rates are likely to return to baseline.

Our response: Sorry for this being unclear, we are indeed collecting all the remotely extracted outcomes at one year. We have clarified this on page 11, paragraph 1.

8. Are the enrolled GPs likely to have a known track record of good response to research projects, or will they receive incentives or training? If not, I wish the researchers luck in getting the GP participants to complete an audit pro forma.

Our response: We specifically are not concentrating recruitment on traditional “research active” practices, but invite all potentially eligible practices in the study region – giving them equal opportunity to enrol. We have clarified this on page 6, paragraph 2. We hope that the combination of research and service support costs will remunerate practices for the time spent filling in pro forma, and that these will be completed.

9. The Control group will be given the option to use software at end of trial (presuming it is successful), but the reminders to the Intervention group are being turned off at this stage. I would have thought it reasonable to leave the intervention running for both groups.

Our response: If the intervention is successful and safe, we hope that the software supplier will make the tool a routine part of their clinical system. We equally hope that all other providers of GP systems in the UK will operationalise the tool (based on our clinical codes) into their systems. As such there is no need to guarantee that just the intervention practices will have continued use of the system. However it will require analysis of the outcome data to demonstrate benefit and confirm safety and therefore adoption is unlikely to be immediate.

10. I am unsure what role, if any, practice nurses play in the intervention. The authors repeatedly refer to “clinicians” – does this mean GPs and nurses?

Our response: Sorry for the lack of clarity. The intervention will work when either practices nurses or general practitioners are logged into the clinical system, and access the clinical records. We have clarified this on page 8, paragraph 1.

11. I presume the real-time reminders will pop up for all users, unless this is
controlled by who is logged-in to the computer. I think GPs are the primary target of the reminders but if all users will see them it may be useful to describe the intervention as including all parties; reminders to receptionists, nurses and others are likely to reinforce the effects of reminders to GPs.

Our response: Further to above, the reminders will be dependent on who is logged in, and will apply to GPs and practice nurses. We only include these as we felt it most appropriate for these two staff member groups to bring up the topic of anticoagulation with patients. We also wish to reduce the exposure of other staff members that are not in a position to act on the reminders to their appearance during their daily activities.