**Author's response to reviews**

**Title:** Trial of an educational intervention on patients' knowledge of atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT)

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**Author's response to reviews:** see over
Reviewer: Eric Smith

Reviewer’s report:
The authors describe a protocol for a randomized controlled trial of an educational intervention designed to improve adherence to warfarin therapy. The primary outcome is the amount of time with INR in the target therapeutic range (TTR). The authors are to be commended for the scientific rigor of this study using a randomized controlled design with a surrogate marker (TTR) of a useful clinical outcome (risk of thrombotic or bleeding events on warfarin). All too often, educational interventions are implemented based on face validity or before vs. after studies that could be confounded by secular trends.

My comments on the study are numerated below.

Major Compulsory Revisions
1. The protocol is sound overall, but I am concerned about the timing of INR checks post-discharge which are not pre-specified but will be determined by usual care. The authors note that clinic staff will be blinded to intervention arm, but the patients will not be. Patient complaints or comments could certainly influence the frequency and timing of INR checks. Because the timing of INR checks will be determined post-randomization there is a risk that bias could be introduced.

Consider a scenario where dietary indiscretions (e.g. spinach binge!) are similar between groups but are more likely to be reported by the better educated group. This might result in more INR checks post-spinach in the better educated group, with more frequent documentation of sub-therapeutic INR. The less educated group would have had a similar time with sub-therapeutic INR, but this would not have been detected because information on dietary indiscretion was not reported to clinic staff. This would bias the study toward a negative result.

I strongly encourage the authors to pre-specify INR checks to avoid the possibility of a biased result.

This is a very pertinent point and one that we did consider in depth when designing the study. The follow-up INR checks post-discharge will take place within the usual care setting and the frequency of these visits will be at the discretion of the OAC clinic staff, in order to maintain a naturalistic setting. This will ensure that the only difference between the two groups is whether the patient has received the educational intervention. We agree with the reviewer that it is possible that the patients receiving the educational intervention may request more frequent INR tests (due to the advice/education). However, the converse may also be true, in that those assigned to usual care may be more anxious about their treatment (due to less knowledge) and attend for more frequent INR tests. It is the practice of the clinics involved only to test more frequently if the INR is out of target range. Unfortunately patients cannot be blinded to which arm of the study they are randomised to, thus this could influence the frequency and timing of INR checks, introducing some bias. However, we will be able to measure the frequency of checks and where patients are checked outside routine monitoring, this will be highlighted [see page 11]. Patients with more frequent INR checks will be invited to an interview to investigate the reasons for the frequent INR checks in more depth.

2. The project is funded by Bayer Healthcare. Can the authors be more explicit
about their independence with regard to study design, analysis of the data, access to
the data and right to publish the results?

Bayer Healthcare has provided funding via an investigator-initiated
educational grant. The TREAT study was designed entirely by our research
team, the data will be analysed by the staff from our department and Bayer do
not have access to the data. We also hold all of the intellectual property rights
for data publication.

3. Randomization will be stratified by age. Please explain the age categories that
will be used.

Patients will be stratified by age [<70 and 70+, see addition on page 9]. These
age categories have been chosen to reduce potential bias where increasing
age is associated with poorer knowledge outcomes and an increased risk of
thromboembolic events.

4. Randomization will be stratified by specialist AF clinic vs. general cardiology
clinic. Please explain how many of each type of clinic will be involved in the trial.

There is one specialist AF clinic vs. two general cardiology clinics involved in
the trial. The specialist clinic is a large clinic receiving AF referrals from the
entire SWBH Trust, therefore providing patient numbers equal to those
provided by the general cardiology clinics [see addition, page 9].

5. Results, description of usual care: "All patients will also receive the standard
yellow book to identify that they are taking OAC therapy". Please omit the local
term "yellow book" and simply explain the information provided in the booklet as
part of usual care.

We have removed reference to the ‘yellow book’ and explained the information
provided on the booklet as the reviewer suggests. Please see the
amendments within the protocol paper [page 9].

6. How long after initiation of warfarin therapy will patients be eligible for recruitment?
It seems like the study will run entirely in the outpatient setting. Will patients started
on OAC while admitted to hospital be eligible to join the study post-discharge?

Patients will be eligible for inclusion into the study up to one month after they
have started on OAC. Patients started on OAC for AF while admitted to
hospital will be eligible to participate in the study provided that they can
complete the baseline questionnaires and attend the educational session (if
randomised to this arm) within one month of starting warfarin.

7. Please be more specific about the assumptions used for your sample size
calculation for the primary endpoint. What TTR is anticipated, and what is the
standard deviation that is assumed?* The power calculation was based on data
from a secondary analysis of TTR from the ACTIVE-W by Connolly et al
2008[page 12]. A sample size of 78 patients (based on a 20% attrition rate) in
each group will provide at least 95% power to detect a difference of 3% in the
standard deviation of the TTR of the INR, at a significance level of 0.05. It was assumed that usual care would have slightly poorer INR control than intervention (between 58-65% in usual care and 65%+ in intervention).

8. For the secondary endpoint, please specify how "increase in knowledge" (page 12) will be measured. What number will be used to compare the groups and how is it derived? An increase in knowledge will be measured by a change in score [+- or no change] from baseline. This information has now been added to page 11.

9. A discussion of the limitations of the trial protocol is warranted. There is no "perfect" trial design, of course. To my way of thinking, limitations could include: a) patients are not blinded (a necessary limitation), b) trial is powered for a surrogate outcome marker, TTR, rather than clinical outcome (although I think this is a very justifiable choice of surrogate marker), c) the results may not be generalizable to patients with cognitive impairment or with limited English ability (who were not included for valid reasons), or patients from other cultures (because educational and lifestyle interventions may be relatively culturally specific). A discussion of the study limitations has now been included [see page 13]

Minor Essential Revisions
1. Last sentence of page 7: "as part standard care" should be "as part of standard care". We have amended this as suggested.

2. Page 9: "...be obtained by the researcher telephoning and an associate researcher..." should be "...be obtained by the researcher telephoning an associate researcher...". We have amended this as suggested.

Discretionary Revisions:
1. Inclusion criteria: Patients with valvular heart disease are excluded--why? For consideration: should the study be restricted to patients with the most common target INR of 2.0-3.0? Patients with valvular heart disease have an increased risk of thromboembolic events and a different target INR. Therefore, we have restricted the study to patients with a target INR range of 2.0 to 3.0.

2. The study results, if positive, would have greater impact if the educational intervention can be applied at other sites. Do the authors have plans to disseminate knowledge of their intervention in the event of a positive result? For example, could the educational video be made available online for download? If the results are positive the educational intervention has potential for online dissemination. The intervention is not site-specific and the materials are such that they can be delivered by a range of health professionals, with suitable training [see page 13].

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer: Gregory Peterson

Reviewer’s report:
Thank you for the submission. It is interesting and well-written. My main methodological concern relates to the control (usual care) group. How will the information that is provided to these patients be controlled and standardised? This will be very difficult, especially when different hospitals are involved. How can the investigators be sure that medical (or pharmacy..or even nursing) staff will not provide more information than simply “information about their condition and the need for anticoagulant therapy only”? This seems very unlikely. For instance, I would expect (and hope) the hospital pharmacists to provide much more information than this on warfarin for a patient commencing therapy. It would be very poor practice not to do so. This issue must be addressed.

The usual care information provided is standardised by using the ‘new patient education checklist’ used in all hospitals within the South west Birmingham hospitals trust and the oral anticoagulation therapy booklet [©National Patient Safety Agency, 2007], provided to all hospitals nationwide. The OAC staff member will go through an educational checklist with each patient. This includes a basic description of the patient diagnosis, purpose of anticoagulation, factors which affect INR control and treatment side effects. This education is delivered by a specialist anticoagulation nurse within an outpatient clinic setting and not by hospital pharmacists. Whilst we cannot control patient information seeking i.e. the questions they ask within a usual care session and the information they gather independently, the standard information given is the same within all ‘general’ clinics.

Adherence /persistence with therapy should be an outcome measure. Hopefully not, but it is possible that the extra information could actually scare some patients and they might decide to cease warfarin therapy. On the other hand, it is to be hoped that persistence will increase with the educational program, if it well designed. Either way, it should certainly be measured.

We agree that adherence is a useful outcome measure; however, reliance on self-reported adherence can produce biased findings [Zeller et al, 2008]. INR is an objective measure of adherence and will highlight where patients are not adhering to treatment and lifestyle changes. Where patients choose to discontinue their warfarin treatment or have their treatment discontinued will be examined in a parallel qualitative study to examine the reasons for discontinuation via exit interviews.
Apart from the TTR, the frequency of INR testing should also be compared in the two groups.

Frequency of INR checks will be added as an outcome measure [see page 11].

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**
I declare that I have no competing interests

Reference