PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial
AUTHORS	ZERAH, Lorene; Bonnet-Zamponi, Dominique; Frappé, Paul; Hauguel-Moreau, Marie; De Rycke, Yann; Magnier, Anne-Marie; Pautas, Eric; Charles, Pierre; Collet, Jean-philippe; Dechartres, Agnes; Tubach, Florence

VERSION 1 - REVIEW

REVIEWER	Cathal Cadogan Royal College of Surgeons in Ireland, Ireland
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	This paper reports on a protocol for an evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults. It is unfortunate that the tool that is being evaluated has not yet been published as the details provided on the tool are vague. I have doubts as to nature of this study and whether it is intended as more of a pilot study than a definitive evaluation. The outcome assessments appear to be based solely on knowledge assessment through clinical vignettes with no assessment of clinical outcomes or real-life clinical practice. Overall, I think that the manuscript falls short of the standard required for publication in BMJ Open. The manuscript is difficult to follow and there are several inconsistencies. The outcomes are not clearly stated and I do not follow the reported sample size calculation. Title Title reads a little strangely: suggest rephrasing: “Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial” Abstract Overall I think the introduction could be condensed and the methods expanded on to enable a reader to have a better idea of what this study is about; I am not clear what the study involves based on the abstract at present

	Not quite clear what you mean by “implementation of risk minimization actions” and in particular “justification” of their implementation; is minimising harm/risk not one of the fundamental principles of medical care - the phrase “primum non nocere” comes to mind “latest recommendations” – this is vague I’m not clear how the study’s objective aligns with an RCT design Methods section: Sentence on randomisation does not read clearly; suggest outlining intervention and control groups more clearly; it is not clear if the tasks outlined will be completed by all participants or just those in the intervention group Study outcomes and methods of analysis have not been outlined Ethics and dissemination: is this a pilot study as opposed to a definitive RCT? Background Not a very strong opening sentence; I would not recommend starting a sentence with “because” particularly the opening sentence; would be better to discuss prevalence of conditions for which antithrombotics indicated –multimorbidity alone does not necessarily directly translate into increased demand/need for antithrombotics “Data on inappropriate AT combination prescriptions are limited to a Canadian primary care cohort” – what about studies involving assessments of appropriate prescribing using validated criteria such as STOPP/START. These have been widely applied and various tools include criteria relating to potentially inappropriate AT prescribing. It would be important to clarify this, as this is central to your study addressing a relevant gap in the literature Line 89: “In this perspective” this doesn’t read correctly; this is also a very long sentence – suggest breaking up “systematic review of international guidelines” – this is also vague The tool that you are referring to appears to be central to this study; I do not have a good sense from this paragraph of what this tool is; does it apply to all patients prescribed AT or just those with specific conditions Study objective There is a lot in this section in terms of objectives and additional forms of analysis (primary and secondary objective; subgrouping according to medical specialty, assessment of use and perceived usefulness); I find it difficult to follow – suggest condensing There also appears to be considerable overlap between your primary and secondary objectives What is a “right prescription” The objective here does not align with the abstract What is the “composite score”? What does “degree of certainty” mean? Study design What is the rationale for having the clinical vignette as the unit of analysis? Line 135 very long sentence “most prescriptions of ATs are related to neuro-cardiovascular diseases” recommend inserting a reference to back this point up “we would provide a synthesis relevant for clinicians in charge of the follow-up ” I don’t follow this

	"easy-to-use tool" – how do you know that this is the case? Is this not part of what you are setting out to assess It is unfortunate that the tool has not yet been published as it will make it more difficult for a reader to locate it; I think the tool's section heading could be outlined more clearly; it would be helpful if images of the two page tool could be included Intervention Line 158: "Selected physicians will be randomized to 2 groups by use or not of the prescription support-tool" this does not read clearly How will the tool be provided to physicians? will they receive any related training/instruction on how/when they should use the tool I don't follow what you mean by "degree of certainty with the prescription" It is not clear as to how physicians will receive the vignettes and when/how they will complete them. Do they need to be completed in one sitting? How have you come up with 3 vignettes as an adequate number? You had mentioned earlier that 30 vignettes had been developed – how will three vignettes be selected from this collection of 30? Will all physicians receive the same three vignettes Outcome Line 170: "right prescription of oral ATs" – this does not read well – the term right prescription is vague – suggest coming up with another way of phrasing "Secondary outcomes are (1) the primary outcome by" - this does not make sense to me Line 174; terminology now appears to be shifting from certainty to confidence Line 179: what do you mean by balance? Line 182; how will they comment on the usefulness of the tool? There has been no mention of a website up to now; I was under the impression that participants received links to an online survey; will participants have secure login details; this needs to be clarified and outlined earlier Line 195 the sentence on sample size is difficult to follow; you appear to be stating that you are basing your sample size on obtaining an improvement in the outcome of interest in the control group which does not make sense to me Has the number of vignettes been factored into the sample size calculation? Three vignettes seems like a very small number of vignettes to base your sample size calculation on Also, what about the fact that you have groups of physicians from different specialties? Ethics and dissemination "we will further consider wide dissemination of the support-tool among physicians and evaluate the impact of this diffusion on patients' clinical outcomes (bleeding events, ischemic events, death)" - this goes back to my earlier comment- is this more of a pilot study? Article summary: strengths and limitations of this study

	"Importance of the study: this study will evaluate a new prescription support-tool for oral antithrombotic (AT) combination. If the intervention is found to be effective, it has the potential to avoid a lot of adverse drugs events" – I am not convinced that the evaluation outlined in this protocol would generate robust evidence to support this claim of the tool reducing harm "Robust intervention development" – there is no mention of a formal methodology underpinning the tool's development; I would have expected to read details of some form of consensus validation It is not clear why a knowledge based tool was chosen; was feedback gathered from the key stakeholder (i.e. the physicians who would ultimately receive the tool) as to the key barriers and facilitators to appropriate prescribing of AT; what makes you believe that a prescription support tool was required?; was there any underpinning theoretical basis to this tool as a form of intervention

REVIEWER	Sarah A Spinler Binghamton University USA
REVIEW RETURNED	21-Sep-2018

GENERAL COMMENTS	1. Please define what "more appropriate" means on page 2, lines 51-52 in the abstract. Looking for an abosolute 5% increase in prescribing appropriateness across all scenarios. 2. Appendix 1: a) It is Cockcroft-Gault formula b) Add that the patient takes no other drugs 3. Clarify that the tool will deliver the questions based upon the prior question answer and clarify that the responder cannot go back and change their answers. 4. Clarify the method that the "guidelines" were identified and what professional organization's guidelines they were. 5. Add the guideline references. 6. Add the trial registration number.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Cathal Cadogan

Institution and Country: Royal College of Surgeons in Ireland, Ireland

Please state any competing interests or state 'None declared': None declared

This paper reports on a protocol for an evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults. It is unfortunate that the tool that is being evaluated has not yet been published, as the details provided on the tool are vague.

The full description of the prescription support-tool is included in another article (reporting the systematic review from which it resulted), under review elsewhere (still under review at the moment). Thus we cannot provide the prescription support-tool in the article submitted to BMJ Open to avoid duplicate publication. Nevertheless, in addition to the description of the prescription support-tool in the intervention paragraph that we have made more precise, we have added the tool and its explanatory guide in Appendix 2 and 3 for reviewers only (Appendix for reviewers) to allow a better understanding of the intervention assessed.

I have doubts as to nature of this study and whether it is intended as more of a pilot study than a definitive evaluation. The outcome assessments appear to be based solely on knowledge assessment through clinical vignettes with no assessment of clinical outcomes or real-life clinical practice.

This is indeed a randomized controlled study with a process outcome, not a clinical outcome. We will use clinical vignettes and not clinical outcomes or real-life clinical practice to evaluate our tool. Such an approach is considered valid to measure the quality of care. Our main hypothesis is that the prescription support-tool improves the prescription of oral AT combinations to comply with guidelines. We believe this is key to reducing the rate of adverse events; however, with this study, we will not demonstrate a decrease in haemorrhages or hospitalizations with the use of our tool. This will be the second step, but we feel that we must first demonstrate that the use of the tool is associated with better prescription appropriateness before launching a trial involving patients with clinical outcomes (ethics and dissemination paragraph: page 10, lines 11-18).

Overall, I think that the manuscript falls short of the standard required for publication in BMJ Open. The manuscript is difficult to follow and there are several inconsistencies. The outcomes are not clearly stated and I do not follow the reported sample size calculation.

We hope that with the changes made thanks to your comments, our manuscript will be clearer.

Title

Title reads a little strangely: suggest rephrasing:

“Evaluation of a prescription support-tool for chronic management of oral antithrombotic combinations in adults using clinical vignettes: protocol of a randomized controlled trial”

We took into account this comment and modified the text as proposed (page 1, lines 1-3)

Abstract

Overall I think the introduction could be condensed and the methods expanded on to enable a reader to have a better idea of what this study is about. I am not clear what the study involves based on the abstract at present.

Not quite clear what you mean by “implementation of risk minimization actions” and in particular “justification” of their implementation; is minimizing harm/risk not one of the fundamental principles of medical care - the phrase “primum non nocere” comes to mind. “Latest recommendations” – this is vague.

I’m not clear how the study’s objective aligns with an RCT design.

Methods section: Sentence on randomization does not read clearly; suggest outlining intervention and control groups more clearly; it is not clear if the tasks outlined will be completed by all participants or just those in the intervention group. Study outcomes and methods of analysis have not been outlined.

Ethics and dissemination: is this a pilot study as opposed to a definitive RCT?

We thank the reviewer for the helpful comments. We agree that this was not presented clearly enough. We have condensed the introduction and further describe the methods (study design, study setting, eligibility criteria, main objective, randomization and the analysis) that will be carried out (page 2).

This is a randomized controlled study with a process outcome. If the prescription support-tool is found to improve the prescription of oral AT combinations to comply with guidelines, we will create an interactive web tool to improve the ergonomics of the tool and to facilitate the updates and will assess its impact in terms of clinical outcomes in real life. This will be the second step, but we feel that we must first demonstrate that the use of the tool is associated with prescription appropriateness before launching a trial involving patients with clinical outcomes (ethics and dissemination paragraph: page 2 lines 22-24 and page 10, lines 11-18).

INTRODUCTION

Background

Not a very strong opening sentence; I would not recommend starting a sentence with “because” particularly the opening sentence; would be better to discuss prevalence of conditions for which antithrombotics indicated. Multimorbidity alone does not necessarily directly translate into increased demand/need for antithrombotics

We agree that this was not presented clearly enough. We changed it and added the following text: “Antithrombotic (AT) drugs, which include antiplatelet (AP) and anticoagulant (AC) therapies, are used to prevent and treat many cardiovascular disorders.[1] With the increase in prevalence of cardiovascular diseases and medical progress, these treatments are increasingly being prescribed all around the world.[1]”(page 4, lines 2 - 5)

“Data on inappropriate AT combination prescriptions are limited to a Canadian primary care cohort” – what about studies involving assessments of appropriate prescribing using validated criteria such as STOPP/START. These have been widely applied and various tools include criteria relating to potentially inappropriate AT prescribing. It would be important to clarify this, as this is central to your study addressing a relevant gap in the literature

We agree that this was not presented clearly enough. We changed it and added the following text:

- “So far, no study has evaluated the rate of prescription of AT combinations not complying with guidelines for adults, taking into account the drugs prescribed but also the dosage and duration of the prescription. Although tools assessing inappropriate prescribing, such as the Beers or STOPP/START

criteria[6,7], have a section dedicated to ATs, they mention only a few conditions for prescribing AT combinations and are relevant for older people only." (page 4, lines 12 - 17)

• "To assess the appropriateness of prescribing AT combinations (considering number of drugs, type of drugs, dosage and duration at the same time) in a French cohort of adults, we performed a systematic review of international guidelines (2012-2017) to define which AT combination is recommended, when and for how long. Guidelines dealing with oral AT combinations were numerous (n=63) and none encompassed all the clinical situations requiring oral AT combinations. This review highlighted the difficulty for a physician to quickly find the most up-to-date recommendation and the one most relevant to the patient's clinical situation. These findings agreed with clinical experience and led us to synthesize all the recommendations into a prescription support-tool (article under review elsewhere) to help physicians prescribe oral AT combinations (page 4 lines 22-25 and page 5 lines 1-8)

Line 89: "In this perspective" this doesn't read correctly; this is also a very long sentence – suggest breaking up. "Systematic review of international guidelines" – this is also vague

The tool that you are referring to appears to be central to this study; I do not have a good sense from this paragraph of what this tool is; does it apply to all patients prescribed AT or just those with specific conditions

It is true that there is only a succinct description of the tool in the introduction, but a more precise description of the tool appears now in the intervention paragraph. Moreover, we included the tool and its explanatory guide in Appendix 2 and 3 for reviewers only. Actually we cannot provide the tool in this article because the systematic review of guidelines and the tool are under review elsewhere (and we want to avoid duplicate publication). This tool applies to all adults, with the exclusion of clinical situations requiring inevitably the advice of specialists: active cancer, autoimmune diseases, haemophilia, HIV, paediatrics and pregnancy.

Study objective

There is a lot in this section in terms of objectives and additional forms of analysis (primary and secondary objective; subgrouping according to medical specialty, assessment of use and perceived usefulness); I find it difficult to follow – suggest condensing

There also appears to be considerable overlap between your primary and secondary objectives

What is a "right prescription". The objective here does not align with the abstract. What is the "composite score"?. What does "degree of certainty" mean?

We thank the reviewer for the helpful comments. We agree that this was not presented clearly enough. Composite score and degree of certainty were not appropriate terms. We have modified and just cited the primary objective (page 5, lines 9-12).

METHODS AND ANALYSIS

Study design

What is the rationale for having the clinical vignette as the unit of analysis?

The primary outcome is the appropriate prescription of ATs, which is measured for each clinical vignette. Therefore, the unit of analysis is the clinical vignette (page 6, lines 21-22).

Line 135 very long sentence, “most prescriptions of ATs are related to neuro-cardiovascular diseases” recommend inserting a reference to back this point up. “We would provide a synthesis relevant for clinicians in charge of the follow-up ” I don’t follow this

We took into account this comment, modified the text that now appears in the intervention paragraph and added a reference ([1]) (page 7 lines 12-17 and 22-25)..

“Easy-to-use tool” – how do you know that this is the case? Is this not part of what you are setting out to assess.

This is true. We removed that term.

It is unfortunate that the tool has not yet been published as it will make it more difficult for a reader to locate it; I think the tool’s section heading could be outlined more clearly; it would be helpful if images of the two page tool could be included

It is true that there is only a succinct description of the tool in the introduction, but a more precise description of the tool appears now in the intervention paragraph. Moreover, we included the tool and its explanatory guide in Appendix 2 and 3 for reviewers only. Actually we cannot provide the tool in this article because the systematic review of guidelines and the tool are under review elsewhere (and we want to avoid duplicate publication).

Intervention

Line 158: “Selected physicians will be randomized to 2 groups by use or not of the prescription support-tool” this does not read clearly

How will the tool be provided to physicians?

Will they receive any related training/instruction on how/when they should use the tool?

It is not clear as to how physicians will receive the vignettes and when/how they will complete them.

Do they need to be completed in one sitting?

You had mentioned earlier that 30 vignettes had been developed – how will three vignettes be selected from this collection of 30?

How have you come up with 3 vignettes as an adequate number?

Will all physicians receive the same three vignettes?

We thank the reviewer for the helpful comments. We agree that this was not presented clearly enough. The paragraph on the intervention now describes the tool (intervention paragraph). A more precise description of the study, formerly the intervention paragraph, is now in the first paragraph of the methods and analysis named “Study design, study setting and eligibility criteria”.

Outcome

Line 170: “right prescription of oral ATs” – this does not read well – the term right prescription is vague – suggest coming up with another way of phrasing.

“Secondary outcomes are (1) the primary outcome by” - this does not make sense to me.

Line 174; terminology now appears to be shifting from certainty to confidence.

We took into account these comments and modified the text (page 7, lines 1-10)

Randomization

Line 179: what do you mean by balance?

We thank the reviewer and we agree that this was not presented clearly enough. This term was removed, and we have rewritten this paragraph (page 8, lines 22-25).

Line 182; how will they comment on the usefulness of the tool?

The questions to evaluate the usefulness of the tool are detailed at the end of the clinical vignette (appendix 4). This sentence is now in the outcomes paragraph (page 7, lines 9-10).

Data collection methods and data management

There has been no mention of a website up to now; I was under the impression that participants received links to an online survey; will participants have secure login details; this needs to be clarified and outlined earlier

We thank the reviewer for this helpful comment. We agree that this was not presented clearly enough. This is an online survey and we added this term in our article (page 2 line 9 and 15, page 5 line 17 and 20, page 8 line 24), Moreover, there will be no login for participants (page 9, line 4)

Sample size and statistical considerations

Line 195 the sentence on sample size is difficult to follow; you appear to be stating that you are basing your sample size on obtaining an improvement in the outcome of interest in the control group which does not make sense to me

We took into account these comments and modified the text (page 9, lines 17 - 9).

Has the number of vignettes been factored into the sample size calculation? Three vignettes seems like a very small number of vignettes to base your sample size calculation on

Yes it was. “Three clinical vignettes per physician was a middle ground to ensure the feasibility of the study considering both participants’ availability (acceptable time to complete answers for the clinical vignettes) and statistical need (number of vignettes needed)” (page 6, lines 22 - 25). Because each involved physician should complete 3 vignettes, this intra-physician correlation will be taken into account in the analysis (page 9, lines 13-14).

Also, what about the fact that you have groups of physicians from different specialties?

Our main objective, on which our sample size is based, includes all physicians whatever their specialty. Then, we stratified by whether the physician is a general practitioner or a cardiologist.

Ethics and dissemination

“we will further consider wide dissemination of the support-tool among physicians and evaluate the impact of this diffusion on patients’ clinical outcomes (bleeding events, ischemic events, death)” - this goes back to my earlier comment- is this more of a pilot study?

This is indeed a randomized controlled study with a process outcome, not a clinical outcome. We will use clinical vignettes and not clinical outcomes or real-life clinical practice to evaluate our tool. Such an approach is considered valid to measure the quality of care. Our main hypothesis is that the prescription support-tool improves the prescription of oral AT combinations to comply with guidelines. We believe this is key to reducing the rate of adverse events; however, with this study, we will not demonstrate a decrease in haemorrhages or hospitalizations with the tool. This will be the second step, but we feel that we must first demonstrate that the use of the tool is associated with better prescription appropriateness before launching a trial involving patients with clinical outcomes (ethics and dissemination paragraph: page 10, lines 11-18).

Article summary: strengths and limitations of this study

“Importance of the study: this study will evaluate a new prescription support-tool for oral antithrombotic (AT) combination. If the intervention is found to be effective, it has the potential to avoid a lot of adverse drugs events” – I am not convinced that the evaluation outlined in this protocol would generate robust evidence to support this claim of the tool reducing harm

This sentence was removed because the editor asked for 5 bullet points that relate specifically to the methods.

“Robust intervention development” – there is no mention of a formal methodology underpinning the tool’s development; I would have expected to read details of some form of consensus validation.

This sentence was removed. The full description of the prescription support-tool is included in another article (reporting the systematic review from which it is issued) that is under review elsewhere (still under review at the moment).

It is not clear why a knowledge based tool was chosen; was feedback gathered from the key stakeholder (i.e. the physicians who would ultimately receive the tool) as to the key barriers and facilitators to appropriate prescribing of AT; what makes you believe that a prescription support tool was required?; was there any underpinning theoretical basis to this tool as a form of intervention

Thanks to our experience and the results of the systematic review, we truly believe that it is particularly difficult for a physician to rapidly find the most up-to-date guidelines about ATs that are relevant for the patient’s clinical situation (page 5 lines 2-8).

To create our tool, an external committee of 14 physicians was set up to assess the layout and the usefulness of this prescription support-tool. Most physicians in the external committee (10/14, 71.4%) were not at all or not really comfortable with the chronic management of oral AT combinations and reported being scared about these prescriptions (11/14, 78.6% totally or moderately agreed with “the prescription of oral AT combinations scares me”). Few declared knowing perfectly where to find the most recent guidelines about chronic management of oral AT combinations (3/14, 21.4%). Overall, the tool was found useful for clinical practice (mean score 9.1 on a 0-10 scale). Many physicians were ready to use it (mean score 9.4 on a 0-10 scale) and to recommend its use (mean score 9.2 on a 0-10 scale). These results are included in another article under review elsewhere (still under review at the moment) and thus cannot be reported here to avoid duplicate publication.

Reviewer: 2

Reviewer Name: Sarah A Spinler

Institution and Country: Binghamton University USA

Please state any competing interests or state ‘None declared’: None

1. Please define what "more appropriate" means on page 2, lines 51-52 in the abstract.

We removed the term “more appropriate” and replaced it with “more prescriptions of ATs to comply with guidelines” (page 2, lines 22-24).

2. Looking for an absolute 5% increase in prescribing appropriateness across all scenarios.

Actually, our goal is to show an overall increase of 5% in AT prescribing appropriateness across all scenarios.

3. Appendix 1: a) It is Cockcroft-Gault formula b) Add that the patient takes no other drugs

It was added and it is now appendix 4.

4. Clarify that the tool will deliver the questions based upon the prior question answer and clarify that the responder cannot go back and change their answers.

We thank the reviewer for the helpful comments and we added this sentence: “Once the answer is given, physicians cannot go back or change their answer. Physicians must answer the questions consecutively; however, they will be allowed to stop and continue at any time (on the same computer).” (page 6, lines 11-13)

5. Clarify the method that the "guidelines" were identified and what professional organization's guidelines they were. Add the guideline references.

We identified international guidelines published between 2012 and 2017 about non-valvular atrial fibrillation, coronary artery disease, ischemic stroke, valvular heart disease, peripheral artery disease, venous thromboembolism and antithrombotics. We have added the guidelines references in Appendix 1 for reviewers only. Because the full description of the guidelines is under review elsewhere, we cannot provide a more detailed method of selecting the guidelines to avoid duplicate publication.

6. Add the trial registration number.

The trial registration number of our study (ClinicalTrials.gov ID: NCT03630874) has been included at the end of our abstract (page 2, line 25 and page 11 line 16).

VERSION 2 – REVIEW

REVIEWER	Sarah Spinler Binghamton University and University of the Sciences, USA
REVIEW RETURNED	15-Dec-2018

GENERAL COMMENTS	This study design paper describes a survey designed to compare antithrombotic therapy prescribing appropriateness using a decision support tool.

	1. The exact statistical tests used to compare the percentages of "appropriate" prescribing should be identified. 2. Unfortunately the use of combination antiplatelet and anticoagulant prescribing is rapidly changing. There are several important guidelines which have just been published. The authors should identify how publication of these guidelines would change the author-identified "appropriate" response to the vignette prescribing. a) 2018 CHEST Guidelines on Antithrombotic Therapy for Atrial Fibrillation: https://journal.chestnet.org/article/S0012-3692(18)32244-X/fulltext b) 2018 ASH Guidelines on Management of Venous Thromboembolism. http://www.bloodadvances.org/content/2/22/3257 c) https://www.ncbi.nlm.nih.gov/pubmed/27803042 d) 2018 Early Management of Stroke Guidelines: https://www.ahajournals.org/doi/abs/10.1161/str.0000000000000158 3. There were three major publications pertaining to the appropriateness of aspirin prescribed for primary prevention of stroke/MI that have been published that may influence prescribing practices in favor of appropriate nonuse of aspirin (ASPREE, ASCEND, ARRIVE) that would be in conflict with the guidelines listed in the APPENDIX. How will the authors deal with these?

REVIEWER	Bethan Copsey University of Oxford, UK
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	This is a well-written protocol and the authors do well in acknowledging the potential limitations of the trial. I have some suggestions on how to improve the manuscript: 1. The statistical analysis planned for the primary outcome is very clear. For the secondary outcomes, please make it clear whether the same methods of analysis will be used. 2. In addition, please give more detail on how confidence and utility will be measured. 3. The outcomes section seems to suggest that subgroup analysis will be performed by specialty. Please make this clearer in the statistical analysis section. Will this be using interaction terms or sub-sample analyses? Which categories will be used for specialty? 4. Why is the information on the support tool in Appendix 2 and 3 only available for reviewers? Surely this is a key part of the protocol to help with implementation.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Sarah A Spinler

Institution and Country: Binghamton University USA

Please state any competing interests or state ‘None declared’: None

This study design paper describes a survey designed to compare antithrombotic therapy prescribing appropriateness using a decision support tool.

We thank the reviewer 2 for these helpful comments.

1. The exact statistical tests used to compare the percentages of "appropriate" prescribing should be identified.

We thank the reviewer for this comment. The method used to compare the percentages of “appropriate” prescribing may have been insufficiently explicit. We have therefore specified it in the statistical paragraph (page 9 lines 208 - 216).

“For each clinical vignette, we will consider that prescription is fully appropriate (versus inappropriate) if answers to each of the first four questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To compare the percentage of fully appropriate prescriptions between the two randomized arms, taking into account that each participant intends to complete 3 clinical vignettes, we will use a logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. We will use the same method to compare the percentage of prescriptions of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately, between the two randomized arms (secondary analyses).”

2. Unfortunately the use of combination antiplatelet and anticoagulant prescribing is rapidly changing. There are several important guidelines, which have just been published. The authors should identify how publication of these guidelines would change the author-identified "appropriate" response to the vignette prescribing.

a) 2018 CHEST Guidelines on Antithrombotic Therapy for Atrial Fibrillation

b) 2018 ASH Guidelines on Management of Venous Thromboembolism: http://www.bloodadvances.org/content/2/22/3257

c) https://www.ncbi.nlm.nih.gov/pubmed/27803042

d) 2018 Early Management of Stroke Guidelines: https://www.ahajournals.org/doi/abs/10.1161/str.0000000000000158

Indeed, the use of combination of oral ATs is rapidly changing. The systematic review of guidelines we have done[9], leading to the development of the prescription support-tool, demonstrated the multiplicity of guidelines dealing with oral AT combinations (n=70 within 5 years).

Since our first submission of this protocol (July 2018), we made an update of our systematic review of guidelines in November 2018 to include all new guidelines published in 2018.[9] We included (as you mentioned): “2018 CHEST Guidelines on Antithrombotic Therapy for Atrial Fibrillation” and “2018 Early Management of Stroke Guidelines”. Nevertheless, there was no change in prescriptions of oral ATs following the publication of these guidelines. We did not select “2018 ASH Guidelines on Management of Venous Thromboembolism” because it was only about management of anticoagulant and one of our exclusion criteria was: “guidelines that focus only on management of treatment”. We did not select “Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A North American Perspective-2016 Update » because it was

not a guideline (exclusion criteria: “Articles other than guidelines: meta-analysis, literature review, advisory, statement, randomized trials, observational studies”).

Since our first submission of this protocol (July 2018), and as it was planned in the first manuscript and revised manuscript, we have started the inclusions in November 2018, which ended on the 02.14.2019 (needed sample size included) just before the publication of our review and the tool[9] (avoiding a possible contamination bias). During this inclusion period, there was no new guideline modifying oral AT prescription strategy. Therefore, we will be able to conclude to the usefulness (or not) of the tool over the period November 2018 - February 2019. If the prescription support-tool is associated with improving the prescription of oral ATs to comply with guidelines, we will create an interactive web tool to improve the ergonomics of the tool and to facilitate updates (page 11 lines 244 - 251).

3. There were three major publications pertaining to the appropriateness of aspirin prescribed for primary prevention of stroke/MI that have been published that may influence prescribing practices in favor of appropriate nonuse of aspirin (ASPREE, ASCEND, ARRIVE) that would be in conflict with the guidelines listed in the APPENDIX. How will the authors deal with these?

Our tool synthesizes prescriptions of oral ATs (monotherapy or combinations) for secondary prevention only. All clinical cases illustrate secondary prevention situations. We have re-clarified this point in the protocol (page 7 line 166; page 8 lines 189 - 190).

Reviewer: 3

Reviewer Name: Bethan Copsey

Institution and Country: University of Oxford, UK

Please state any competing interests or state ‘None declared’: None declared

This is a well-written protocol and the authors do well in acknowledging the potential limitations of the trial. I have some suggestions on how to improve the manuscript:

1. The statistical analysis planned for the primary outcome is very clear. For the secondary outcomes, please make it clear whether the same methods of analysis will be used.

2. In addition, please give more detail on how confidence and utility will be measured.

3. The outcomes section seems to suggest that subgroup analysis will be performed by specialty. Please make this clearer in the statistical analysis section. Will this be using interaction terms or sub-sample analyses? Which categories will be used for specialty?

We thank the reviewer 3 for these helpful comments.

- We have added a description on how confidence (page 6, lines 125 – 127) and how utility (pages 6, lines 128 – 131) will be measured (on a scale of 0 to 10)

- We have precised specialties for the subgroup analysis (cardiologist and general practitioner) (page 10 lines 220 – 221)

• We have developed the statistical paragraph as follow to respond to comments from the reviewer (pages 9 – 10, lines 208 – 223):

o "For each clinical vignette, we will consider that prescription is fully appropriate (versus inappropriate) if answers to each of the first four questions (number of drugs, drug class, dosage and duration) comply with the guidelines. To compare the percentage of fully appropriate prescriptions between the two randomized arms, taking into account that each participant intends to complete 3 clinical vignettes, we will use a logistic mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. We will use the same method to compare the percentage of prescriptions of oral ATs that comply with guidelines in terms of number of drugs, drug class, duration and dosage, each assessed separately, between the two randomized arms (secondary analyses). To compare the degree of confidence that physicians have that their prescription of oral AT combinations complies with guidelines (quantitative variable: scale from 0 and 10), taking into account that each participant intends to complete 3 clinical vignettes, we will use a linear mixed model with a clinical-vignette effect and a physician-effect nested in the trial arm. A sub-group analysis for general practitioners and for cardiologist will be done. Finally, to assess the overall usefulness of the tool, we will describe the data of the experimental arm (mean ± SD, median (25–75 interquartile range))."

4. Why is the information on the support tool in Appendix 2 and 3 only available for reviewers? Surely this is a key part of the protocol to help with implementation.

When we submitted this protocol for the first time to BMJ Open (July 2018), the article reporting the systematic review and the development of the tool was under review at Plos One. To avoid duplicate publication, the prescription support-tool and its explanatory guide were in Appendix only available for reviewers in the article on the protocol submitted to BMJ Open. Since then, our systematic review has been published in Plos One with the prescription support-tool and its explanatory guide. In accordance with the editor of Plos One, the prescription-support tool is now provided also in the article submitted to BMJ Open, in Figure 1, with its explanatory guide (Appendix 1).

VERSION 3 - REVIEW

REVIEWER	Sarah A Spinler Binghamton University, USA
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	1. I am not sure I was able to view the actual vignettes with the prior draft. Per the authors response to my comment, they indicated that these guidelines pertain to "secondary prevention" only. So technically as defined in the US, this is not exactly true. If I see that Example one is antithrombotic therapy for TAVR. Technically that is prevention of stroke and not secondary prevention of stroke. In Example three the antithrombotic therapy is for stroke prevention in AF not secondary prevention of stroke. So this is not primary prevention of CVD in patients with NO other CVDs but it is not secondary prevention. So I think somewhere in the introduction/methods, the authors need to indicate exactly what scenarios are covered and refer to the figures. It would be less ambiguous that way. So the tool covers prevention of ischemic events in patients with a history of ACS, PAD, stroke/TIA, TAVR, or mechanical heart valve.

	Would add that to the background. It does not cover primary prevention in other scenarios such as patients without those conditions but at low or high-risk for ischemic events.

REVIEWER	Bethan Copsey University of Oxford, UK
REVIEW RETURNED	28-Mar-2019

GENERAL COMMENTS	Thank you for responding to the comments in a clear and comprehensive manner. I am satisfied with the responses and suggest that the manuscript is acceptable for publication in its current form.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Sarah A Spinler

Institution and Country: Binghamton University USA

Please state any competing interests or state ‘None declared’: None

I am not sure I was able to view the actual vignettes with the prior draft.

Per the authors response to my comment, they indicated that these guidelines pertain to "secondary prevention" only. So technically as defined in the US, this is not exactly true. If I see that Example one is antithrombotic therapy for TAVR. Technically that is prevention of stroke and not secondary prevention of stroke. In Example three the antithrombotic therapy is for stroke prevention in AF not secondary prevention of stroke. So, this is not primary prevention of CVD in patients with NO other CVDs but it is not secondary prevention. So I think somewhere in the introduction/methods, the authors need to indicate exactly what scenarios are covered and refer to the figures. It would be less ambiguous that way. So the tool covers prevention of ischemic events in patients with a history of ACS, PAD, stroke/TIA, TAVR, or mechanical heart valve. Would add that to the background. It does not cover primary prevention in other scenarios such as patients without those conditions but at low or high-risk for ischemic events.

We thank the reviewer 2 for this helpful comment. We added this sentence in the paragraph intervention: page 8 (methods and analysis section):

“Therefore, this tool covers prevention of ischemic and /or embolic events in patients with a history of coronary disease (stable coronary disease or acute coronary syndrome), non-valvular atrial fibrillation, peripheral artery disease, venous thromboembolism disease, ischemic stroke (and transient ischemic attack) and/or valvular heart disease (bioprosthesis, mechanical valve and transcatheter aortic valve replacement). It does not cover primary prevention in other scenarios such as patients without those conditions but at low or high-risk for ischemic events (Figure 1).[9]”

Reviewer: 3

Reviewer Name: Bethan Copsey

Institution and Country: University of Oxford, UK

Please state any competing interests or state ‘None declared’: None declared

Thank you for responding to the comments in a clear and comprehensive manner. I am satisfied with the responses and suggest that the manuscript is acceptable for publication in its current form.

We thank the reviewer 3 for this comment.