PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Economic evaluation of a shortened standardised treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistance tuberculosis (STREAM): Study protocol
AUTHORS	Gama, Elvis; Madan, Jason; Langley, Ivor; Girma, Mamo; Evans, Denise; Rosen, Sydney; Squire, Bertie

VERSION 1 - REVIEW

REVIEWER	Dr. Roland Diel Institute of Epidemiology, University Hospital Schleswig-Holstein, Campus Kiel, Germany
REVIEW RETURNED	08-Apr-2016

GENERAL COMMENTS	The submitted study protocol is well written and the structure convincing. I have only very few comments: Page 3, line 41: „There is also the potential for increased adverse events in the shortened regimen, which have cost implications." I am not sure whether I am understanding the sentence correctly: Why are the adverse events "increased" compared to the long-term regime recommended by the WHO? Please clarify! Page 8, line 21: "Costs that are incurred over more than one year will be discounted at the rate of 3% per annum" Please clarify which costs are expected to incur over more than 1 year? Page 9, line 3: How will sensitivity analyses be performed? Please provide some information on the intented methodology, e.g. using the lower and upper bound of confidence intervals etc.

REVIEWER	Tom Hwang Harvard University, USA
REVIEW RETURNED	24-Apr-2016

GENERAL COMMENTS	The authors provide a protocol for a cost/economic evaluation of a shortened treatment regimen (or the Bangladesh regimen) for the treatment of MDR-TB. The clinical protocol for the RCT of this regimen (the STREAM trial) was separately reported (Nunn AJ, et al. Trials 2014;15:353). The study objectives, design, and primary outcome measures are well described and seem sensible. When the study is completed, I believe the results will prove valuable to policymakers, national TB programs, clinicians, and patients.

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	I have only minor comments on this protocol: 1) The authors state that the economic evaluation will only occur in 2 of the 4 countries enrolling patients in the STREAM trial. The reader would benefit from a brief explanation of why this was done, and the potential limited generalizability of subsequent estimates (although these are high-burden countries). In the manuscript (not necessary for this protocol), some discussion of how treatment costs are shared (mostly public health system? or private?) in these countries would be helpful 2) Please provide the survey instrument as an appendix with this protocol. 3) The cost survey will be conducted at baseline and then at subsequent 3 month intervals. The authors may wish to explain how that timing was chosen (paralleling treatment follow-up? convenience?). Can costs reasonably and reliably be assessed with surveys administered 3 months apart? Minor comments: 4) Some odd spacing issues throughout the manuscript. Please remove double/triple/extraneous spaces 5) Some capitalization issues in the Abstract should be corrected. 6) An additional reference for Clofazimine costs and availability is: BMJ Open 2014;4:e004143.

REVIEWER	Janna Manjelievskaia Department of Health Policy and Public Health University of the Sciences in Philadelphia United States
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	The authors tackle a very relevant and important issue: whether a new, shorter MDR-TB drug regimen can be more cost effective as compared to the current WHO standard regimen. The methodology is sound. Data analysis uses an innovative approach. My only question is why are they authors choosing to conduct an economic evaluation in 2/4 trial sites (only Ethiopia and SA), while economic data will be collected from all sites. They could perhaps expand upon their rationale for choosing to do so.

REVIEWER	Matthias Arnold Ludwig-Maximilians-University Munich (LMU), Germany
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	Overall, I think the topic you are addressing is very important and your research design is suitable to create new insights. However, the study protocol does have gaps in many important aspects. Major compulsory revision 1) You do address that non-participation might be a problem. At the moment, you only indicate that you are aware of it, but you do not offer any solution to avoid bias. A potential bias could be that patient cost is too high for some of the participants and they either drop out

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	within the trial or they decide to not participate. While checking missing data for bias is helpful to identify problem, you could put in measure to avoid bias. You should think about collecting additional information about the reasons for non-participation and drop out. 2) Tuberculosis and especially MDRTB may come with co-morbidity. Co-morbidities can affect the MDRTB treatment effects and treatment cost. While your sampling mechanism should theoretically ensure that levels of co-morbidities are similar in intervention and controls, you still need to check that this is actually the case. I suggest including health status information to ensure comparability of intervention and control patients. 3) Economic evaluations require a comparison of cost and treatment effects. While you provide detailed descriptions about how you plan to measure treatment cost, you do not describe the effect side. Will you be using a cost-effectiveness or cost-utility approach? What are your primary treatment outcomes? Minor revisions 1) Patient time costing: It is not perfectly clear how you assess productivity loss in patients and caregivers. Do you collect employment information from both patients and care-givers or only from patients? Do you use human capital costing or a friction-based costing scheme? 2) Study description: You mention that you aim at including two facilities per, one secondary and one tertiary with one of them urban and one rural. How are the selected facilities representing these categories? 3) Adverse events: you should provide a clear description which adverse events you track. 4) You suggest to estimate staff cost on the basis of time spent with patient by conducting interviews. This might lead to different time estimations than time estimates from independent observers as used in most time motion studies. 5) You suggest using a discrete event simulation which was initially designed to assess the cost-effectiveness of diagnostic TB tests in Tanzania. You should describe your motivation to use exactly this model, despite the differences in context, and what steps you plan to take to validate the model in your context.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Dr. Roland Diel
Institution and Country: Institute of Epidemiology, University Hospital Schleswig-Holstein, Campus Kiel, Germany Competing Interests: None declared

The submitted study protocol is well written and the structure convincing. I have only very few comments:

Page 3, line 41: „There is also the potential for increased adverse events in the shortened regimen, which have cost implications."
I am not sure whether I am understanding the sentence correctly: Why are the adverse events "increased" compared to the long-term regime recommended by the WHO? Please clarify!
We are not certain that there are increased adverse events in the proposed regimes, we are just pointing out that, just like any clinical trial (New treatment) there might be increased adverse events. This will however be established at the end of the trial.

Page 8, line 21: "Costs that are incurred over more than one year will be discounted at the rate of 3% per annum" Please clarify which costs are expected to incur over more than 1 year?
Diagnostic equipment e.g Electrocardiogram (ECG)

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Page 9, line 3: How will sensitivity analyses be performed? Please provide some information on the intented methodology, e.g. using the lower and upper bound of confidence intervals etc.
Uncertainty in the estimated costs due to uncertainty to cost input parameter values will be evaluated by employing probalistic sensitivity analysis using the lower and upper bound of confidence intervals.

Reviewer: 2
Reviewer Name: Tom Hwang
Institution and Country: Harvard University, USA Competing Interests: None declared.

The authors provide a protocol for a cost/economic evaluation of a shortened treatment regimen (or the Bangladesh regimen) for the treatment of MDR-TB. The clinical protocol for the RCT of this regimen (the STREAM trial) was separately reported (Nunn AJ, et al. Trials 2014;15:353).

The study objectives, design, and primary outcome measures are well described and seem sensible. When the study is completed, I believe the results will prove valuable to policymakers, national TB programs, clinicians, and patients.

I have only minor comments on this protocol:

1) The authors state that the economic evaluation will only occur in 2 of the 4 countries enrolling patients in the STREAM trial. The reader would benefit from a brief explanation of why this was done, and the potential limited generalizability of subsequent estimates (although these are high-burden countries). In the manuscript (not necessary for this protocol), some discussion of how treatment costs are shared (mostly public health system? or private?) in these countries would be helpful.
The economic evaluation will only occur in 2 countries due to lengthy research clearance and regulatory procedures in the other 2 countries. While we recognise the potential limitation in the generalizability of the subsequent estimates, the results will provide evidence on the resources and costs related to treatment and management of MDR-TB patients using the short regimen as compared to the WHO MDR-TB treatment regimen in many low income settings similar to Ethiopia and South Africa.

2) Please provide the survey instrument as an appendix with this protocol.
The tool has been provided
3) The cost survey will be conducted at baseline and then at subsequent 3 month intervals. The authors may wish to explain how that timing was chosen (paralleling treatment follow-up? convenience?). Can costs reasonably and reliably be assessed with surveys administered 3 months apart?
The choice of three month interval is due to paralleling data collection with treatment follow-up. Cost data is will be collected every three months, the assessment of cost will take place at the end of the survey.

Minor comments:
4) Some odd spacing issues throughout the manuscript. Please remove double/triple/extraneous spaces – This has been corrected .
5) Some capitalization issues in the Abstract should be corrected.
This has been corrected .
6) An additional reference for Clofazimine costs and availability is: BMJ Open 2014;4:e004143.
This is a very good paper

Reviewer: 3
Reviewer Name: Janna Manjelievskaia
Institution and Country: Department of Health Policy and Public Health, University of the Sciences in Philadelphia, United States Competing Interests: None declared

The authors tackle a very relevant and important issue: whether a new, shorter MDR-TB drug regimen can be more cost effective as compared to the current WHO standard regimen.

The methodology is sound. Data analysis uses an innovative approach.

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My only question is why are they authors choosing to conduct an economic evaluation in 2/4 trial sites (only Ethiopia and SA), while economic data will be collected from all sites. They could perhaps expand upon their rationale for choosing to do so.
The economic evaluation will only occur in 2 countries due to lengthy research clearance and regulatory procedures in the other 2 countries. While we recognise the potential limitation in the generalizability of the subsequent estimates, the results will provide evidence on the resources and costs related to treatment and management of MDR-TB patients using the short regimen as compared to the WHO MDR-TB treatment regimen in many low income settings similar to Ethiopia and South Africa.

Reviewer: 4
Reviewer Name: Matthias Arnold
Institution and Country: Ludwig-Maximilians-University Munich (LMU), Germany Competing Interests: None declared

Overall, I think the topic you are addressing is very important and your research design is suitable to create new insights. However, the study protocol does have gaps in many important aspects.

Major compulsory revision
1) You do address that non-participation might be a problem. At the moment, you only indicate that you are aware of it, but you do not offer any solution to avoid bias. A potential bias could be that patient cost is too high for some of the participants and they either drop out within the trial or they decide to not participate. While checking missing data for bias is helpful to identify problem, you could put in measure to avoid bias. You should think about collecting additional information about the reasons for non-participation and drop out.
In the trial all necessary measures to reduce or avoid drop out due to patient costs have been put in place. These measures include providing financial support to cater for food, accommodation and transport.

2) Tuberculosis and especially MDRTB may come with co-morbidity. Co-morbidities can affect the MDRTB treatment effects and treatment cost. While your sampling mechanism should theoretically ensure that levels of co-morbidities are similar in intervention and controls, you still need to check that this is actually the case. I suggest including health status information to ensure comparability of intervention and control patients.
To ensure comparability of the two arms, we will use EQ5D-5L to capture health status information

3) Economic evaluations require a comparison of cost and treatment effects. While you provide detailed descriptions about how you plan to measure treatment cost, you do not describe the effect side. Will you be using a cost-effectiveness or cost-utility approach? What are your primary treatment outcomes?
This economic evaluation is being conducted alongside a clinical trial as such all the effect side have been fully documented in the trial protocol (Main Protocol) (13). The cost side is less covered in the trial/main protocol hence the emphasis on cost in this protocol.

Minor revisions
1) Patient time costing: It is not perfectly clear how you assess productivity loss in patients and caregivers. Do you collect employment information from both patients and care-givers or only from patients? Do you use human capital costing or a friction-based costing scheme?
Since the economic evaluation will be conducted in two countries, we will cost the paid work loss by converting self-reported income into USA dollar in 2015 using purchasing price parities obtained from World Bank. For unpaid work productivity loss, we will use the 2015 minimum hourly earnings reported by government in each country.

2) Study description: You mention that you aim at including two facilities per, one secondary and one tertiary with one of them urban and one rural. How are the selected facilities representing these categories?
3) Adverse events: you should provide a clear description which adverse events you track.
Adverse events resulting in hospitalisation

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4) You suggest to estimate staff cost on the basis of time spent with patient by conducting interviews. This might lead to different time estimations than time estimates from independent observers as used in most time motion studies.

Time motion studies included in the text

5) You suggest using a discrete event simulation which was initially designed to assess the cost-effectiveness of diagnostic TB tests in Tanzania. You should describe your motivation to use exactly this model, despite the differences in context, and what steps you plan to take to validate the model in your context.

The motivation for using a similar model is based in the similarity of disease under study and in our view the country contexts.

VERSION 2 – REVIEW

REVIEWER	Tom Hwang Harvard University, USA
REVIEW RETURNED	22-Jun-2016

GENERAL COMMENTS	I would urge the authors / editors to ensure that the full survey instrument is uploaded alongside this protocol (I was not able to access it during this review).

REVIEWER	Matthias Arnold Ludwig-Maximilians-University Munich (LMU), Germany
REVIEW RETURNED	24-Jun-2016

GENERAL COMMENTS	Thank you for addressing all comments and clarifying all aspects. I only have one minor point for revision. I understood that you do not describe the effect side, because another study protocol describes this. I think you should clarify on page 4, line 5 that you focus on the costing methodology of the economic evaluation, while the effects are described elsewhere.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

I would urge the authors / editors to ensure that the full survey instrument is uploaded alongside this protocol (I was not able to access it during this review).

Full survey instruments are now uploaded alongside the protocol

Reviewer: 2

I understood that you do not describe the effect side, because another study protocol describes this. I think you should clarify on page 4, line 5 that you focus on the costing methodology of the economic evaluation, while the effects are described elsewhere.

This has been clarified in the highlighted text

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