PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Protocol for estimating direct medical costs of Type 2 diabetes mellitus in the Philippines |
|---------------------|----------------------------------------------------------------------------------------|
| AUTHORS             | Ng, Junice; Clement, Ivan John; Jimeno, Cecilia; Sy, Rosa; Mirasol, Roberto; De La Pena, Pepito; Panelo, Araceli; Tan, Rima; Santillan, Melanie; Bayani, Dana; Wiebols, Erik |

VERSION 1 – REVIEW

| REVIEWER            | Rachelle Louise Cutler Graduate School of Health; University of Technology Sydney, Sydney, Australia |
| REVIEW RETURNED     | 20-Dec-2018 |

GENERAL COMMENTS

1. Greater exploration of the economic impact of diabetes on a worldwide scale may be beneficial to set the scene, in addition to it being a national problem.

2. Need to be more specific about what guidelines, recommendations etc. have informed the decisions to run the trial in this particular way.

3. Introduction:
   - need to link more clearly the burden of complications to the cost implication on the health care system.
   - streamlining of terminology would be beneficial. Are components costs?
   - health care and financing of health care may be explored as different concepts, be careful grouping them together.

4. Methods and analysis
   - Overall methodology is quite sound.
   - Greater details of outcome measures should be described in the protocol not only listed in the appendices
   - How are you going to determine if eligible patients were prescribed the anti-diabetic medication primarily for diabetes? e.g. metformin also used to treat polycystic ovarian syndrome
   - what is the reasoning/rationale behind the statement diabetes patients are followed up every 3-6 months. Need to provide evidence to support this.
   - How is the quality of the data to be determined as a result of EHR systems?

5. A note on data management should be included in the protocol. How is the data you capture from the different databases etc going to be handled etc.

| REVIEWER            | Adrianna Murphy |

1
This will be a very interesting study on an important topic. The methodological approach is a huge undertaking, and may represent a good template for future studies in the country, as the authors propose.

I would suggest some minor revisions to clarify a couple of points:
1. The average reader may not know what IQVIA is. Some further details on who IQVIA are and where their data come from would be helpful.
2. There is an important section that in its current form is difficult to understand (on page 9) - The section starts with: "Drug costs in IQVIA’s MIDAS database have been used as a reference for studies in other countries” and ends with “which will be used to verify against the total drugs cost obtained from the final total direct medical cost estimate.” How is IQVIA’s drug sales audit conducted? You say sales will also be obtained from the prescription audit database - do you mean the one that collects data from physicians? Are prescriptions a reliable predictor of sales in the Philippines?
3. The representativeness of the selected hospitals is mentioned very briefly, as a potential limitation. I believe this will be a major consideration in interpreting the results and that the potential bias and its effect need to be discussed more explicitly.
4. In the description of indirect costs it is not clear to me whether the study will be able to address wages lost to those working in the informal sector (will labour participation be based on statistics of those in the formal sector?). Is this an issue that should be considered in the Philippines?
5. The assumptions listed on page 11 - some discussion of whether these are reasonable in the context of the Philippines (preferably with reference to evidence) would be helpful.

This is a very good protocol for estimating the economic burden of Type 2 diabetes mellitus in the Philippines.

My only concern is about Sensitivity Analysis. Firstly, since the Monte Carlo simulation will be used, why not use probabilistic sensitivity analysis over and above two-way sensitivity analysis. Furthermore, I do consider a 10% variation as quite low. A 25% appears to me as more appropriate. In any case, more clarification is needed why 10%.
Reviewer: 1  
Reviewer Name: Rachelle Louise Cutler  
Institution and Country: Graduate School of Health; University of Technology Sydney, Sydney, Australia  
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
1. Greater exploration of the economic impact of diabetes on a worldwide scale may be beneficial to set the scene, in addition to it being a national problem. 
We have added a line at the start of the paragraph. 
Systematic review on cost of diabetes has revealed a large economic burden affecting patients in low-middle income countries. 

2. Need to be more specific about what guidelines, recommendations etc. have informed the decisions to run the trial in this particular way. 
We have streamlined our methodology, as we found that some of the data sources were not viable. The current approach will be reported according to STROBE guidelines. 

3. Introduction: 
- need to link more clearly the burden of complications to the cost implication on the health care system. 
We have included an additional line to describe the potential impact on the health care system. 
The cost burden from diabetes particularly affects patients in low-middle income countries. Presence of complications could also potentially increase the medical expenditure, which have a significant impact on the direct health system costs of diabetes. 
- streamlining of terminology would be beneficial. Are components costs? 
For better clarification, we have changed “components” to “cost components”. 
The components refer to individual items adding up to the total costs. 
- health care and financing of health care may be explored as different concepts, be careful grouping them together. 
Both health care financing and the system are fragmented, as substantiated by the World Bank and the Philippines Department of Health. 

4. Methods and analysis 
- Overall methodology is quite sound. 
Thank you. 
- Greater details of outcome measures should be described in the protocol not only listed in the appendices 
Due to the infeasibility of a few data sources, we have narrowed our scope to just direct medical costs of patients with and without complications. This has been further expounded under the Methodology section. 
- How are you going to determine if eligible patients were prescribed the anti-diabetic medication primarily for diabetes? e.g. metformin also used to treat polycystic ovarian syndrome 
Thank you for the feedback. We have revised our selection criteria and are described in the following text. 
Patients with T2DM were identified by the ICD-10 code, E11 from the databases of NKTI and SLMC. 
Specific keywords from the list of diagnosis in the DSCI and algorithms were used to search for patients with T2DM and its complications from the free-text diagnosis in the database of ONM. This data extraction was conducted by two independent coders using different algorithms. Differences in coding were then reconciled by a reviewer. 
- what is the reasoning/rationale behind the statement diabetes patients are followed up every 3-6 months. Need to provide evidence to support this. 
As we have simplified our approached, we have removed this assumption.
How is the quality of the data to be determined as a result of EHR systems? We based it on the 3x3 DQA Guideline. Briefly, quality of data is considered if they are complete, correct and current.

Complete: All records of patients, including medical, financial and clinical results, in these 3 institutions are captured in the system.

Correct: The birth dates and gender remained the same for each patient.

Current: All data are capture real-time.

5. A note on data management should be included in the protocol. How is the data you capture from the different databases etc going to be handled etc.

We have added the following.

Dataset from each institution will be managed independently. Resource utilization will be standardized across each institution and categorized into the following: drugs, procedures, dialysis, surgery, supplies and others.

Reviewer: 2
Reviewer Name: Adrianna Murphy
Institution and Country: London School of Hygiene and Tropical Medicine
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This will be a very interesting study on an important topic. The methodological approach is a huge undertaking, and may represent a good template for future studies in the country, as the authors propose.

I would suggest some minor revisions to clarify a couple of points:

1. The average reader may not know what IQVIA is. Some further details on who IQVIA are and where their data come from would be helpful.

We have removed this component, as we found that some of the data sources were not suitable. If we pursue these data sources, assumptions will be made, and these could introduce uncertainties.

2. There is an important section that in its current form is difficult to understand (on page 9) - The section starts with: "Drug costs in IQVIA's MIDAS database have been used as a reference for studies in other countries" and ends with "which will be used to verify against the total drugs cost obtained from the final total direct medical cost estimate." How is IQVIA's drug sales audit conducted? You say sales will also be obtained from the prescription audit database - do you mean the one that collects data from physicians? Are prescriptions a reliable predictor of sales in the Philippines?

We have removed this component, as mentioned above.

3. The representativeness of the selected hospitals is mentioned very briefly, as a potential limitation. I believe this will be a major consideration in interpreting the results and that the potential bias and its effect need to be discussed more explicitly.

We have expanded our point.

Although this study is fortified with data from leading hospitals in the Philippines, with complete electronically captured data, it is not without limitations. Generalizability of this study could be limited by the selection of hospitals, as they may not be representative of all hospitals in the Philippines. These hospitals provide tertiary care and are mainly serving as referral centres in Manila. Hence, these institutions are more likely to see patients with more severe conditions.

4. In the description of indirect costs it is not clear to me whether the study will be able to address wages lost to those working in the informal sector (will labour participation be based on statistics of those in the formal sector?). Is this an issue that should be considered in the Philippines?

An instrumental data source, PhilHealth, was found to be unsuitable for this study. We have removed the component on indirect cost calculation.
5. The assumptions listed on page 11 - some discussion of whether these are reasonable in the context of the Philippines (preferably with reference to evidence) would be helpful. Due to the infeasibility of a few data sources, we have narrowed and simplified our scope. Therefore, all assumptions are removed.

Reviewer: 3
Reviewer Name: Savvas Zannetos
Institution and Country: Neapolis University Pafos - Cyprus
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a very good protocol for estimating the economic burden of Type 2 diabetes mellitus in the Philippines.

My only concern is about Sensitivity Analysis. Firstly, since the Monte Carlo simulation will be used, why not use probabilistic sensitivity analysis over and above two-way sensitivity analysis. Furthermore, I do consider a 10% variation as quite low. A 25% appears to me as more appropriate. In any case, more clarification is needed why 10%.

We have removed the component on estimation the national burden. All per capita costs will be presented as per tertiary care institution, namely from a public hospital, a public-private hospital and a private hospital. This will be complemented with the estimation of cost for patients seeing primary care physicians. This is summarized in the following figure.

### GENERAL COMMENTS
The scope of the study has been narrowed, and as a result some of my earlier concerns are no longer applicable. The others have been addressed.

### REVIEWER
Adrianna Murphy
London School of Hygiene and Tropical Medicine

### REVIEW RETURNED
08-Jul-2019

### REVIEWER
Savvas Zannetos
Neapolis University Pafos
Cyprus

### REVIEW RETURNED
19-Jul-2019
The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Adrianna Murphy
Institution and Country: London School of Hygiene and Tropical Medicine
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The scope of the study has been narrowed, and as a result some of my earlier concerns are no longer applicable. The others have been addressed.

Noted.

Reviewer: 3
Reviewer Name: Savvas Zannetos
Institution and Country: Neapolis University Pafos, Cyprus
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
No further comments
Noted.