## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Study protocol for a cluster-randomised controlled trial of an NCD access to medicines initiative: evaluation of *Novartis Access* in Kenya |
| **AUTHORS** | Rockers, Peter; Wirtz, Veronika; Vian, Taryn; Onyango, Monica; Ashigbie, Paul; Laing, Richard |

## VERSION 1 - REVIEW

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| **REVIEWER** | Corrina Moucheraud<br>University of California Fielding School of Public Health, Los Angeles CA USA<br><br>CM has coauthored and collaborated with VW. |
| **REVIEW RETURNED** | 15-Aug-2016 |

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| **GENERAL COMMENTS** | I think that this study sounds interesting and very important, thanks for the opportunity to review the manuscript. I have a few comments about how the manuscript itself is presented (minor revisions), plus a few questions about the study design itself (discretionary revisions).<br><br>Minor revisions:<br>- I would suggest adding some information about what patients pay for medicines at different types of facilities -- this would help the reader gain a better sense of what exactly would be affected by this Novartis program. For example, if patients don't pay for any medicines at public sector facilities, then this intervention should not affect expenditures on medicines among those households that use the public sector in the intervention counties -- and in this case, changes in household-level med availability might be due to improved supply rather than the reduced cost (since this is faced by the facility but not by the patient).<br>- It might be good to address a couple of possible limitations, and what steps can be taken to address these. For example, possible recall bias w/r/t med prices? Also, since follow-ups will happen by phone, will this subsample necessarily be representative of the broader sample? What are the implications of this?<br>- The qualitative instrument is mentioned a couple of times but only very briefly. It should be described in more detail -- ideally, I would suggest attaching the questionnaire as an appendix. Otherwise, would be good to at least provide some info about what domains will be queried, etc.<br>- I would suggest adding a bit more info about the compensation that will be provided -- how much, to whom (at the facilities), etc.<br><br>Discretionary reviews (mostly re study design rather than manuscript per se):<br>- Why exclude the level 6 hospitals? Might this limit the sample in |

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| | those counties where there are level 6 hospitals, vs counties without these hospitals where all facilities (levels 3-5, and a random subset of level 2) will be included? And, could this introduce bias?<br>- What if there are multiple drug sellers identified as alternatives for a given facility? Will 1 be selected at random from this list?<br>- Some medicines are taken indefinitely, while others (namely those for breast cancer) are taken for defined periods. Someone who had taken tamoxifen would be included in this sample (by the selection criteria) but the expectation might be different about whether she would still have the drug on-hand (available) etc – vs someone who's taking hypertension medicines for his/her entire lifetime. How to reconcile this?<br>- For household expenditure data, will these only be gathered for the Novartis drug, or for other drugs too? How about for other types of health services and commodities? And, even broader than that, for other types of goods and services -- education, food -- if you suspect the possibility of spillovers? This is mentioned briefly on p5, but I would suggest also addressing it elsewhere because it seems like an important possible finding. |

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| **REVIEWER** | Jeffrey L. Sturchio<br>Rabin Martin<br>104 W. 40th Street, 3rd floor<br>New York, NY 10018<br>USA<br><br>I have received consulting fees, travel and accommodations in the past in connection with Novartis corporate responsibility activities and also to moderate a stakeholder meeting about Novartis Access (in November 2015). I have no relationship with Novartis at present. |
| **REVIEW RETURNED** | 22-Aug-2016 |

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| **GENERAL COMMENTS** | This study has an exemplary design and should make an important contribution to our understanding of how medicines are distributed and used in Kenya. My main concern has to do with the definition of "impact" used, which is limited to the availability and price of NCD medicines in the Kenyan counties involved in the study. It would be good to know more about the differentiated impact of Novartis Access medicines vs. generics and other therapeutic alternatives, as well as whether the Novartis program has any effect on the health outcomes of the populations observed. I realize that the latter is difficult to ascertain, given that those effects may take longer to emerge and would be multifactorial in outcome. At a minimum, I would encourage the authors to add a paragraph or two on the limitations of this study and some reflections on what other data they would like to collect (or other analyses that might be possible to design) that would get at this broader definition of health impact. (For instance, could their study design enable them to explore the persistence of therapy among study subjects at the facility and household levels?)<br><br>A few additional questions for the authors to consider. (They may already have done so, and taken these considerations into account in their plans - if so, it would be good for them to articulate the points in the revised manuscript):<br><br>1. Is it possible to give some indication of how NCD medicines access varies in selected vs. non-selected counties by the end of the |

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| | two years?<br><br>2. Similarly, is there any way to show whether there is a difference in availability and price of NCD medicines in private for-profit facilities and drug sellers in the same counties as compared to the facilities and households studied?<br><br>3. On page 6 and Table 2, I was surprised to see that availability was defined as "having at least one treatment medicine in stock, whether a Novartis Access medicine, a generic equivalent, or a therapeutic alternative". Wouldn't it be preferable to know which of these alternatives was present, so that the impact of the Novartis Access program can be ascertained more precisely?<br><br>4. In the same table, it wasn't clear to me why only certain therapeutic alternatives were listed. (A few additional ones, off the top of my head, would be lisinopril, felodipine, candesartan, enalapril, losartan.) I may have missed the criteria for listing therapeutic alternatives - perhaps these are the only ones stocked by MEDS - but if not, the criteria should be specified.<br><br>5. On page 9, when a sample of facilities and households are visited, will the interviewers plan to ask to see the medicines in question to verify the phone responses?<br><br>I realize that some of these questions may go beyond what this particular study is designed to accomplish, but I think readers would appreciate some indication from the authors (who have clearly given these issues sustained thought) of how these questions might be addressed in future studies building on this one. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Corrina Moucheraud
Institution and Country: University of California Fielding School of Public Health, Los Angeles, CA, USA

Minor revisions:

1. I would suggest adding some information about what patients pay for medicines at different types of facilities -- this would help the reader gain a better sense of what exactly would be affected by this Novartis program. For example, if patients don't pay for any medicines at public sector facilities, then this intervention should not affect expenditures on medicines among those households that use the public sector in the intervention counties -- and in this case, changes in household-level med availability might be due to improved supply rather than the reduced cost (since this is faced by the facility but not by the patient).

Thank you for this comment. We have added additional information on NCD medicine pricing at facilities in Kenya to the Introduction (pgs. 1-2):

“Pricing policies for NCD medicines sold through the public sector in Kenya are determined at the county-level, and substantial variation exists. The price paid by patients in the public sector is generally lower than in the private sector. For example, the median public sector price paid for glibenclamide, a common treatment for diabetes, is less than one-quarter of the price paid in the private for-profit sector.14”

2. It might be good to address a couple of possible limitations, and what steps can be taken to address these. For example, possible recall bias w/r/t med prices? Also, since follow-ups will happen by phone, will this subsample necessarily be representative of the broader sample? What are the implications of this?

We have added a Limitations section (pgs. 6-7):

“There are important limitations to this work. First, household data on medicine prices will rely on participant reporting which may be subject to recall bias. In particular, if patients purchased multiple medicines at once, they may have difficulty recalling prices paid for individual medicines. Second, households without a mobile phone will be excluded from surveillance data collection, which may introduce bias. However, high mobile phone coverage is expected in the study population—according to the 2014 Demographic and Health Surveys, around 90% of households in Kenya have a mobile phone.21 A thorough analysis of this potential bias will be conducted using household baseline data. Finally, no health outcome data will be collected, and it will therefore not be possible to draw any conclusions as to the health impacts of Novartis Access. If the intervention is found to improve medicine price and availability, future studies should explore impacts on health outcomes.”

3. The qualitative instrument is mentioned a couple of times but only very briefly. It should be described in more detail -- ideally, I would suggest attaching the questionnaire as an appendix. Otherwise, would be good to at least provide some info about what domains will be queried, etc.

We appreciate this suggestion. We have added a sentence to the end of the manuscript (pg. 7) to make it clear that all quantitative and qualitative study instruments (as well as other important study information) can be found at the study website:

“All study materials including quantitative and qualitative instruments are available on this website.”

We are also happy to include the instruments as appendices for the manuscript if the editor would prefer it.

4. I would suggest adding a bit more info about the compensation that will be provided -- how much, to whom (at the facilities), etc.

We have added on pg. 7:

“They will each receive 30 minutes of mobile phone airtime, a value of $0.53.”

Discretionary reviews (mostly re study design rather than manuscript per se):

5. Why exclude the level 6 hospitals? Might this limit the sample in those counties where there are level 6 hospitals, vs counties without these hospitals where all facilities (levels 3-5, and a random subset of level 2) will be included? And, could this introduce bias?

Thank you for pointing this out. There are only two Level 6 hospitals in the country, as these are national referral hospitals, and none of them are located in any of the study counties. We have removed mention of Level 6 hospitals in the manuscript as they are not relevant for this study.

6. What if there are multiple drug sellers identified as alternatives for a given facility? Will 1 be selected at random from this list?

The enumerators will be trained to probe when collecting this information to determine the single "main alternative" drug seller.

7. Some medicines are taken indefinitely, while others (namely those for breast cancer) are taken for defined periods. Someone who had taken tamoxifen would be included in this sample (by the selection criteria) but the expectation might be different about whether she would still have the drug on-hand (available) etc – vs someone who's taking hypertension medicines for his/her entire lifetime. How to reconcile this?

This is a very valid point. To clarify, participants are asked the following question: "Do you currently have any medicines that you are taking for this condition?" If the patients answers 'No' they are asked for the reason. We reasonably expect that the patients explain that tamoxifen is not required anymore. We would exclude this case as the patient does not need the medicine for this condition.

8. For household expenditure data, will these only be gathered for the Novartis drug, or for other drugs too? How about for other types of health services and commodities? And, even broader than that, for other types of goods and services -- education, food -- if you suspect the possibility of spillovers? This is mentioned briefly on p5, but I would suggest also addressing it elsewhere because it seems like an important possible finding.

We will collect two forms of household medicine spending data: 1) recent price paid for specific medicines, including Novartis Access medicines as well as other relevant NCD medicines; and 2) recent monthly expenditure on medicines overall. General household expenditure data will also be captured, on other health spending, food, education, transportation, communication/phone, and other spending.

Reviewer: 2
Reviewer Name: Jeffrey L. Sturchio
Institution and Country: Rabin Martin, 104 W. 40th Street, 3rd floor, New York, NY 10018, USA

1. My main concern has to do with the definition of "impact" used, which is limited to the availability and price of NCD medicines in the Kenyan counties involved in the study. It would be good to know more about the differentiated impact of Novartis Access medicines vs. generics and other therapeutic alternatives, as well as whether the Novartis program has any effect on the health outcomes of the populations observed. I realize that the latter is difficult to ascertain, given that those effects may take longer to emerge and would be multifactorial in outcome. At a minimum, I would encourage the authors to add a paragraph or two on the limitations of this study and some reflections on what other data they would like to collect (or other analyses that might be possible to design) that would get at this broader definition of health impact. (For instance, could their study design enable them to explore the persistence of therapy among study subjects at the facility and household levels?)

Thank you for this comment. We have added a Limitations section (pgs. 6-7):

"There are important limitations to this work. First, household data on medicine prices will rely on participant reporting which may be subject to recall bias. In particular, if patients purchased multiple medicines at once, they may have difficulty recalling prices paid for individual medicines. Second, households without a mobile phone will be excluded from surveillance data collection, which may introduce bias. However, high mobile phone coverage is expected in the study population—according to the 2014 Demographic and Health Surveys, around 90% of households in Kenya have a mobile phone.21 A thorough analysis of this potential bias will be conducted using household baseline data. Finally, no health outcome data will be collected, and it will therefore not be possible to draw any

conclusions as to the health impacts of Novartis Access. If the intervention is found to improve medicine price and availability, future studies should explore impacts on health outcomes."

While we fully agree that it would be ideal to collect data on health outcomes, we feel it is appropriate to first establish whether medicine price and availability are improved, as this is the most likely pathway through which health outcomes would improve.

A few additional questions for the authors to consider. (They may already have done so, and taken these considerations into account in their plans - if so, it would be good for them to articulate the points in the revised manuscript):

2. Is it possible to give some indication of how NCD medicines access varies in selected vs. non-selected counties by the end of the two years?

We appreciate this suggestion. While we will not have the granular study data from non-selected counties, and will therefore be limited in our ability to draw conclusions about medicine access in these counties, we could potentially use data from MEDS to explore this relationship.

3. Similarly, is there any way to show whether there is a difference in availability and price of NCD medicines in private for-profit facilities and drug sellers in the same counties as compared to the facilities and households studied?

We appreciate this suggestion. We will have data from multiple private for-profit drug sellers in each county, and we will be able to estimate variation in price within and across counties.

4. On page 6 and Table 2, I was surprised to see that availability was defined as "having at least one treatment medicine in stock, whether a Novartis Access medicine, a generic equivalent, or a therapeutic alternative". Wouldn't it be preferable to know which of these alternatives was present, so that the impact of the Novartis Access program can be ascertained more precisely?

We agree that this more precise description of the impact of Novartis Access on the availability of alternative medicines is of great interest, and we plan to investigate this as a secondary analysis. However, our primary analysis is concerned with availability of medicine from the patient perspective, and from this perspective the exact alternative is less important than whether there is at least one treatment.

5. In the same table, it wasn't clear to me why only certain therapeutic alternatives were listed. (A few additional ones, off the top of my head, would be lisinopril, felodipine, candesartan, enalapril, losartan.) I may have missed the criteria for listing therapeutic alternatives - perhaps these are the only ones stocked by MEDS - but if not, the criteria should be specified.

We have purposely limited the list of therapeutic alternatives to study only a selection rather all that are marketed in Kenya. We decided to choose those therapeutic alternatives that are included in the core medicines list of the World Health Organization/Health Action International manual for measuring availability, price and affordability. Choosing these therapeutic alternatives provides us with the opportunity to compare availability, prices and affordability found in our study with the results of other studies conducted in other countries or past surveys in Kenya.

6. On page 9, when a sample of facilities and households are visited, will the interviewers plan to ask to see the medicines in question to verify the phone responses?

Thank you for this comment. The interviewers will ask to see the medicines. We have clarified this

point (pg. 6):

“A 5% subsample of surveilled health facilities and households will be visited in person to audit phone responses and confirm medicine price and availability through direct observation.”

**VERSION 2 – REVIEW**

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| **REVIEWER** | Jeffrey L Sturchio<br>Rabin Martin, USA |
| **REVIEW RETURNED** | 25-Oct-2016 |

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| **GENERAL COMMENTS** | The authors' responses have adequately addressed the points raised in my referee report. I recommend acceptance and publication. |