

BMJ -  
Decision  
on  
Manuscript  
ID  
BMJ-2019-  
051258

**Body:** 21-Aug-2019

Dear Dr. Ogbuoji

# BMJ-2019-051258 entitled "Economic consequences of better health: insights from clinical data"

Thank you for sending us your article, which we read with interest. Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again. We would very much like to encourage a re-submission, and this is part of the usual publishing process. In regards to Editor's notes vs Reviewer notes, if there is any difference, please address the editors comments and make note of this on your response letter.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

Editors notes:

1. This needs to be clearer for the non-economist. Please remember when re-writing this that the BMJ's main audience are generalist healthcare physicians, not economists, so some phrasings may need to assume this. Some definitions may need spelling out at it were.
2. In regards to the examples used, might be useful to explain in one sentence or two why they were chosen. Also order them in the chronology of the life cycle, will make it read better. Ie birth to death.
3. Should consider a paragraph on intergenerational benefits as well.
4. The conclusion needs to be stronger. You can assert your expert opinion here, as you have should have explained your rationale through the rest of the article so you can be stronger in your conclusions.
5. Needs some more focus on the clinical research paragraph as well, this could do with being stronger as well. This is very important and likely of most interest to our readership.
6. Overall the language is too dense, and needs to be more of an oversight rather than as much detail in regards to the 'jargon' or methodology of health economics.

The reviewers' comments are at the end of this letter.

Please don't hesitate to contact me if you wish to discuss this further.

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I hope you will find the comments useful. Please email me if you have any questions and we can arrange a call if needed.

Yours sincerely

Greta McLachlan  
gmclachlan@bmj.com

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**Reviewer(s)' Comments to Author:**

Reviewer: 1

**Recommendation:**

**Comments:**

The article briefly describes the topic rather than an analysis of the topic. While some attempts have been made to present in some depth, the article is mostly descriptive. Authors have used a range of terms which will confuse readers. For example, authors have used terms such as economic consequences, economic benefit, economic outcome, economic endpoint, economic assessments, and economic return interchangeably.

Authors have made the introduction section unnecessary lengthy, which could be significantly reduced. The 'implications for clinical research' sections is an important part of the article but lacks reasonable argument and reasonable inferences from available information. In other words, the authors have not provided many details as needed to make a clear argument. The points and arguments are oversimplified. For example, the

authors have argued that "treatment with higher economic returns should be prioritised" (page 7, line 22-24). It is not, however, clear what does economic returns means. Whatever the economic returns might be, judging the treatment based on benefit only without considering the cost involved in developing the treatment is a naive argument and largely ignore the notion of economic evaluation in healthcare.

The authors have described EGMs in details but did not mention the problems, challenges and issues of EGM in clinical research. Just a general description of the EGM does not make the argument that EGM is a better method. The authors need to acknowledge the opposing view.

Finally, the authors have not addressed the second aim of the paper in sufficient detail i.e. "we point to a research agenda that would leverage clinical trials and routine data collection to provide, at relatively low cost, a mechanisms for expanding the range, robustness, and practical utility of the literature on the economic consequences of better health".

Other comments:

repeated text and unclear statements

Additional Questions:

Please enter your name: Amrit Banstola

Job Title: Research Associate

Institution: University of the West of England

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:

Positive notes

The analysis paper is relevant to the general audience and body of researchers on economic benefits of health and treatment. The arguments are well presented in a clear, logical and coherent manner. The authors combine original ideas from multiple sources to present supporting and diametrically opposing views providing explanation for unexpected direction vis-à-vis the economic effect of specific disease and treatment which further stimulated debate and discussion for future research.

The 3 examples cited by the authors (HIV in sub-Saharan Africa, Spanish Flu, effect of adverse utero condition) on economic consequences of health, the suggested framework on which future researchers can explore for economic evaluation of disease and treatment and the proposed low cost approach integrating research agenda into clinical trial and routine data collection are all noteworthy. The paper is also written in sound academic language. The authors have adhered to the available guidance for articles in the analysis section: length, presentation, evidence base, contributors and sources, boxes/tables/figs, references, key message boxes

Please find my comments below:

The authors have made a case for new approach that evaluates the economic benefits of specific disease and its treatment. While this approach is promising, I am particularly worried about the omission of patient groups with co-morbidities and what would be the additive or possibly interactive effect of such multi-morbidities (e.g. HIV and Tuberculosis, HIV and diabetes, eating disorders (ED) and schizophrenia etc) on economic benefits (employment, earnings, labor productivity etc) in the long run. For instance, Samnaliev and colleagues found that individuals with eating disorders (in employment) have lower (though not significant) earnings (\$2093,  $p = 0.48$ ), compared to individuals without ED. The authors further noted that among individuals with eating disorders, the presence of mental health co morbidities was associated with lower borderline significant odds of employment (OR = 0.41, 95% CIs [0.14, 1.20]), and significantly lower earnings (\$19,374,  $p < 0.01$ ).

From the foregoing article, it will be interesting to see how the authors factor in the additional morbidity and the interactive effect in the analysis and the modification of the proposed framework.

In addition, it will be good to differentiate/stratify the economic benefits of disease and treatment vis-a-vis labor productivity and earnings in light of type of employment (executive/professional jobs, manual labor, business etc). We do know that higher-ordered cognitive functioning is a proxy to educational attainment hence employment at executive level. Diseases with neurocognitive sequel suffered in childhood may result in lower earnings in the long-run not necessarily because of physical disability but the neurological deficits which affect higher mental functioning and learning of such individual. With this inputs, I think the authors have done justice to the topic and the topic is useful for general readership and research audience, policy makers and also Ministries of Health and Education departments.

Additional Questions:

Please enter your name: Dr Adepoju Victor

Job Title: Project Manager

Institution: KNCV Tuberculosis Foundation

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:

The study argued that RCTs and clinical records should be the "new venue" to yield evidence supporting a casual link between health and economic consequences. This topic is important and relevant to the general readers, since there is a lack of studies establishing casual relationships between health and economic outcomes.

Authors laid a good foundation in the background/introduction section through a comprehensive review of the prior literature on the conceptual pathways between health and economic consequences, and three examples illustrating that conflicting results may arise due to a lack of studies examining causal relationship between health and economic outcomes. Authors then proposed two solutions in the research agenda to address the aforementioned issue, however the first solution is conducting systematic literature reviews and creating evidence gap maps, which seems unrelated to the goal of getting insights on economic consequences of health using clinical data and deviating from the rest of the manuscript. The second solution is measuring economic outcomes in existing clinical trials and cohorts. In terms of economic outcomes, authors gave examples such as cognitive development, educational attainment, and social functioning, which would be considered indirectly related to economic outcomes but not economic outcomes themselves. Authors need to expand their augment by including what would be considered traditional economic outcomes (i.e. direct and indirect costs), or clarify when they shouldn't be included if authors have a specific reason not to.

Moreover, I don't believe author's reasoning around IV. Authors stated that treatment is an IV for disease which means treatment can only be correlated with economic outcomes through its effect on disease per IV theory. However this is not true, since receiving treatment or control in an RCT will not affect whether the participant has disease or not. Participants usually included in an RCT should already have the disease in the first place. In addition, it is not clear how authors propose to add economic assessments to existing or historic clinical cohort studies which were initiated many years ago. Authors may need to provide more information on this.

Furthermore, authors did not acknowledge or discuss the potential opposing view, such as the challenges associated with including economic outcomes in RCTs and clinical cohorts, which left authors' claim that these investments will not be very large unfounded.

In conclusion, I would suggest this manuscript to be accepted after major revisions.

Additional Questions:

Please enter your name: Yuchen Ding

Job Title: Manager, Health Economics and Outcomes Research

Institution: Novo Nordisk Inc.

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 4

Recommendation:

Comments:

This paper offers a good summary of existing literature about the economic consequences of improved health. The paper is well written, arguments are presented clearly, and the sub-sections with headings help reader follow along. The boxes are also helpful.

Below are a few questions and comments for the authors:

1) HIV section (pg. 5) – Wagner et al used quasi-experimental design to evaluate impact of increased access to ART on employment in Africa. Consider including: <https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2014.1006> See also additional research by Thirumurthy about the economic functioning of people at various stages of HIV disease.

2) In-utero section (pg. 5-6): some of the studies mentioned are classics, but others are less known (at least to this reader). I would have liked to see another sentence added about the Chernobyl and Ramadan studies that would briefly explain the main findings (e.g. what outcomes were studied).

3) Economic effects of adult malnutrition (pg. 6) – What about the flip side of malnutrition? More and more adults around the world are eating unhealthy diets that are leading to obesity, hypertension, diabetes. What is the evidence of these conditions on productivity and economic functioning?

4) Implications for clinical research: In several places the authors discuss that any changes in economic functioning may be lagged and that evaluation of long-run economic effects is

needed. I couldn't agree more. Yet I was surprised that a stronger case for examining long-term consequences of disease on economic functioning was not made. Do the authors think that doing economic follow-ups to existing trials could be of value? What do the authors recommend in terms of the length of follow-up needed to make valid economic assessments?

5) In general, a discussion of multigenerational effects was missing from the piece. What do we know about the impact of improved adult health status on child schooling outcomes? More healthy and productive adults could translate to fewer children needing to care for ill individuals or substitute for lost labor. Improved life expectancies and subjective expectations could change the calculus for making human capital investments (longer horizons = more time for returns of investments). The multigenerational effects should not be overlooked.

6) Could the authors add a discussion of longer life expectancies affecting human capital investments? (Becker and Ben-Porath for theory; Delavande, Fortson, Jayachandran, Thirumurthy, Soares, Hurd etc. for empirical evidence)

Additional Questions:

Please enter your name: Aleksandra Jakubowski

Job Title: Postdoctoral Fellow

Institution: Stanford University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 5

Recommendation:

Comments:

I really enjoyed reading this paper. A couple of minor points:

1. I think more description about the nuts and bolts of regression threshold analysis and instrumental variable analyses needs to be include (1-2 sentences) as some readers may not be familiar with the techniques.



2. Adding economic outcomes to some clinical trials might be very expensive especially if long term followup is necessary. The effort and expense of maintaining the cohorts and preventing attrition need to be considered.

Minor point:

1. Extra "th" in Box 3

Additional Questions:

Please enter your name: Carlo Marra

Job Title: Professor and Dean

Institution: University of Otago

Reimbursement for attending a symposium?: No

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Reviewer: 6

Recommendation:

Comments:

The authors highlight the importance of the measurement economic consequences of diseases and treatment. The article is quite general. I did not clearly see the additional benefits of this work to existing knowledge on this issue.

Additional Questions:

Please enter your name: Nathorn Chaiyakunapruk

Job Title: Professor

Institution: University of Utah

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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