Author’s response to reviews

Title: The IMPROVE-GAP Trial aiming to improve evidence-based management of community-acquired pneumonia: study protocol for a stepped-wedge randomised controlled trial.

Authors:

Elizabeth Skinner (elizabeth.skinner@wh.org.au)
Melanie Lloyd (melanie.lloyd@wh.org.au)
Edward Janus (edwarddj@unimelb.edu.au)
May-Lea Ong (maylea.ong@wh.org.au)
Amalia Karahalios (emily.karahalios@unimelb.edu.au)
Terry Haines (terrence.haines@monash.edu)
Anne-Maree Kelly (anne-maree.kelly@wh.org.au)
Melina Shackell (melina.shackell@wh.org.au)
Harin Karunajeewa (Harin.Karunajeewa@wh.org.au)

Version: 1 Date: 11 Dec 2017

Author’s response to reviews:

Dec 4, 2017

Doug Altman
Jeremy Grimshaw
Editors-in-Chief, Trials

Dear Editors,

Thank you for considering our revised manuscript for publication in Trials.

We have addressed the reviewer comments below and also note the inclusion of 30- and 90-day mortality as additional secondary outcomes. We have also made some other minor text modifications to improve the clarity of our reporting (all changes tracked).

Thank you for considering our work, we look forward to your opinion on our revised manuscript.
Yours sincerely,

Dr Elizabeth Skinner

Corresponding author on behalf of all authors

Western Health

Reviewer reports: I read the paper about the protocol of the IMPROVE-GAP trial and I think it is well designed and reported.

Author response: Thank you for your positive feedback.

I just have some minor comments:

1) To allow reproducibility and to protect against selective outcome reporting risk of bias, please either provide a fully specified Statistical Analysis Plan, or state that this SAP will be provided before opening the database —for example, in the form of a Trials (free) Update. Please, specify if you will (logarithmically) transform LOS. Please, specify how you will treat deaths (13%?) in your analysis.

Author response: Based on our prior data, we expect mortality at our institution to be around 7%. We have outlined our preliminary Statistical Analysis Plan in our trial registration, see www.ClinicalTrials.gov Registry number: NCT02835040. We will provide the final SAP before opening the database, in the form of a Trials update, as suggested by the reviewer.

2) On page 17, line 10 you state that your analysis will be based on the “intention to treat” population (please, review your “n/a” in your Spirit table, item 20c). Please note that now Consort and Spirit recommend “as randomized”. Please, find useful advice to prevent and treat missing data at http://www.nejm.org/doi/full/10.1056/NEJMs1203730.

Author response: Thank you, we have updated the text and the Spirit table, item 20c.

3) Please, note that the Consort figure (flowchart) is for the results, not the design; but Spirit suggests an alternate figure to highlight that recruitment precedes allocation. Please, consider to include a Spirit figure adapted to a SW design.

Author response: We have included two additional Figures (Figure 3 and 4) to address the reviewer’s comments.
4) You stated that patients will be masked; but this could not be true (because they could know the intervention administered in each cluster). Please, consider to address how will you control, analyse or protect your design against selection (patients avoiding some clusters), attrition or evaluation bias.

Author response: Thank you for raising your concerns. We feel that the risks of possible selection, attrition and evaluation bias are mitigated as follows:

Selection bias: It is extremely unlikely that patients know the intervention in each cluster. This study was not publicized in media or even internally within the organization. Because of the waiver of consent, the study is not discussed with individual patients, who are admitted for acute illness as an emergency, rather than elective admission.

Allocation to treating unit (and therefore to control or intervention group) is determined by established practice according to day of admission or previous admission under treating unit in previous 3 months. Individual patients do not have a choice as to which unit they are admitted under. For selection bias to occur, patients would have to be aware of study, aware of which units were intervention and control (during phases 2-4) and then delay their presentation by at least a day or request transfer from one unit to another. We feel that this is extremely unlikely.

Attrition bias: Our primary outcome LOS is measured in 100%, as are secondary outcomes clinical cost, inpatient mortality. Births, deaths and marriages is a robust way to capture all deaths occurring in Australia (30 and 90 day mortality). Therefore, we feel that only outcome that could be susceptible to attrition bias would be readmissions (as our data won’t capture readmission to other health services).

Evaluation bias: Our outcome measures are either very well-defined continuous variables (LOS, clinical cost) or binary (death vs survival, readmission vs non-readmission). Therefore, it is difficult to see where the reviewer might have concerns of evaluation bias.

We have added some text to address these points in the Discussion.

5) Please, specify if alpha will be one or two-sided in your sample size rationale.

Author response: Two-sided.