Reviewer's report

Title: Sample size considerations using mathematical models: an example with Chlamydia trachomatis infection and its sequelae pelvic inflammatory disease

Version: 2
Date: 26 January 2015
Reviewer: Edward Waters

Reviewer's report:

This is an interesting paper, and fits squarely into one of my main research areas---sampling protocols for understanding biological processes. At the moment it is a good paper, but I think it could be made better by a fuller discussion of some of the assumptions it makes about the underlying biology. In particular, I have things I would like explained about the parameter $f$. I have classed these as major compulsory revisions because they will make the paper easier to understand and may require some additional work.

Major compulsory revisions

1. In the supplementary material, the steady state prevalence of women with PID is equal to $s_{3}=p(\gamma / (r+\gamma))$. So is not the fraction of infected women who develop PID in the control group, $f$ (defined this way in lines 159--160), equal to $\gamma / (r+\gamma)$ in $s_3$? Please explain in more detail.

2. Check that your interpretation of $\gamma=fr/(1-f)$ is correct. I believe setting $\gamma=fr/(1-f)$ will ensure that a desired proportion of the control group will develop $PID$ by the end of the one year follow up, but I am not sure if it ensures the same duration of infection across progression types. Is it the basis of your argument above the assumption that duration of infection is equal to $\gamma$ plus $r$ in the constant progression scenario? Please check this assumption is correct mathematically and demonstrate it in the appendix.

3. Please comment further on the biological implications and generalisability of your results. The way I see it, theoretically any values of $s_3$ and $f$ between $0$ and $p$ could be obtained by varying the parameters $r$ and $\gamma$, and using any set of assumptions about progression. Please discuss how your results will hold for situations where $f$ increases in value, or if you relax the constraint $\gamma=fr/(1-f)$ in the constant progression scenario. Line 242 would be a good place to insert this discussion. To some extent you do this in Figure 2, but it would be good to discuss this more generally. Do you expect the sample size required in all scenarios to continue to decrease as $f$ increases, and if so why? I also advise you to include a discussion of the implications of your results for sample size calculations for other types of infection, framed around $R_0$, because this quantity is intimately related to the proportion infected---typically this equals $1-1/R_0$. I believe this is also true for your model.
Minor essential revisions
These are spelling or typographical errors.
1. Line 100: Should read "structure BY taking advantage"
2. Line 108: Missing full stop in Herzog et al.
3. Line 196: Should read 21,000 not 21’000
4. Line 316: Change to "suggested the fraction of women who develop PID to be 10\%..."
5. Line 317: Change CrI in second confidence interval to CI.

Discretionary revisions
Suggested amendments to the text that may improve readability.
1. Perhaps the notation \$s_{1}, s_{2}, s_{3}\$ in the Supplementary material could be changed to read \$s, i_{1}, i_{2}\$. Using the notation \$s_{i}\$ to refer to a fraction of the infected population could be quite confusing.
2. Lines 48-49: suggest reword to "its sequelae can be accounted for in sample size calculations by using mathematical modelling."
3. Lines 60-61: long and confusing sentence, consider splitting into two sentences.
4. Line 189: Suggest "Scenario 1 utilises the assumption that..."
5. Line 191: Suggest "Scenario 2 models a disease process where PID develops..."
6. Line 242: Suggest "There are optimal follow-up times that minimise the sample size needed per group..."
7. Line 251: suggest "This study showed..."
8. Line 252: Suggest "RCTs. The implications of our findings were illustrated using the example of chlamydia infection and its sequelae PID by re-"
9. Line 253: Suggest "Different temporal dependency assumptions regarding chlamydia and PID are reflected in different PID incidence, and hence different RR values used in sample size calculations. Changing the underlying temporal dependency assumption can affect required sample size considerably, even for small changes in..."
10. Line 320: Suggest "implications for the future planning of RCTs."

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests