PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A double blind, randomised, placebo-controlled trial to evaluate the efficacy of metformin to treat preterm pre-eclampsia (PI2 Trial): study protocol
AUTHORS	Cluver, Catherine; Walker, Susan; Mol, Ben; Hall, David; Hiscock, Richard; Brownfoot, Fiona; Kaitu'u-Lino, Tu'uhevaha; Tong, Stephen

VERSION 1 - REVIEW

REVIEWER	Elizabeth S Langen, MD University of Michigan, United States
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	The authors are proposing a prospective randomized controlled trial to evaluate the effect of metformin as a therapeutic option to allow for delayed delivery among women with early onset preeclampsia. The question is important and the study design is appropriate. I have the following questions / concerns regarding their study proposal which would be helpful to answer prior to publication. 1. Table 1 is unclear as to what specific definitions are being used to make the diagnoses that allow a patient to be included. How is pre-eclampsia being defined for inclusion criteria? What qualifies as "preexisting hypertension with evidence of preeclampsia" that is listed as an inclusion criteria? What is "unclassified proteinuric hypertension"? The authors should list specific clinical guidelines for inclusion to the study. 2. The exclusion criteria should specify what qualifies as "Severe renal impairment" and "Severe Hypertension." 3. For the neonatal outcomes, will NEC be graded? How is bronchopulmonary dysplasia defined? 4. For maternal outcomes, will complications of metformin be included (not noted on Table 3)? 5. How will side effects of metformin be managed? 6. The protocol states that betamethasone will be given once and then repeated 1 week later. This is not the standard of care in the United States. Please clarify if betamethasone is being given in this way because this is the standard of care locally and or provide references for administering betamethasone like this. 7. Please clarify why 5 days chosen as the amount of increased latency that would be clinically significant. 8. Please stated in the text of the article that the CONSORT guidelines will be followed (this is stated in the appendix).

	9. The pre-specified covariate of absent umbilical artery Doppler flow is identified as a marker for women at higher risk for a short latency period. As there are many clinical markers of a likely shorter latency period, please clarify why this was chosen in particular and or provide an appropriate reference. 9. A fetal death will be treated as "zero" days of pregnancy prolongation. Please provide literature to support handling this complication in this way. 10. What are the "simple statistics" that will be used to compare the expression of sFlt-1 and other markers. As these levels are being drawn at multiple time points, which levels are being compared? 11. The text states that the expected latency without treatment in this hospital setting has been a MEAN of 11 (SD 7) or 13.1 (SD 12.2) days in previous studies. For the sample size calculation, they assume a MEDIAN pregnancy prolongation of 8.3 days for the control group. Where did the 8.3 days come from? 12. In the discussion, the authors highlight the safety of metformin. The authors should, however, acknowledge that metformin is not FDA approved for use in pregnancy, it does cross the placental barrier, and its long term impact on fetal development is unknown. These concerns and the ultimate conclusion that metformin can be reasonably used in pregnancy is highlighted in the ACOG practice bulletin #190 from February, 2018.

REVIEWER	John Petrie University of Glasgow
REVIEW RETURNED	03-Oct-2018

GENERAL COMMENTS	As far as I can tell from the registry information, this trial has not yet commenced so there is the opportunity for the investigators to make improvements to this Protocol. I regret that the concerns listed below make it impossible to recommend acceptance of this manuscript in its current form. 1) Primary outcome - both ITT and on treatment analyses are proposed as "primary outcomes" and for each there are three proposed methods of adjustment. No account has been taken of multiplicity. There should be only one primary outcome analysis (perhaps with sensitivity analyses pre-specified). 2) The secondary outcomes, that include composites, are reasonably well-defined in parts of the Protocol but there is repetition and they are too vague when summarised in the manuscript. I would suggest reducing the number and being really clear (again given concerns re multiplicity). Will there be a hierarchical approach to testing, and if not why not? 3) I would recommend reducing the number of tertiary outcomes listed (some could be exploratory). 4) The previous study of n=120 with esomepazole was unable to detect an increase in gestation of 3 days - I am not sure that a 5-day difference can confidently be detected with n=150 particularly as the rate of drop-out could be much higher with metformin than with esomeprazole (e.g. 25% vs 13% as predicted here), particularly at 3g/day. See the EMPOWAR trial as cited. I found

	the sample size calculation confusing with use of "CV" rather than standardised deviation of the difference so difficult to replicate. 5) On the registry entry searched today (3rd Oct) it says "ethics status "not approved" - this may be a technical problem but this must be corrected before FPFV. 6) Is it intended that the trial sample will be representative of the demographics of the local population, including for self-identified ethnicity? This would be important for understanding the generalisability of the results. 7) The PI should not be involved in the unblinding procedure - although this will not be used often (as stated), and witnesses have to be present for sealed envelopes to be opened, this is too risky a system. I recommend a more secure approach with a much lower risk of bias, ideally an IVRS or IWRS system with an emergency unblinding helpline (open to any health professional but with usage capped and recorded so that it is not open to malicious abuse). 8) On page 8 there is a "recommendation" for the size of the blocks - in the protocol the decision on this should be clearly stated rather than recommended. 9) It may not be necessary to record "all" non-serious adverse events with a well-established medicine like metformin: some of those that are expected could be excepted by protocol (other than those pre-specified as of medical interest).

REVIEWER	Jonathan Williman University of Otago, Christchurch New Zealand
REVIEW RETURNED	11-Nov-2018

GENERAL COMMENTS	I found this to be an interesting and very well written protocol. I have only one minor editorial comment and one question. On page 15 the abbreviation CV appears on lines 1 to 5, prior to its definition on line 10. In the analysis, page 12, why perform an unadjusted analysis given that you have identified gestational age as an important predictor and stratified by it? I understand that most of the analysis do include gestational age strata (as recommend in the literature, https://doi.org/10.1136/bmj.e5840), but I suspect that what will be presented in the abstract of the final article, and quoted as the 'primary' result, will be the unadjusted analysis (as you have done for the esomeprazole trial). I wish the authors all the best with the conduct of the PI2 trial.

REVIEWER	Magnus Westgren Karolinska Institutet Stockholm Sweden
REVIEW RETURNED	14-Nov-2018

GENERAL COMMENTS	This is an important and interesting project with a well written study protocol. I have a few questions in regard to 1. Definition of Inclusion and exclusion criteria. Obviously this will have implications for the external validity of this study. 2. Primary endpoint 5 days. Why 5 days? Why not treat time as a continues variable ?

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1, Elizabeth S Langen, MD

University of Michigan, United States

The authors are proposing a prospective randomized controlled trial to evaluate the effect of metformin as a therapeutic option to allow for delayed delivery among women with early onset preeclampsia. The question is important, and the study design is appropriate. I have the following questions / concerns regarding their study proposal which would be helpful to answer prior to publication.

1. Table 1 is unclear as to what specific definitions are being used to make the diagnoses that allow a patient to be included. How is pre-eclampsia being defined for inclusion criteria? What qualifies as "preexisting hypertension with evidence of preeclampsia" that is listed as an inclusion criteria? What is "unclassified proteinuric hypertension"? The authors should list specific clinical guidelines for inclusion to the study.

Thank you for this. We have added the following under Inclusion criteria on page 7, lines 9 to 17.

“Inclusion criteria:

We will recruit women with a singleton pregnancy diagnosed with pre-eclampsia and chronic hypertension with superimposed preeclampsia defined according to the criteria published by The International Society for the Study of Hypertension In Pregnancy (ISSHP),9 and require the presence of significant proteinuria (more than 300 milligrams in a 24 hour urine collection). Some women only present for antenatal care after 20 weeks gestation. We will classify these women as having unclassified proteinuric hypertension during the pregnancy according to the classification of Davey and MacGillvray.10 Postpartum, they will be reclassified as having pre-eclampsia or chronic hypertension depending on their blood pressure and need for antihypertensive medication more than 6 weeks after the expected due date.”

2. The exclusion criteria should specify what qualifies as "Severe renal impairment" and "Severe Hypertension."

We have added the following definitions to table 2, page 27.

“Severe hypertension (defined as a systolic blood ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg that cannot be controlled with antihypertensive medication within 48 hours of admission)

Severe renal impairment (defined as a creatinine level ≥ 125 µmol/l or a need for dialysis.”

3. For the neonatal outcomes, will NEC be graded? How is bronchopulmonary dysplasia defined?

The following definitions have been added to table 3 page 28.

“Necrotizing enterocolitis (diagnosed on radiological studies)

Bronchopulmonary dysplasia (defined as needing oxygen at day 28 of life, either on a ventilator, by CPAP or via a nasal catheter)”

4. For maternal outcomes, will complications of metformin be included (not noted on Table 3)?

The side effects of the trial medication will be presented in a separate table. This is detailed in the statistical analysis plan (Supplementary Information 4). We will present outcomes for nausea, vomiting, diarrhoea, headache and the need to decrease or stop the trial medication.

5. How will side effects of metformin be managed?

The following has been added to the manuscript. See page 9, lines 10-13

“Participants will be started on 6 tablets daily in divided doses. If side effects develop the dose of the medication will be decreased until the side effects improve and then increased again if tolerated.”

6. The protocol states that betamethasone will be given once and then repeated 1 week later. This is not the standard of care in the United States. Please clarify if betamethasone is being given in this way because this is the standard of care locally and or provide references for administering betamethasone like this.

This is the local standard and a reference has been added. See page 10, line 4. The reference added is the following:

Hall DR. Understanding expectant management of pre-eclampsia. Obstet Gynaecol Forum 2016; 26: 22–7.

7. Please clarify why 5 days chosen as the amount of increased latency that would be clinically significant.

It is widely accepted that expectant management to delay delivery of the preterm fetus is likely to be beneficial as it may decrease the early and late sequelae of prematurity

Our justification in nominating a 5-day gain as a basis of our power analysis are as follows:

1) There is evidence that at the severe preterm gestations we are examining (26-32

weeks), even a gain of a few days can be beneficial for the fetus. Studies show that for

the survival of a healthy baby gestational age at delivery and birthweight are the primary

positive factors associated with survival. Please refer to the following references:

1. Derham RJ, Hawkins DF, Elder MG, Vries LSD, Aber, VR. Outcome of pregnancies complicated by severe hypertension and delivered before 34 weeks; stepwise logistic regression analysis of prognostic factors. BJOG: An International Journal of Obstetrics & Gynaecology, 96: 1173–1181. doi: 10.1111/j.1471-0528.1989.tb03193.

2. Hall DR, Odendaal HJ, Kirsten GF, Smith J, Grové, D. Expectant management of early onset, severe pre-eclampsia: perinatal outcome. BJOG: An International

Journal of Obstetrics & Gynaecology, 107: 1258–1264. doi: 10.1111/j.1471-

0528.2000.tb11617.

As such, we believe a gain of 5 days is likely to be beneficial.

2) Given metformin has not been tested yet as a therapeutic for preterm pre-eclampsia, we believe the correct pragmatic balance is to choose the surrogate marker of a gain in length of gestation. If this phase II trial yields a positive result, it would then form the basis of a phase III trial that will be powered to harder clinical/neonatal endpoints. Given we do not have any indication that this treatment will work yet, it is premature to launch straight into a trial powered to neonatal outcomes given we are likely to need far greater numbers.

An analogy to our situation is the trials performed to examine whether progesterone can

prevent preterm birth. The initial trials examined whether progesterone could lengthen

gestation.1,2 A larger follow-up trial showed that this treatment resulted in neonatal

benefits.3

1. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.

2. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. AJOG 2003;188(2):419-424.

3. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, Creasy GW. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. UOG 2011;38(1):18-31.

We have also added the following to the discussion to explain the use of prolongation as our primary outcome. Page 23, lines 12 to 13.

“This surrogate primary outcome marker has been chosen as it provides a sample size that is feasible and attainable for a phase II study to assess efficacy.”

8. Please state in the text of the article that the CONSORT guidelines will be followed (this is stated in the appendix).

We have added the following on page 17, lines 22-24

“The trial report will include the requirements laid out in the CONSORT statement (http://www.consort-statement.org/).”

There is also an example of the CONSORT flow diagram we will use in the Statistical Analysis Plan (Supplementary Information 4).

9. The pre-specified covariate of absent umbilical artery Doppler flow is identified as a marker for women at higher risk for a short latency period. As there are many clinical markers of a likely shorter latency period, please clarify why this was chosen in particular and or provide an appropriate reference.

Thank you for this comment. We agree and have added a number of other sensitivity analyses that may have affected prolongation of gestation. Please see page 15 lines 6 to 12.

“The sensitivity analyses that will be conducted on the primary outcome are firstly the treatment received, secondly gestational age as an effect modifier, thirdly covariate adjusted for an estimated fetal weight less than the 10th and 3rd centile on ultrasound at the time of randomisation and absent umbilical artery end diastolic flow as these are more likely to be associated with shorter randomisation

to delivery times and lastly a survival analysis will be performed using Cox proportional hazards regression (CPH) adjusted for gestational age strata and Kaplan-Meier survivorship curves."

10. A fetal death will be treated as "zero" days of pregnancy prolongation. Please provide literature to support handling this complication in this way.

We have decided to use "zero" days prolongation in the case of a fetal death as we want to assess whether the intervention is able to prolong a pregnancy that results in a live born baby. We do not want to show that an intervention works to prolong gestation at the expense of the life of the fetus. This is the same strategy used in the PIE study and was a suggestion from a reviewer of the PIE protocol.1,2

1. Cluver CA, Walker SP, Mol BW, et al Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol BMJ Open 2015;5:e008211. doi: 10.1136/bmjopen-2015-008211

2. Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial. Am J Obstet Gynecol 2018;219:388.e1-17.

11. What are the "simple statistics" that will be used to compare the expression of sFlt-1 and other markers. As these levels are being drawn at multiple time points, which levels are being compared?

We have removed the biomarkers from this study protocol. The biomarker work is now a sub study with a separate protocol and statistical analysis plan.

12. The text states that the expected latency without treatment in this hospital setting has been a MEAN of 11 (SD 7) or 13.1 (SD 12.2) days in previous studies. For the sample size calculation, they assume a MEDIAN pregnancy prolongation of 8.3 days for the control group. Where did the 8.3 days come from?

We are using the median gestation in the control group from the PIE study. This is 8.3 days.1

1. Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial. Am J Obstet Gynecol 2018;219:388.e1-17.

13. In the discussion, the authors highlight the safety of metformin. The authors should, however, acknowledge that metformin is not FDA approved for use in pregnancy, it does cross the placental barrier, and its long term impact on fetal development is unknown. These concerns and the ultimate conclusion that metformin can be reasonably used in pregnancy is highlighted in the ACOG practice bulletin #190 from February, 2018.

Thank you for this. We have added this to the discussion and referenced the ACOG practice bulletin #190. See page 22, line 22 to 24.

"Metformin does cross the placental barrier and it's long term effect on fetal development is unknown but a recent ACOG practice bulletin has concluded that it can reasonably be used in pregnancy.26"

Responses to Reviewer: 2, John Petrie

Institution and Country: University of Glasgow

1. As far as I can tell from the registry information, this trial has not yet commenced so there is the opportunity for the investigators to make improvements to this Protocol. I regret that the concerns listed below make it impossible to recommend acceptance of this manuscript in its current form.

Thank you for your detailed comments and suggestions. We have started recruitment but we feel that your comments are valid and helpful, so we have amended the trial protocol and have added a trial statistical analysis plan. Please see the comments.

2. Primary outcome - both ITT and on treatment analyses are proposed as "primary outcomes" and for each there are three proposed methods of adjustment. No account has been taken of multiplicity. There should be only one primary outcome analysis (perhaps with sensitivity analyses pre-specified).

Thank you for this. We have now specified one primary outcome measure with pre-specified sensitivity analysis. We have also added our statistical analysis plan as supplementary information (Supplementary information 4) which provides more detail.

See page 15, lines 1-5

“For the primary outcome a covariate adjusted analysis with both treatment group and gestational age design-based strata modelled as fixed will constitute the primary analysis outcome. Unadjusted and adjusted CPH analysis are only supplemental to this primary analysis. For the secondary outcomes composite binary outcomes will be modelled using a logistic regression model containing both treatment group and gestation aged based strata.”

3. The secondary outcomes, that include composites, are reasonably well-defined in parts of the Protocol but there is repetition and they are too vague when summarised in the manuscript. I would suggest reducing the number and being really clear (again given concerns re multiplicity). Will there be a hierarchical approach to testing, and if not why not?

Thank you for this comment. We will now only assess 2 secondary outcomes, the maternal composite and neonatal composite outcome. The secondary outcomes will only be tested if there is a significant difference in the primary outcome. The two secondary outcomes will each be tested at a significance level of 0.025.

Please see page 13, line 24 to page 14 line 6.

“The primary outcome will be measured from the time of randomisation to delivery. Secondary maternal and neonatal outcomes will be measured from the time of recruitment until six weeks after the due date. The significance level for the primary outcome is set at 0.05 and all hypothesis testing will be two-sided. If, and only if, there is a significant difference for the primary outcome, the two secondary outcomes will be tested at a significance level of 0.025. Standard 95% confidence interval (CI) will be used to present the analysis of the primary outcome. The width of the CI used will be adjusted for the secondary outcomes if tested. For raw results data, the primary outcome will be summarized using median [25th – 75th percentile] along with minimum and maximum values.”

Please see section D of the statistical analysis plan for further details.

4. I would recommend reducing the number of tertiary outcomes listed (some could be exploratory).

Thank you for this excellent suggestion. We have now changed all the tertiary outcomes to being exploratory. See page 11 line 20 to 22.

“All other outcomes, including outcomes nested within the composite secondary outcomes will be classified as exploratory outcomes. These are listed in Table 3.”

5. The previous study of n=120 with esomepazole was unable to detect an increase in gestation of 3 days - I am not sure that a 5-day difference can confidently be detected with n=150 particularly as the rate of drop-out could be much higher with metformin than with esomeprazole (e.g. 25% vs 13% as predicted here), particularly at 3g/day. See the EMPOWAR trial as cited. I found the sample size

calculation confusing with use of "CV" rather than standardised deviation of the difference so difficult to replicate.

We have attached the statistical analysis plan (SAP) which provides more detail and clarity on the sample size calculation. Please see section 11 in the SAP. The patients in this trial are all being managed in hospital which makes it less likely for us to have drop-outs as they are seen every day by our staff. The EMPOWAR trial was a prevention trial and the patients were all outpatients and were not seen daily by a research midwife.

6. On the registry entry searched today (3rd Oct) it says "ethics status "not approved" - this may be a technical problem, but this must be corrected before FPFV.

Thank you for this. It was a technical problem and has been updated. See comment 4 under the editors' comments for more detail.

7. Is it intended that the trial sample will be representative of the demographics of the local population, including for self-identified ethnicity? This would be important for understanding the generalisability of the results.

In our hospital at the time of admission the women self-identify their ethnicity. In our previous trial (PIE trial) self-identified ethnicity matched the ethnicity group that they were allocated to.

8. The PI should not be involved in the unblinding procedure - although this will not be used often (as stated), and witnesses have to be present for sealed envelopes to be opened, this is too risky a system. I recommend a more secure approach with a much lower risk of bias, ideally an IVRS or IWRS system with an emergency unblinding helpline (open to any health professional but with usage capped and recorded so that it is not open to malicious abuse).

Thank you for this suggestion. We have already commenced this trial with this unblinding procedure (which we have not yet needed) but in our next trial we will use a more secure system.

9. On page 8 there is a "recommendation" for the size of the blocks - in the protocol the decision on this should be clearly stated rather than recommended.

Thank you for this. We have changed the text as suggested. See page 8, lines 23-24

"We will use blocks of 4 to 6 with the size and order randomly assigned."

10. It may not be necessary to record "all" non-serious adverse events with a well-established medicine like metformin: some of those that are expected could be excepted by protocol (other than those pre-specified as of medical interest).

Yes, we agree. We are collecting adverse events which include nausea, vomiting diarrhoea, abdominal pain and medication discontinuation. Please see Reviewer 1, comment 4 for more details on this.

Responses to Reviewer: 3, Jonathan Williman

University of Otago, Christchurch - New Zealand

I found this to be an interesting and very well written protocol.

Thank you

I have only one minor editorial comment and one question.

1. On page 15 the abbreviation CV appears on lines 1 to 5, prior to its definition on line 10.

Thank you for this. We have corrected this on page 15

2. In the analysis, page 12, why perform an unadjusted analysis given that you have identified gestational age as an important predictor and stratified by it? I understand that most of the analysis do include gestational age strata (as recommend in the literature, https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1136%2Fbmj.e5840&data=02%7C01%7C%7C72070bafae1c45f0eda808d660f8af3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636803018534556573&sdata=5tovFId%2BV%2F3dOWY4GW6NIldEmZKbp9NQeRQui%2FopIiA%3D&reserved=0), but I suspect that what will be presented in the abstract of the final article, and quoted as the 'primary' result, will be the unadjusted analysis (as you have done for the esomeprazole trial).

Yes, we will present the primary result as an unadjusted analysis. Only the primary outcome will be group difference adjusted for stratification by gestation. Please also see reviewer 2 comment 2 for more details.

Responses to Reviewer: 4, Magnus Westgren

Karolinska Institutet, Stockholm, Sweden

This is an important and interesting project with a well written study protocol. I have a few questions in regard to

1. Definition of Inclusion and exclusion criteria. Obviously, this will have implications for the external validity of this study.

Agreed. We have used internationally accepted inclusion and exclusion criteria that most units performing expectant management for preterm preeclampsia would use to make the study valid in other settings.

2. Primary endpoint 5 days. Why 5 days? Why not treat time as a continues variable ?

Thank you for this comment. We have made a few adjustments in the text to make this clearer to the reader. We are treating time as continuous in the analysis and a binary outcome is not used. We use 5 days as a clinical meaningful difference in prolongation. Please also see reviewer 1, comment 7.

VERSION 2 – REVIEW

REVIEWER	John Petrie University of Glasgow
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	Thank you for addressing my comments - I hope they were helpful - good luck with the trial! Remaining minor comments:

	1) Although as you say you should not get many "drop-outs" in an in-patient setting in this population, the power of the intention to treat analysis could be diminished by treatment dose reductions and discontinuations due to adverse effects. 2) An unblinding system involving the PI (as you acknowledge) is not ideal and may be perceived as a source of potential bias by referees - but I understand that it is too late to change that for this trial.

REVIEWER	Jonathan Williman University of Otago, Christchurch New Zealand
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	Thank you. I am happy that the authors have addressed my previous comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 3

Reviewer Name: Jonathan Williman

Institution and Country: University of Otago, Christchurch
New Zealand

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

Thank you. I am happy that the authors have addressed my previous comments.

Thank you

Reviewer: 2

Reviewer Name: John Petrie

Institution and Country: University of Glasgow

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for addressing my comments - I hope they were helpful - good luck with the trial!

Remaining minor comments:

1) Although as you say you should not get many "drop-outs" in an in-patient setting in this population, the power of the intention to treat analysis could be diminished by treatment dose reductions and discontinuations due to adverse effects.

2) An unblinding system involving the PI (as you acknowledge) is not ideal and may be perceived as a source of potential bias by referees - but I understand that it is too late to change that for this trial.

Thank you