PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	CoMET: A Protocol for a Randomised Controlled Trial of Co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine
AUTHORS	Siskind, Dan; Friend, Nadia; Russell, Anthony; McGrath, John; Lim, Carmen; Patterson, Sue; Flaws, Dylan; Stedman, Terry; Moudgil, Vikas; Sardinha, Savio; Suetani, Shuichi; Kisely, Steve; Winckel, Karl; Baker, Andrea

VERSION 1 – REVIEW

REVIEWER	Hung-Yu Chan Taoyuan Psychiatric Center, Ministry of Health and Welfare, Taiwan
REVIEW RETURNED	24-Dec-2017

GENERAL COMMENTS	Authors would like to investigate the efficacy of metformin to attenuate weight gain and metabolic syndrome for patients with schizophrenia who newly commenced on clozapine. The study is meaningful with important clinical implications. I have only some recommendations about the study design and discussion. 1. Authors will recruit both patients with schizophrenia and schizoaffective disorder. Besides antipsychotics, patients with schizoaffective disorder frequently receive mood stabilizers or antidepressants. These medications may influence body weight of patients. Authors can describe why they need to recruit both patients with schizophrenia and schizoaffective disorder. 2. Authors can list all the prohibited medications and explain the reasons of limitation. 3. There are several outcome measures in the study. Authors can describe who will perform these assessments and whether they are qualified to perform these assessments. 4. Authors use block randomization to equalize the number of both groups with the block length of 4. They plan to recruit 86 patients and wish the patient number in both group is 43. However, the result may be 44 vs 42 due to the block length. Therefore, the patient number in Figure 1 can be presented as 42~44 after randomization. 5. The withdrawal criteria about the study medications are non-adherence for 7 or more consecutive days. It may be a little bit of loose. If a patient use only 1 day of study medication in one week, they still can remain in this study. Under such circumstances, the real efficacy of study medication would be unreliable. Authors can describe why they use this criterion as study termination. Some studies use 80~120% of study medications adherence as the criteria for adherence.

	6. The limitations of a randomized, placebo control trial can be described further.

REVIEWER	Amir Krivoy Geha Mental Health Center, Sackler Faculty of Medicine, Tel-Aviv Univeristy, Israel
REVIEW RETURNED	25-Dec-2017

GENERAL COMMENTS	In this proposed trial the authors aim to explore the weight-gain control qualities of concomitant metformin, starting from clozapine initiation, for 24 weeks follow-up. The study protocol is well written, clear and concise. The trial is well rationalized and the methodology is solid. Few minor points/suggestions: Exclusion criteria: The authors might consider adding these to the criteria: 1) Concomitant psychotropic drugs that might affect weight gain – such as mood stabilizers or anticonvulsants, 2) previous clozapine trial Randomization: May consider stratification of randomization by baseline BMI i.e obese (>29) and non-obese (<29) as they may have different trajectories in the response to metformin Primary outcome – it is not clear what is "adjusted for baseline" – does it mean divided by baseline ? i.e ratio? Protocol: advised to monitor addition of concomitant psychotropic drugs, during the naturalistic trial, as clinicians may wish to augment clozapine if it is not effective enough Protocol table: last raw – clozapine blood levels – not needed at baseline

VERSION 1 – AUTHOR RESPONSE

Dear Editor,

Many thanks for the opportunity to revise and resubmit our manuscript "CoMET: An RCT of Co-commencement of METformin as an adjunctive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine".

We have addressed each of the reviewers comments in turn, and made corresponding changes to the manuscript in track changes.

Respectfully,

Dan Siskind

Reviewer: 1
Reviewer Name: Hung-Yu Chan
Institution and Country: Taoyuan Psychiatric Center, Ministry of Health and Welfare, Taiwan
Please state any competing interests or state 'None declared': None.

Please leave your comments for the authors below
Authors would like to investigate the efficacy of metformin to attenuate weight gain and metabolic syndrome for patients with schizophrenia who newly commenced on clozapine. The study is meaningful with important clinical implications. I have only some recommendations about the study design and discussion.

Comment 1.1. Authors will recruit both patients with schizophrenia and schizoaffective disorder. Besides antipsychotics, patients with schizoaffective disorder frequently receive mood stabilizers or antidepressants. These medications may influence body weight of patients. Authors can describe why they need to recruit both patients with schizophrenia and schizoaffective disorder.

Response 1.1 We agree with the reviewer that concomitant medications in naturalistic studies can be potential confounders. For this reason, we will be collecting information on concomitant medications, and paying close attention to those that may lead to weight gain. These will be adjusted for in the final analysis. In the clinics and hospitals from which we recruit the use of mood stabilisers and anti-depressants does not always correspond to clinical diagnoses. We will be using the Diagnostic Interview for Psychosis (DIP) to clarify the diagnoses, and suspect there may be discordance between the clinical and research diagnoses. Clozapine is an effective mono-therapy for schizoaffective disorder. For these reason, we feel it would unnecessarily limit the recruitment pool if we excluded research diagnoses of schizoaffective disorder.

We have added to the trial visits, assessments and outcome measures section “We will record use and dose of concomitant psychotropic medications” and to the data analysis section “We will test for the impact of potential confounders, such as concomitant medications, on the results and adjust for these as appropriate.”

Comment 1.2. Authors can list all the prohibited medications and explain the reasons of limitation.

Response 1.2 The prohibited medications are listed in Appendix 1 Inclusion/Exclusion Criteria. We have added reasons for those that did not already have reasons. We have removed warfarin and diuretic use as exclusion criteria.

Comment 1.3. There are several outcome measures in the study. Authors can describe who will perform these assessments and whether they are qualified to perform these assessments.

Response 1.3 We have added to page 12 “All assessments will be conducted by trained members of the research team.”

Comment 1.4. Authors use block randomization to equalize the number of both groups with the block length of 4. They plan to recruit 86 patients and wish the patient number in both group is 43. However, the result may be 44 vs 42 due to the block length. Therefore, the patient number in Figure 1 can be presented as 42~44 after randomization.

Response 1.4 We have adjusted Figure 1 accordingly.

Comment 1.5. The withdrawal criteria about the study medications are non-adherence for 7 or more consecutive days. It may be a little bit of loose. If a patient use only 1 day of study medication in one week, they still can remain in this study. Under such circumstances, the real efficacy of study medication would be unreliable. Authors can describe why they use this criterion as study termination. Some studies use 80~120% of study medications adherence as the criteria for adherence.

Response 1.5 We have chosen 7 or more days of non-adherence of study drug as study drug non-adherence is likely to occur in concert with non-adherence with clozapine. Cessation of clozapine of 7 or more days would likely lead to non-rechallenge of clozapine. We have added "Non-adherence of more than 50% of study medication on pill count" to the withdrawal criteria in Appendix 3 "Withdrawal Criteria"

Comment 1.6. The limitations of a randomized, placebo control trial can be described further.

Response 1.6 – we have added a paragraph in the discussion section on limitations
"There are limitations inherent to randomized, placebo control trials, that apply here. The study population who enrol in this trial may not be generalizable to all people commencing on clozapine, nor can the findings for a trial of people commencing clozapine be translatable to other antipsychotic medications."
Reviewer: 2
Reviewer Name: Amir Krivoy
Institution and Country: Geha Mental Health Center, Sackler Faculty of Medicine, Tel-Aviv Univeristy, Israel
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
In this proposed trial the authors aim to explore the weight-gain control qualities of concomitant metformin, starting from clozapine initiation, for 24 weeks follow-up.
The study protocol is well written, clear and concise. The trial is well rationalized and the methodology is solid.
Few minor points/suggestions:
Exclusion criteria:
The authors might consider adding these to the criteria:

Comment 2.1 Concomitant psychotropic drugs that might affect weight gain – such as mood stabilizers or anticonvulsants,

Response 2.1 This has been discussed in Response 1.1. We will record the use of concomitant mood stabiliser use and adjust for this in the final analysis.

Comment 2.2 previous clozapine trial

Response 2.2 We are only including people who are clozapine naïve.

Comment 2.3 Randomization: May consider stratification of randomization by baseline BMI i.e obese (>29) and non-obese (<29) as they may have different trajectories in the response to metformin

Response 2.3 We believe we have sufficient numbers to be able to adjust for baseline BMI in the final analysis, and as such do not need to stratify at the point of recruitment.

Comment 2.4 Primary outcome – it is not clear what is "adjusted for baseline" – does it mean divided by baseline ? i.e ratio?

Response 2.4 We will use ANCOVA to analyse the final body weight, with the baseline weight as a covariate. We have clarified this language throughout the manuscript.

Comment 2.5 Protocol: advised to monitor addition of concomitant psychotropic drugs, during the naturalistic trial, as clinicians may wish to augment clozapine if it is not effective enough

Response 2.5 We will be monitoring concomitant psychotropics as discussed in responses 1.1 and 2.1.

Comment 2.6 Protocol table: last raw – clozapine blood levels – not needed at baseline

Response 2.6 As participants may have been on clozapine for up to 13 days at time of recruitment, we will collect baseline clozapine levels.

VERSION 2 – REVIEW

REVIEWER	Hung-Yu Chan Taoyuan Psychiatric Center, Ministry of Health and Welfare, Taiwan
REVIEW RETURNED	20-Jan-2018

GENERAL COMMENTS	Authors have responded appropriately to all of the queries.

REVIEWER	Amir Krivoy Geha Mental Health Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel
REVIEW RETURNED	21-Jan-2018

GENERAL COMMENTS	No further comments, I am satisified with the authors' reply I wish the authors success with the upcoming trial