Author’s response to reviews

Title: Clinical and cost-effectiveness of contingency management for cannabis use in early psychosis: the CIRCLE randomised clinical trial

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Author's response to reviews:

Editorial comments:

In addition to addressing the reviewers' comments, please also address the following editorial concerns:

1.) Please change to Abstract headings 'Findings' and 'Interpretation' to 'Results' and 'Conclusions', respectively.

2.) Please move the keywords so they appear just after the Abstract.

3.) Please add a list of abbreviations.

4.) Please add the heading 'Conclusions' to the main text.

5.) Please move the list of declarations to the end of the main text.

6.) Please move your declaration 'Funding' to this list.

7.) Please add the declarations 'Ethics approval and consent to participate' and 'Consent for publication'.

8.) Within the declaration 'Authors contributions', please differentiate between the 2 sets of 'JS' and 'MC' authors.

9.) Please ensure all figures are uploaded as separate figure files, and list the figure legends at the end of the main text.

10.) Authors Thomas Craig, Paul McCrone, Joanne Taylor, Sophie Colman, Amie Randhawa and Marina Christoforou still need to confirm authorship for this manuscript. We have resent the email requesting this, but we'd appreciate it if you could encourage them to complete this.

We have now made the requested changes to the paper. The list of abbreviations can be found on page 19. The statisticians are currently preparing the figures to submit. We are in the process of chasing the authors to confirm by email, as requested.
Reviewer reports:

Reviewer #1: Michael Mcdonell

This study addresses a very significant issue, determining whether or not incentives can be used to reinforce cannabis abstinence in a sample of youth with FEP. It has a large sample and seeks to investigate if the intervention is associated with reductions in psychiatric relapse. The paper describes cost-outcomes associated with changes in psychiatric and related outcomes. While no conceptual model is provided, the authors hypothesize that reductions in cannabis use will result in reductions in acute psychiatric care and associated costs.

Point 1. While the introduction describes some research to support an association between cannabis use and psychotic symptoms, they do not describe literature that specifically supports their hypothesis. Some studies support the association of cannabis use with acute psychiatric care and these should be discussed.

We agree that this would be a useful addition. We have now added a summary of some of the key literature to the first paragraph of the introduction.

Point 2. The authors do not describe studies of contingency management for people with serious mental illness, including Bellack 2006, Tidey et al, 2011, McDonell et al, 2013, McDonell et al, 2017. Rabin et al 2018 investigated a contingency management intervention for cannabis in people with serious mental illness and found results similar to those described here. Similarly, there is a body of literature on contingency management for cannabis use that is not discussed, such as Stanger et al., 2015 and the work of Budney and colleagues in general. This relatively large literature needs to be described to place the finding of this study in the context of what is already known about contingency management for those with co-occurring disorders and cannabis. Also there is a relatively large body of literature on the cost-effectiveness of contingency management, including one study (Murphy et al., 2015) that demonstrated the cost effectiveness of contingency management in people with serious mental illness. These studies, particularly Murphy et al., provide already existing frameworks for cost-analyses.
We agree that this is would be helpful. We have added a discussion of the literature to the second and third paragraphs of the introduction, which we think helps contextualise our trial better.

Point 3. Did the authors based their economic on these models or another model? It appears they utilized a different approach and a justification for this approach, eg not including savings related to changes in PANSS scores or abstinence should be offered.

For our economic analysis, we followed a common practice used in economic evaluations, which is to measure and cost resource use and then link those costs to quality adjusted life years (QALYs) gained. As the reviewer says, we didn’t use PANSS scores or abstinence rates but instead followed the approach recommended by NICE ([https://www.nice.org.uk/process/pmg9/chapter/the-reference-case](https://www.nice.org.uk/process/pmg9/chapter/the-reference-case))

Point 4. Throughout the study the authors refer to relapse when they mean psychiatric relapse or acute care. This is a study of a drug use intervention so the term psychiatric relapse should be use as relapse typically refers to using drugs again after abstinence.

We agree that this is also a helpful point, and we have now clarified this throughout the paper.

Point 5. In terms of the methods. It is unclear why the only outcome of the study is psychiatric care utilization, not cannabis use, when the link between drug use changes in contingency management (or treatment of addiction) and psychiatric care utilization is under-developed. Further cannabis, out of all drugs (and alcohol) may have the weakest association to acute care utilization.

This is an important issue and one that we currently discuss in our limitations section (the final limitation we mention). There are several advantages of using acute care as a proxy for relapse. It is likely that most relatively severe acute episodes result in some form of acute admission, and using all forms of acute care, not only inpatient admission, is much more likely to capture most episodes than admission alone. It is also a pragmatic choice which is relatively easy to ascertain and to follow-up with a high level of completeness through patient records. But we also acknowledge that a potential limitation to this outcome is that not everyone will experience a psychiatric relapse requiring acute care, for example it may be handled by the EIP team instead,
and also that thresholds for admission to acute care may vary considerably, for example by clinician and by area. We have now expanded this section slightly to make the rationale for our choice clearer. Secondly, we do include two measures of cannabis use as secondary outcomes, so that the direct effects of the intervention on cannabis use are explored.

Point 6. In terms of the statistical analyses, an end of treatment and follow up assessment is unusual and fails to utilize the power of repeated measurement. Best practice analyses of contingency management assessments of drug outcomes is not to look at end of treatment abstinence, but rather to utilize approaches like generalized estimating equations. This allows for data during treatment to be considered. It may be that reductions in use, rather than complete abstinence are clinically significant. The conclusion that contingency management is not effective for cannabis use is not appropriate unless more sophisticated analyses are conducted.

We acknowledge that a repeated measures approach has been used in some evaluations of CM, such as Rabin et al. 2018, and that such an approach can be helpful for understanding patients’ response to therapy. However, in this study we were interested in point prevalence abstinence (PPA) at follow-up, which is another common way of evaluating effect (e.g. Budney et al. 2006). We are unable to use the suggested approach to compare groups during treatment as we did not take weekly urine samples from participants in the control condition during the treatment period: we felt this would not be feasible or a justifiable use of resources. However, we did conduct the timeline follow back (TLFB) at all three assessment points, which is a self-reported measure of cannabis use in which participants indicate on a calendar which days they used during the period being considered. This data was used as part of the planned secondary analyses to identify whether the total number of self-reported cannabis using days over the last 3 months (3-month follow-up) or 6 months (18-month follow-up) differed between groups at follow-up. A further analysis of the form suggested by the referee could be a possibility, examining differences in either daily or weekly use between groups. However, the view of our statisticians (RM, LM) is that because the secondary analysis that we have conducted indicates that there is very little difference in urinalysis results between groups at either 3-month follow-up (OR=0.85, 95% CI = 0.55, 1.32) or 18-month follow-up (OR=0.85, 95% CI = 0.50,1.43), a further repeated measures analysis would add little. Such an analysis would result in a slightly different estimate of the difference between groups in cannabis use (a weighted average), but it is very unlikely to be substantially different from that already reported, resulting in little further insight into the data.

Point 7. In terms of the lack of efficacy of the contingency management intervention, it is likely that the frequency of reinforcement, rather than the magnitude of incentives/costs of the
reinforcers would lead to a null finding. The amount paid to participants is consistent with other effective contingency management interventions.

This is an important point, and we have now added it to the fourth paragraph and to the final paragraph of the conclusion. Our CM schedule was adapted from two trials by Budney et al. (2000; 2006), and both trials found a beneficial effect from the CM in cannabis misuse. The reward sessions in one of those trials occurred once per week, while in the other they occurred twice per week. Bellack et al. (2006), which is the only other trial of CM to include cannabis in severe mental illness also used a twice weekly reward schedule. CIRCLE was intended to be a pragmatic trial of a CM intervention in an EIP context and based on feedback from EIP clinicians, it was thought that delivering sessions more frequently than once per week would not be feasible.

Point 8. It is also possible that a 50 ng/mL cutoff for abstinence might have been too conservative. That is, it may have made it challenging for individuals to meet criteria for reinforcement, especially heavy or daily users. A higher cutoff that is more likely to assess very recent abstinence in regular users might have been more effective.

During the CM intervention, we did not use a 50 ng/ml threshold for reinforcement. Instead, we checked whether the patient’s urinary THC concentration had fallen since the previous reward session. To measure urinary THC concentration, we used a benchtop analyser that could give us a rapid reading within 5 minutes. At each session, if the patient’s urinary THC concentration was above 50 ng/ml, we checked to see if it had fallen since the previous session, which we took to be an indication that they had not used between sessions. We acknowledge that this wasn’t clear from the paper before, and we have now expanded the sections on our procedures (in the methods section). Paragraphs 1-3 now describe the contingency management and psychoeducation treatments in more detail.

Urinalysis using a 50 ng/ml threshold was used for the outcomes/assessments. We have now added to our limitations section (item 5) that a lower threshold may have helped identify differences between groups at assessment.

Point 9. Defining psychiatric relapse as acute care utilization, as opposed to psychiatric symptoms misses important and cost associated clinical outcomes.
We have addressed this point in our response to point 5. Acute care use is a relatively good proxy for relapse, with much greater data completeness possible than when ascertainment depends on an interview in a clinical group such as our study group. Whether it has occurred or not is also relatively clear-cut, and it is a measure that is meaningful to service users and of economic importance for service users. However, the considerable limitations have already been discussed (item 7). We do also include psychiatric symptoms as one of our small array of secondary outcomes.

Point 10. Why were QALYs not based on the PANSS scores?

CIRCLE was funded through the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme. For our health economics, we based the QALYS on the EQ-5D as this is the approach recommended for NIHR HTA studies and by the National Institute of Health and Care Excellence (NICE). This approach has been used in numerous economic evaluations conducted in the UK and internationally.

Point 11. Exclusions included homelessness and court involved individuals, those who would have mostly likely benefited from the intervention.

People who were street homeless were excluded as it was thought that they would likely be very transient, and it would be difficult to follow them up for eighteen months, potentially even through patient records. Secondly, we only excluded people on probation if it required drug testing for cannabis. This was to avoid contamination of the control condition through a legal requirement for drug testing.

Point 12. This study proposes a mediating model but does not test mediation. This seems strange, especially as they have the sample size to test mediation.

We agree that this would be an interesting analysis. However, as there was no effect from the CM on either clinical or cannabis use outcomes in the intention-to-treat analysis, senior statistical advice from co-authors LM and RO is that there would be little justification in this paper.
Point 13. Given the sample size it would be important to conduct additional analyses to determine why the intervention didn't work or perhaps identify individuals who it might have worked best for (e.g., those with less severe cannabis use).

We conducted a post-hoc analysis that examines whether CM had a benefit amongst those who complied with the PE. It is described in our results section, under ‘CM in the context of psychoeducation’. We can include the tables for this analysis either to the paper or as a supplementary file if it is seen as useful. Participants were stratified based on severity of cannabis use at randomisation (the groups were: using more than 3 times per week or using 3 times per week or less). However, only a small proportion of those randomised were using 3 times per week or less (77 controls and 78 in CM group), suggesting subgroup analysis is not likely to be worthwhile.

Point 14. There are a number of findings that are described as differences, but they are not statistically significant. None significant findings should not be discussed as being different.

Although we say which group had higher or lower estimates for a number of secondary outcome variables, we have checked that it is clear throughout that these comparisons do not approach statistical significance at the conventional level. We believe that this is a statistically valid description of the outcomes of the study.

Point 15. In terms of the conclusions of the study, without a more refined approach like GEE, it is uncertain if contingency management is effective or not in this sample. Just because it is not associated with reductions in psychiatric care and cost doesn't mean it's not effective.

We agree that a repeated measures approach can help understand patients’ response to CM treatment. However, as discussed in our response to point 6, we are not able to do this or do not think it would be helpful in this case. Based on the outcomes of the trial, the intention-to-treat analysis indicated no benefit from the CM to either use of psychiatric patient care or our secondary outcomes, including cannabis use and clinical outcomes like PANSS scores. Given the lack of any effect, a GEE or multi-level analysis is unlikely to provide further insight into the data.
Rather the post-hoc analysis suggested that amongst those who engaged with treatment, the CM may have been beneficial.

Point 16. The findings of this study must be placed in the larger literature on contingency management. How were the results similar or different and why didn't the intervention demonstrate efficacy on outcomes? The paper overall, tends to "throw the baby out with the bath water" in terms of suggesting that results of this study indicate the lack of the intervention's efficacy. Placing them in the context of the literature would allow readers to determine exactly how this study contributes to what is already known.

We agree that this is a helpful addition. We have now expanded our conclusions section (paragraphs 4-8) to include a discussion of our mixed findings in the context of the literature and why we may have not found an effect in our intention-to-treat analysis despite the relatively robust effects of CM in the literature more generally. However, the results of our post-hoc and cost-effectiveness analyses perhaps suggest that CM is potentially effective in this cohort. More work is needed to explore whether a pragmatic and effective CM interventions can be developed for this cohort.

Reviewer #2: Corinne Cather

This study randomized 551 patients 18-36 yrs of age with a history of at least one psychotic episode who self-reported using cannabis at least once weekly in 12 of the past 24 weeks to a 12 week CM intervention which incentivized biochemically verified decreased use of cannabis + 6 weeks of weekly psychoeducation or to the 6 weeks of psychoeducation alone. The primary outcome was time to readmission to psychiatric hospitalization/crisis service over the 18-month period following randomization. No differences were found in time to readmission to psychiatric hospitalization/crisis service. In terms of secondary outcomes, no differences were seen between groups in the severity of positive symptoms of psychosis, social functioning based on self-reports of engagement in work or study, proportion of cannabis-free urines at assessment, self-reported number of days' cannabis use in the previous 3 months at 3-month follow-up, or the previous six months at 18 months, or number of admissions over 18 months follow-up. Costs were not different. Participants with high levels of engagement with psychoeducation (defined as 4/6 sessions) assigned to CM had an increased time to relapse compared with those in the control group with the same level of engagement in psychoeducation.
Strengths include a large sample size, with very good capture of follow-up data for the primary outcome (95-98%), blinded raters to the primary outcome variables, and a focus on a relatively homogenous group of individuals early in the course of a psychotic illness. The question of how to reduce cannabis use among those early with recent-onset psychosis is clinically meaningful. The paper is well-written and concise.

Weaknesses include lack of blinding for secondary outcomes, and low retention for the assessments conducted at both 3 mos (67%) and 18 mos (50%).

A few comments and suggestions below:

Point 1. The section entitled 'CM in the Context of Psychoeducation' requires some re-working to be more understandable, particularly in terms of specifying the dependent variable, which I gather from reading the Results section is time to relapse?

We agree that this section could be clearer, and we have now clarified it more. The outcome was the primary outcome, time to psychiatric relapse.

Point 2. Would suggest presenting the results from secondary analyses in the same order in which they are specified in the "Outcomes" section.

We agree that this is helpful, and we have now reorganised the secondary outcomes paragraph of our results section so that the results are reported in the same order as they are specified in the secondary analyses section of our methods.

Point 3. I am not a health economist, but found the conclusions about lower costs of CM difficult to follow given that: 1) the intervention costs were higher in the CM group, 2) the costs for drug and alcohol services were higher for the CM group, and 3) intervention and other service use was about the same across groups. Yet, somehow, after imputation, the costs are lower in the CM group? Requires explanation and/or additional statistical review and conclusions do not appear supported by analyses as presented currently.
We found that inpatient costs were lower in the CM group and this (after imputation) offset the extra intervention and drug and alcohol service costs. QALYs were higher for the CM group and so overall the CM intervention was ‘dominant’. However, there was much uncertainty around the results, as shown by the cost-effectiveness planes. Overall, while we found that there was an approximately 80% chance of the intervention being effective, the costs associated with the CM and control conditions were not statistically different. However, we also think that interpretation of this finding is complex as there was no clear benefit from the CM intervention in the study results. We have included this in our limitations section (item 7) and stated that our results need to be interpreted carefully.

Point 4. How many participants achieved the criterion of attendance at 4/6 psychoeducation sessions in each condition? Consider adding percentages to Table 2.

We agree that this is useful information to include in the paper. We now state the numbers and percentages in the ‘CM in the context of psychoeducation’ section of our results and in table 2.

Point 5. Were analyses done separately for heavier vs. light cannabis users? The authors may want to comment at whether testing at the 50 ng/ml cut-off threshold may have over-estimated abstinence among light users in both conditions.

We agree that this is a potential limitation to the study, and as we note in our response to reviewer 1 (point 8) that we have added to our limitations section (number 5) that a lower threshold may have helped identify differences between groups at assessment.