PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Study Protocol for the Hummingbird Study, a Multicenter Exploratory Trial to Assess the Acceptance and Performance of a Digital Medicine System in Adults With Schizophrenia, Schizoaffective Disorder, or First-Episode Psychosis
AUTHORS	Fowler, J.; Cope, Nathan; Knights, Jonathan; Phiri, Peter; Makin, Andrew; Peters-Strickland, Tim; Rathod, Shanaya

VERSION 1 - REVIEW

REVIEWER	hayden Bosworth Duke University, USA have consulted for Otsuka in the last 12 months
REVIEW RETURNED	01-Nov-2018

GENERAL COMMENTS	The authors describe an interesting study protocol paper. Beyond describing the study, it would be important for the authors to describe what knowledge/experience can this protocol benefit the broader research environment. A study protocol can be useful, but to have the paper impactful, it would be important to describe how information can be generalized to others. The authors use research terminology like coproduction methodology as well as other terms information governance personnel, clinical commissioners groups without describing/defining. Readers are not all going to be familiar with these terms Goal is to examine acceptance and performance – these terms need to be defined. What defines acceptance? Details on the logic for the sample size of 60 patients was not clear. Nor why the investigators would expect a 25% discontinuation rate for such a short period? Minor It is not conventional to end the abstract with a section referred to as discussion and ethics. The ethics part would be expected to be in the text and frankly would be expected to be obtained. The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality; however, who these data are communicated to is not clear nor how are these data used. The paragraph that starts off ‘In an open-label, 8-week study, 78% of patients and 72% of HCPs reported being somewhat satisfied,

	satisfied, or extremely satisfied with the DMS [24].' Does not seem to fit with the logic flow of the introduction. It also was not clear if these results pertain to the current study or a different one. The responses also seemed biased to agreement Page 10 – what results were obtained from the focus groups? Page 11 – what constitutes dependable and robust internet or wireless connection? Please clarify if the participants enrolled constitute a stable clinical group? How feasible is it that the HCPs will confirm proper patch application? Are these individuals nurses or psychiatrists? Page 15 is the first time they mention caregivers. Would introduce the involvement and how earlier in the paper Page 17 it is not clear how the inconsistency finding of mems to self-report necessarily one way or the other supports the use of DMS While hummingbirds are nice, the reference in the title is not clear. There does not seem to be a reason to include all of the study measures

REVIEWER	Davide Papola WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona (Italy)
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	This is an exploratory study on the DMS, released on the market in November 2017 by Otsuka Pharmaceutical Company. A wealth of research existed in this area1-5 exploring quite the same research questions as for the present manuscript. I am wondering what new, additional information this exploratory study will provide to the existing literature that can move our knowledge forward in the research area of adherence to pharmacological treatments? Abstract: Authors claim that "digital technology has shown success in schizophrenia assessment and treatment". This sentence is way too generic and simplistic and could be misleading. So I would omit it, or at least I would move it to the introduction, with some references. Introduction: Pg 7 Line 11. I would change "to manage schizophrenia" with "to help people with schizophrenia dealing with their disease" or something similar. Line 31. "The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality"; this only can happen if patients are compliant with the use of the

	DMS and willing to constantly insert data in the application. Such a reflection brings us to introducing the “selection bias” issue. Line 41. “In an open-label, 8-week study, 78% of patients and 72% of HCPs reported..”. Please report the satisfied patients/total number of patient ratio; in this case: 47/60 and 43/60, respectively. A better reference for [24] could be: Peters-Strickland T, Pestreich L, Hatch A, Rohatagi S, Baker RA, Docherty JP, Markovtsova L, Raja P, Weiden PJ, Walling DP. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594. Line 49. Same as above. Methods and analysis. I suggest moving the inclusion and exclusion criteria paragraph after the study design. Pg 9 Line 17. Please make clear if HCPs can access the web portal with or without the patient consent. Outcomes: Knowing that the DMS can detect and report medication ingestion with an accuracy ranging from 93.1% to 100%4, what is the use of exploring the main outcome (proportion of days with good patch coverage during the assessment defined as having ≥80% patch data available or IEMs detected within each day of the assessment period)? It could be argued that this is a rethorical question. This outcome has been already verified4. As we already know that DMS is reliable (change in performances of a tested digital system are unexpected) what is the sense of exploring it again? The secondary outcome is of poor clinical meaning for at least two reasons: 1) it is likely that this trial will suffer from some sort of selection bias, as only individuals motivated to participate in the study and willing to use such a device will enter the study. Furthermore, although participants must have a diagnosis of psychotic disorder, following the inclusion / exclusion criteria it’s likely that only those with a relatively low level of impairment, good insight of disease and good functioning will be enrolled6. As a consequence, participants will be more likely to adhere to the treatment. Thus, this study might render an overemphasised view of the beneficial effects of the DMS. For this reason, the study is far from being considered “pragmatic” as claimed by authors in the abstract. If the study authors want to retain their statement about the pragmatism of the study, they should present a PRECIS-2 tool assessment in the protocol7. 2) It has poor clinical meaning to make claims on adherence as proposed by the authors, namely without a control group composed of patients not using the DMS. I would be eager to read about a pragmatic trial with broad inclusion criteria, randomly allocating participant either to DMS or “per os” assumption, to assess if there are changes in outcomes like relapse episodes or hospital admissions (both compulsory and on a voluntary basis). This is not a study on treatment adherence, so much so that “ingestion adherence” outcome does not appears nor in the title nor in the abstract, nor in the conclusion. About the latter issue.

	The study's outcomes are not presented in a consistent way through the manuscript: in the title and at the beginning of the abstract authors mention "acceptance" and "performance" of the DMS, at the end of the abstract the "proportion of days with good patch coverage" (is this the "performance"?) and "ingestion adherence". In the methods again they talk about "proportion of days with good patch coverage" and "ingestion adherence", but in the conclusion they state that "usability" and "acceptance" will be examined. Statistical analysis How has the sample size been determined? Discussion Pg 16 Line38: "Because it can be implemented discreetly, patients may feel destigmatized and assimilate back into society more readily". Authors take a leap linking the use of DMS with patient recovery! This is totally misleading. This sentence could be good for an advertising campaign, but it's amiss for a scientific paper. Please, remove it. As the only limitations, in the study key points, the authors mention the short trial time-frame and the small sample size. No mention of any study limits are in the discussion. I think that the generalizability issue is as connected to selection bias as it is to the small sample size considered for the study. Authors should clarify this point. From my perspective, there are more possible limitations that should be considered. The first one is that this device may complicate the patient daily routine, as they should not only remember to take the medication but also deal with all the possible everyday setbacks related to the patch stuck on the chest, such as remembering to change it every week, adherence problems in case of sweating, and the possible need to depilate the skin for better adherence. Considering that patients with low illness insight often struggle to comply with relatively simple therapeutic regimes, how can they adhere to such a complex routine? Second, among reasons for refusing medications, perceived coercion and control is often reported and one may argue that this device may likely worsen these subjective feelings, particularly in patients with high levels of suspiciousness, paranoid thoughts and, most of all, passivity experiences and external control of thoughts or body functions. Paradoxically, only patients with good insight and adherence, who would probably not need electronic monitoring, are most likely to comply with all the requirements related to DMS. Third, it is not clear whether the function of the sensor in the pill can be somehow manipulated (for example, by melting the tablet in the water or other liquids)8. Authors must articulate a better dissertation on study limits. I deem pivotal a thorough discussion on selection bias. To date, information on the cost of the DMS on a monthly basis is not available. This hampers the possibility to assess its cost-effectiveness. I would be pleased if the authors could add some information about this issue. Finally, 5 out of 7 of the authors are on the Otsuka payroll. This could lead to think that they are motivated to cast a bright light on the DMS.

	1. Kane, J. M.; Perlis, R. H.; DiCarlo, L. A.; Au-Yeung, K.; Duong, J.; Petrides, G., First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. The Journal of clinical psychiatry 2013, 74 (6), e533-40. 2. Rohatagi, S.; Profit, D.; Hatch, A.; Zhao, C.; Docherty, J. P.; Peters-Strickland, T. S., Optimization of a Digital Medicine System in Psychiatry. The Journal of clinical psychiatry 2016, 77 (9), e1101-e1107. 3. Kopelowicz, A.; Baker, R. A.; Zhao, C.; Brewer, C.; Lawson, E.; Peters-Strickland, T., A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. Neuropsychiatr Dis Treat 2017, 13, 2641-2651. 4. Profit, D.; Rohatagi, S.; Zhao, C.; Hatch, A.; Docherty, J. P.; Peters-Strickland, T. S., Developing a Digital Medicine System in Psychiatry: Ingestion Detection Rate and Latency Period. The Journal of clinical psychiatry 2016, 77 (9), e1095-e1100. 5. Peters-Strickland, T.; Pestreich, L.; Hatch, A.; Rohatagi, S.; Baker, R. A.; Docherty, J. P.; Markovtsova, L.; Raja, P.; Weiden, P. J.; Walling, D. P., Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594. 6. Masand, P.; Han, C.; Pae, C. U., Will the Proteus sensor enhance adherence to aripiprazole or other antipsychotics? Expert review of neurotherapeutics 2017, 17 (4), 319-321. 7. Dal-Re, R.; Janiaud, P.; Ioannidis, J. P. A., Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC medicine 2018, 16 (1), 49. 8. Papola, D.; Gastaldon, C.; Ostuzzi, G., Can a digital medicine system improve adherence to antipsychotic treatment? Epidemiol Psychiatr Sci 2018, 27 (3), 227-229.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1 (Hayden Bosworth – Duke University)

Major

1. The authors describe an interesting study protocol paper. Beyond describing the study, it would be important for the authors to describe what knowledge/experience can this protocol benefit the broader research environment. A study protocol can be useful, but to have the paper impactful, it would be important to describe how information can be generalized to others.

Response:

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health.

The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language. This has been added to the discussion section.

2. The authors use research terminology like coproduction methodology as well as other terms information governance personnel, clinical commissioners groups without describing/defining. Readers are not all going to be familiar with these terms

Response:

The following definitions have been added at first occurrence of the terms.

Co-production in this protocol is the involvement of people with lived experience of mental illness (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and contribution to the protocol.

Information Governance (IG) refers to the way in which the NHS handles, stores and processes information, in particular personal and sensitive information relating to patients and employees. It was vital to ensure that IG individuals were happy with the privacy and storage features of the digital medicine system

Clinical Commissioning Groups (CCGs) are clinically led groups within the NHS that are responsible for the planning and commissioning of healthcare services for their local area.

3. Goal is to examine acceptance and performance – these terms need to be defined. What defines acceptance?

Response:

We are particularly interested in assessing the acceptance of the digital medicine technology in individuals from different care settings. Acceptance will be assessed by study completion and feedback from subjects from patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare providers using the system; this will be assessed by how their clinical decisions altered whilst using the system and through HCP Utility questionnaire evaluations.

In respect to performance, the study will be assessing multiple hardware and software from a varied population. Based on operational feedback of different phones and OS and any technical

troubleshooting that occurs, the study will be able to determine areas of the app that need to be enhanced to ensure that the app functions across multiple hardware and operating systems.

This has been added to the introduction.

4. Details on the logic for the sample size of 60 patients was not clear. Nor why the investigators would expect a 25% discontinuation rate for such a short period?

Response:

The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed in the USA. The discontinuation rate is assumed based on similar discontinuations for other psychiatry studies and the fact that an actively clinical stable population is not being recruited. This has been added to the statistical analysis section.

Minor

5. It is not conventional to end the abstract with a section referred to as discussion and ethics. The ethics part would be expected to be in the text and frankly would be expected to be obtained.

Response:

If required, this can be removed or relocated at the editor's discretion. Previous methodology papers have followed this format hence the reason for providing this.

6. The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality; however, who these data are communicated to is not clear nor how are these data used.

Response:

The data is communicated to the psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the patient choose to share their data, they are able to invite additional healthcare providers, carers and/or family or friends. Recipients of the data, through a web-based password protected platform, are able to view this data and assist the patient with their treatment plan. It is envisioned that HCPs will be able to use this data to make more informed clinical decisions such as whether individuals need dose adjustment, medication changes or conversations on lifestyle, adherence or other parameters. This has been added to the introduction.

7. The paragraph that starts off 'In an open-label, 8-week study, 78% of patients and 72% of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24].' Does not seem to fit with the logic flow of the introduction. It also was not clear if these results pertain to the current study or a different one. The responses also seemed biased to agreement

Response:

These results pertain to a different study (Peters-Strickland et al., Neuropsychiatric Disease and Treatment, 2016) and have been included to highlight previous acceptance of digital medicine system in US population during early acceptability assessments. The inclusion of the specific sentences highlighted in this part of the paper is that it follows a general introduction on how digital tools have been used to assist with schizophrenia management before a detailed overview of the digital medicine system that is being tested. This has been addressed in the introduction and the reference has been updated.

8. Page 10 – what results were obtained from the focus groups?

Response:

The objective of the focus groups was to obtain feedback on the app technology and assess the completion of specific app tasks. The groups identified issues that may have prevented the completion of key tasks and whether greater explanation would be needed, for instance in ensuring the app could send notifications to patients. Furthermore, general feedback on colour and language was obtained. This has been added to the coproduction and patient involvement section.

9. Page 11 – what constitutes dependable and robust internet or wireless connection?

Response:

Subjects should have WiFi at home and/or at work, or at the very least have access to free WiFi hot spots. Alternatively, subjects should have a sufficient data plan from their mobile provider and/or coverage on their phone. Such assessments are made during the screening of potential subjects.

This has been added to the inclusion and exclusion criteria in table 1.

10. Please clarify if the participants enrolled constitute a stable clinical group?

Response:

The degree of clinical stability will be varied across participants that enroll. In short, a fully stable patient population will not be actively recruited, instead a range of clinical populations (crudely based on CGI-S) from different care settings will participate. This has been added to the patient selection section.

11. How feasible is it that the HCPs will confirm proper patch application? Are these individuals nurses or psychiatrists?

Response:

HCPs will confirm proper patch application when patients commence their usage of the digital medicine system, so called on boarding. These individuals will either be psychiatrists or research assistants for the site. During time in-between the only required site visits at weeks 4 and 8, patients will perform patch changing themselves and be guided, if required, through videos contained within the app. There is a freephone technical support line to assist individuals should they wish. This has been added to the procedures section.

12. Page 15 is the first time they mention caregivers. Would introduce the involvement and how earlier in the paper.

Response:

There may be some formatting errors since caregivers is mentioned 8 times prior to page 15. Caregivers are able to participate in the study, but of course requires the subject to confirm/endorse. Should caregivers participate there are consent forms that are required to be signed in terms of data privacy (since names will be collected to allow registration with the online platform) and indeed surveys to complete at the end to understand whether the system assisted them in engaging with their patient. This has been added to the introduction.

13. Page 17 it is not clear how the inconsistency finding of mems to self-report necessarily one way or the other supports the use of DMS

Response:

Electronic medication bottle caps are used as the current gold-standard surrogate for 'objective' adherence data. Few reports in this space exist and the need for more robust objective adherence data is supported through this discrepancy and the limitations of electronic medication bottle caps as an 'objective' measure, given it only measures an intermediate step in the ingestion process. This has been added to the discussion.

14. While hummingbirds are nice, the reference in the title is not clear.

Response:

This is the trial name. Digital medicine studies are being branded using bird names. We expect there to be a number of others arising in the future.

15. There does not seem to be a reason to include all of the study measures.

Response:

Study is exploratory in nature, so we are assessing a range of measures and how they may or may not be affective by a digital medicine system.

Response to Reviewer #2 (Davide Papola– WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona (Italy))

1. This is an exploratory study on the DMS, released on the market in November 2017 by Otsuka Pharmaceutical Company. A wealth of research existed in this area1-5 exploring quite the same research questions as for the present manuscript. I am wondering what new, additional information this exploratory study will provide to the existing literature that can move our knowledge forward in the research area of adherence to pharmacological treatments?

Response:

Authors agree and have incorporated the following in response from Major 1, Reviewer 1 and Reviewer 2.

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language

Abstract:

2. Authors claim that "digital technology has shown success in schizophrenia assessment and treatment". This sentence is way too generic and simplistic and could be misleading. So I would omit it, or at least I would move it to the introduction, with some references.

Response:

This statement has been removed from the abstract.

Introduction:

3. Pg 7 Line 11. I would change “to manage schizophrenia” with “to help people with schizophrenia dealing with their disease” or something similar.

Response:

Suggested edits are acceptable to the authors and the introduction has been changed as suggested.

4. Line 31. “The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality”; this only can happen if patients are compliant with the use of the DMS and willing to constantly insert data in the application. Such a reflection brings us to introducing the “selection bias” issue.

Response:

The subjective data that the system captures is reliant on individuals being engaged with the system; however, other data (medication, activity, rest) is objectivity recorded via the patch, which of course does require engagement but potentially less so than active engagement with the app.

One of the purposes of the study will be to assess individuals engagement with the patch as assessed by the time they wear it – such participants in this study will be from a range of clinical severities, as assessed by CGI-S.

To address the reviewer’s concerns the sentence has been revised:

“The DMS also enables patients to share data on… rest quality, which can be generated while the patient is engaged with the system.”

5. Line 41. “In an open-label, 8-week study, 78% of patients and 72% of HCPs reported..”. Please report the satisfied patients/total number of patient ratio; in this case: 47/60 and 43/60, respectively. A better reference for [24] could be: Peters-Strickland T, Pestreich L, Hatch A, Rohatagi S, Baker RA, Docherty JP, Markovtsova L, Raja P, Weiden PJ, Walling DP. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594.

Response:

Both comments have been edited within the paper; namely the absolute and relative scores, and the reference change.

6. Line 49. Same as above.

Response:

We have added the absolute number for the percentage of patients utilizing the call center and the number of schizophrenia patients included in the rate of ingestion adherence.

Methods and analysis.

7. I suggest moving the inclusion and exclusion criteria paragraph after the study design.

Response:

This has been moved as requested.

8. Pg 9 Line 17. Please make clear if HCPs can access the web portal with or without the patient consent.

Response:

We have included the following:

HCPs can only access the portal for a specific patient once he/she has consented to give them access to their information in the system.

Outcomes:

9. Knowing that the DMS can detect and report medication ingestion with an accuracy ranging from 93.1% to 100%4, what is the use of exploring the main outcome (proportion of days with good patch coverage during the assessment defined as having ≥80% patch data available or IEMs detected within each day of the assessment period)? It could be argued that this is a rethorical question. This outcome has been already verified4. As we already know that DMS is reliable (change in performances of a tested digital system are unexpected) what is the sense of exploring it again?

Response:

Previous studies performed using the DMS were conducted in relatively stable individuals of schizophrenia. For this study, we have broadened out the inclusion criteria and will be assessing the technology in a range of clinical groups from different care settings, such as those individuals managed in the community or on specialized services such as Early Intervention in Psychosis services to determine the performance in these different environments. This has been added to the introduction.

10. The secondary outcome is of poor clinical meaning for at least two reasons: 1) it is likely that this trial will suffer from some sort of selection bias, as only individuals motivated to participate in the study and willing to use such a device will enter the study. Furthermore, although participants must have a diagnosis of psychotic disorder, following the inclusion / exclusion criteria it's likely that only those with a relatively low level of impairment, good insight of disease and good functioning will be enrolled6. As a consequence, participants will be more likely to adhere to the treatment. Thus, this study might render an over emphasised view of the beneficial effects of the DMS. For this reason, the study is far from being considered "pragmatic" as claimed by authors in the abstract. If the study

authors want to retain their statement about the pragmatism of the study, they should present a PRECIS-2 tool assessment in the protocol7.

Response:

Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it is designed to be conducted, a post assessment use of the tool confirms the use of the term pragmatic. For example, from the nine PRECIS-2 domains:

Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified in usual care. The study does exclude inpatients, which in the “real world” could in theory participate but we felt the DMS intervention was of limited benefit in this setting since inpatients have observed adherence

Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads and assessment of patients who may need help with adherence measures. No advertisements have been conducted.

Setting: Would score 4-5 since the care settings used in the study are those in usual care. We have a range of participants from community and specialist mental health services

Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to usual care, the study does use NHS research staff to assist with training and screening, as is commonplace with all clinical studies in the UK

Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this would occur naturally since the w4 visit is to collect a new prescription (which would occur in the real world) and the w8 visit is the completion of the study. Patients do not experience any other “forced” visits.

Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the patch/app the site can contact the patient to found out why they are not engaging and try to encourage; however, this would be the same if the DMS was indeed normal practice; this is the intention of the tool to promote conversations between visits when individuals are not adherent.

Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the outcome has been supported from conversations with HCPs and payers. The good patch coverage days are essential to provide insight into medication taking so again, if the intervention become standard, the metric would be used since it would determine whether objective and insightful data was being captured.

Primary analysis: Would score 4 since all individuals will be included in the analysis with all available data.

Based on the above, the average score is approx. 4 which equates to “Rather pragmatic”

The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself does cause changes to current care but we are not stating how individuals should respond to these changes. They are free to decide for themselves.

Would the reviewer prefer if we include the above as a supplementary figure/text? Or is the above explanation sufficient?

11. 2) It has poor clinical meaning to make claims on adherence as proposed by the authors, namely without a control group composed of patients not using the DMS. I would be eager to read about a pragmatic trial with broad inclusion criteria, randomly allocating participant either to DMS or “per os” assumption, to assess if there are changes in outcomes like relapse episodes or hospital admissions (both compulsory and on a voluntary basis). This is not a study on treatment adherence, so much so that “ingestion adherence” outcome does not appears nor in the title nor in the abstract, nor in the conclusion. About the latter issue. The study’s outcomes are not presented in a consistent way through the manuscript: in the title and at the beginning of the abstract authors mention “acceptance” and “performance” of the DMS, at the end of the abstract the “proportion of days with good patch coverage” (is this the “performance”?) and “ingestion adherence”. In the methods again they talk about “proportion of days with good patch coverage” and “ingestion adherence”, but in the conclusion they state that “usability” and “acceptance” will be examined.

Response:

The study is not intended to measure and report or make any claims of adherence, but instead, to report the observed ingestions recorded by the DMS. Our goal is to look at the impact of patients improvements as a result of participation (e.g. reduced need for follow-up care, knowledge of adherence to medication to help physicians decide whether patients are medication compliant or require a long acting injectable or other follow-up care) with the hypothesis that DMS will reduce overall healthcare utilization burden. This has been added to the introduction.

Statistical analysis

12. How has the sample size been determined?

Response:

The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed in the USA. This has been added as requested by Reviewer 1 comment 4.

Discussion

13. Pg 16 Line38: “Because it can be implemented discreetly, patients may feel destigmatized and assimilate back into society more readily”. Authors take a leap linking the use of DMS with patient recovery! This is totally misleading. This sentence could be good for an advertising campaign, but it’s amiss for a scientific paper. Please, remove it.

Response:

For the context of the reviewer: The emphasis behind the original statement was that the patch was “hidden” reducing any feelings of stigmatization that, say a visible wearable may bring.

The following has been added to the discussion for context. The DMS provides this feedback discreetly, through user-owned and operated applications and a patch that is not readily visible as it is worn on the torso underneath clothing, reducing any potential stigmatization if it (the patch) was visible.

14. As the only limitations, in the study key points, the authors mention the short trial time-frame and the small sample size. No mention of any study limits are in the discussion. I think that the generalizability issue is as connected to selection bias as it is to the small sample size considered for the study. Authors should clarify this point. From my perspective, there are more possible limitations that should be considered. The first one is that this device may complicate the patient daily routine, as they should not only remember to take the medication but also deal with all the possible everyday setbacks related to the patch stuck on the chest, such as remembering to change it every week, adherence problems in case of sweating, and the possible need to depilate the skin for better adherence. Considering that patients with low illness insight often struggle to comply with relatively simple therapeutic regimes, how can they adhere to such a complex routine?

Response:

In addition, another limitation would be selecting a specific mental health population within the UK which may not generalize to other patient populations. Although the DMS does require the patient to engage more with their own care, the benefits of increasing their awareness of medication, activity, rest, and mood patters outweighs risks/burden for most patients. The DMS was not developed for all mental health patients, but for a subset of patients who have difficulty with adherence and want to improve their status by self-monitoring with potential for their HCP’s to make better clinical decisions based on objective data from the DMS. Patients with poor insight into their illness will likely be a better candidate for a long-acting injectable atypical antipsychotic than this DMS. We have added these additional limitations to the study in the limitations section.

15. Second, among reasons for refusing medications, perceived coercion and control is often reported and one may argue that this device may likely worsen these subjective feelings, particularly in patients with high levels of suspiciousness, paranoid thoughts and, most of all, passivity experiences and external control of thoughts or body functions. Paradoxically, only patients with good

insight and adherence, who would probably not need electronic monitoring, are most likely to comply with all the requirements related to DMS. Third, it is not clear whether the function of the sensor in the pill can be somehow manipulated (for example, by melting the tablet in the water or other liquids)8. Authors must articulate a better dissertation on study limits. I deem pivotal a thorough discussion on selection bias.

Response:

The DMS was developed to facilitate patient-physician discussions about their medication adherence and overall health status; this system was not developed for “big brother” to spy on patients in between their physician/clinic visits. As with any new technology, the DMS may be used constructively to have a discussion based on objective evidence or destructively to tell the patient how bad they are behaving. In addition, literature suggests that patients with psychosis can and will engage with mobile technology tools if they perceive some benefit (i.e., connection with their doctor, management of voices, etc.) (Firth J, et al. Schizophr Bull. 2015;doi:10.1093/schbul/sbv132.). The authors disagree that all patients with “good insight” would not benefit from the DMS. The DMS provides objective adherence information that even patients with good insight and intermittent adherence would find helpful to assist in managing their illness. Finally, the sensor has been tested by Proteus Digital Health and is not able to be manipulated or tricked. The ingestible sensor signal is activated to generate a small electrical signal once it is swallowed and comes into contact with stomach fluid; the electrical unique identifiable code signal is transmitted through the skin to the wearable sensor on the left torso. The signal is not transmitted out of the body (i.e., not RFID). Regarding selection bias for this study, the authors attempted to permit a wider range of patients with psychosis into the study to determine if they could benefit from the DMS (i.e., more sub-acute patients rather than completely stable as were done in previous pilot studies). The data collected in this study will indicate how useful or not the DMS may be to this particular UK mental health population.

16. To date, information on the cost of the DMS on a monthly basis is not available. This hampers the possibility to assess its cost-effectiveness. I would be pleased if the authors could add some information about this issue.

Response:

Cost of DMS will vary from market to market and it would be too early to speculate, and inappropriate, to share costs in markets where the system is not available. The study is not designed to make cost-effectiveness claims.

17. Finally, 5 out of 7 of the authors are on the Otsuka payroll. This could lead to think that they are motivated to cast a bright light on the DMS.

Response:

We agree that 5 out of 7 authors are employees of Otsuka Pharmaceuticals. This is a protocol paper from an Otsuka sponsored study, hence the inclusion of Otsuka individuals who contributed to the design. The other two individuals on the author list are the PI and head of research from the lead site. Otsuka tries to execute studies and present data in an objective manner to move the field forward.

The paper emphasizes (or will enhance following the review of the manuscript) that the study is exploratory in nature and there are no comparisons being conducted or indeed powered statistics to make definitive claims. The Otsuka authors all meet the ICMJE criteria for authorship and it would be inappropriate to not include them as authors on this work.

Suggested list of references form Reviewer #2:

1. Kane, J. M.; Perlis, R. H.; DiCarlo, L. A.; Au-Yeung, K.; Duong, J.; Petrides, G., First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. The Journal of clinical psychiatry 2013, 74 (6), e533-40.

2. Rohatagi, S.; Profit, D.; Hatch, A.; Zhao, C.; Docherty, J. P.; Peters-Strickland, T. S., Optimization of a Digital Medicine System in Psychiatry. The Journal of clinical psychiatry 2016, 77 (9), e1101-e1107.

3. Kopelowicz, A.; Baker, R. A.; Zhao, C.; Brewer, C.; Lawson, E.; Peters-Strickland, T., A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. Neuropsychiatr Dis Treat 2017, 13, 2641-2651.

4. Profit, D.; Rohatagi, S.; Zhao, C.; Hatch, A.; Docherty, J. P.; Peters-Strickland, T. S., Developing a Digital Medicine System in Psychiatry: Ingestion Detection Rate and Latency Period. The Journal of clinical psychiatry 2016, 77 (9), e1095-e1100.

5. Peters-Strickland, T.; Pestreich, L.; Hatch, A.; Rohatagi, S.; Baker, R. A.; Docherty, J. P.; Markovtsova, L.; Raja, P.; Weiden, P. J.; Walling, D. P., Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594.

6. Masand, P.; Han, C.; Pae, C. U., Will the Proteus sensor enhance adherence to aripiprazole or other antipsychotics? Expert review of neurotherapeutics 2017, 17 (4), 319-321.

7. Dal-Re, R.; Janiaud, P.; Ioannidis, J. P. A., Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC medicine 2018, 16 (1), 49.

8. Papola, D.; Gastaldon, C.; Ostuzzi, G., Can a digital medicine system improve adherence to antipsychotic treatment? Epidemiol Psychiatr Sci 2018, 27 (3), 227-229.

VERSION 2 – REVIEW

REVIEWER	hayden Bosworth Duke University Working on a grant funded by Otsuka to the VA conduct a trial to evaluate adherence among individuals with severe mental health illness
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	line 69 define IG line 83 type and suggest adding may outweigh

	line 85 - it was not clear how investigators know whether an individual is having adherence problems line 94 - not sure what 'it' is in reference to here line 101 - these data are outdated line 159 - delete out line 168 - relative to what? it is not clear what the comparison is? pre/post, users versus non-users? line 187 - CGIs since this is a general audience, it is important to spell out what this line 393 - remove meticulous

REVIEWER	Davide Papola WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation Department of Neuroscience, Biomedicine and Movement Sciences Section of Psychiatry, University of Verona, Italy.
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	Dear authors, thank you for your response and for addressing some of the points I've raised. I also appreciated the intense editing that improved the level of quality and transparency of the manuscript. Still, some concerns remain. I will unfold them below to carry on this profitable exchange of perspective. Reply to point 1. Authors keep mentioning the stakeholders involvement, stressing the description of the robust engagement strategy they want to adopt to conduct the study. Of course patient involvement is fine. Anyway, the study outcomes are not related to this process of patient engagement. Put in other words. It is important to involve patient representatives in healthcare decision-making activities, but – as I can read from the protocol - the study will not dig on how this involvement could have an impact on the study's outcomes. This is because study outcomes are focused on the technical reliability of the device, just as much as previous studies that I cared to mention in the first round of comments. This is the reason why I continue to believe that – in its substance - this study is going to be not more than a mere restatement of the previous studies on the topic. It is conducted in the UK, it provides for patients coproduction, but hardly it will move the field forward. Reply to point 9. My point still stands. Of course, to broaden the inclusion criteria is fine. But a DMS has already proven reliability in reporting medication ingestion with accuracy in relatively stable individuals, do we expect different results from a different cohort of patients? As the main outcome is "good patch coverage", being stable or unstable from a psychopathological point of view will not make any difference. Reply to point 10. It would be good to include the PRECIS evaluation as a supplementary figure/text. Reply to point 11. 1) I appreciated what the authors added to the introduction with regards to this matter. Still, some degree of confusion remains.

	Authors state that “The study is not intended to measure and report or make any claims of adherence” but, in the text, the secondary endpoint is: “ingestion adherence, defined as …” (line 274). This could be misleading. Maybe authors should cancel “ingestion adherence” as the definition for the secondary endpoint and rephrasing the sentence as follows: “The secondary endpoint is the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage”. This would be in line with what the authors stated above. 2) Authors hypothesize that “DMS will reduce overall healthcare utilization burden”, but no study outcome is intended to test that. Authors should characterize this claim more precisely. Reply to point 14. - I totally agree. This is crucial for putting the DMS into the correct perspective. DMS is not intended to help all patients with mental health conditions, but just “a subset” of them. I strongly recommend making this clear in the inclusion criteria. Restricting the “P(opulation)” of the “PICO” (in this case the “PIO”, as the study is exploratory and doesn’t provide for a Comparison) from “people affected by schizophrenia, schizoaffective disorder, or first-episode psychosis” to “people affected by schizophrenia, schizoaffective disorder, or first-episode psychosis with good insight and willing to improve their status by self-monitoring with potential for their HCP’s to make better clinical decisions based on objective data from the DMS”. - Then authors should rephrase (or delete) the sentence: “Poor insight into schizophrenia can increase risk of medication nonadherence” (line 99) as we agree on the fact that DMS is not thought to help patients with poor illness insight. For this reason the above-mentioned sentence is out of context. - Finally, I would reconsider the fact that “patients with poor insight into their illness will likely be a better candidate for a long-acting injectable atypical antipsychotic”, as it is not automatic that a patient with poor insight must take an antipsychotic. Maybe it would be best to end the sentence stressing the importance of strategies to improve the illness insight. Reply to point 15. - “The authors disagree that all patients with “good insight” would not benefit from the DMS”. Now I see their point. I hope they can understand mine about the DMS not being thought for all patients diagnosed with schizophrenia, schizoaffective disorder, or first-episode psychosis, but only for a subset of them. And the need for making this clear throughout the manuscript. - I thank the authors for their intention to broaden the range of patient with psychosis. This issue should be addressed in the discussion, along with a comment on selection bias and what can be done to prevent it. Reply to point 17. I wonder what are the chances to come across a study funded by the company that invested in a new device, that encourages the reader not to use it. This study is probably biased toward the use of DMS for the reasons I mentioned in the previous comments. In comparison to previous studies there are some differences (study context - UK instead of USA - and the involvement of patients in the study

	production) but outcomes are still quite the same. For this reason is likely that the main study results will repeat what is already known from other publications on the same topic: “DMS is safe, accepted and welcomed by patients”. Concluding remarks 1) As long as the population considered for the study inclusion will remain “all” patients diagnosed with schizophrenia, schizoaffective disorder, or first-episode psychosis, the selection bias issue remains and must be carefully addressed in the manuscript. If the authors will opt for restricting the inclusion criteria to “a subset of people” affected by schizophrenia, schizoaffective disorder, or first-episode psychosis, then the selection bias issue will not be as pivotal anymore. 2) The important sentences the authors added at the end of the abstract/introduction should also be addressed in the discussion.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer #1 (Hayden Bosworth – Duke University)

Major

1. The authors describe an interesting study protocol paper. Beyond describing the study, it would be important for the authors to describe what knowledge/experience can this protocol benefit the broader research environment. A study protocol can be useful, but to have the paper impactful, it would be important to describe how information can be generalized to others.

Our Original Response:

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it’s a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language. This has been added to the discussion section.

Response Accepted No Further Action Needed

2. The authors use research terminology like coproduction methodology as well as other terms information governance personnel, clinical commissioners groups without describing/defining. Readers are not all going to be familiar with these terms

Our Original Response:

The following definitions have been added at first occurrence of the terms.

Co-production in this protocol is the involvement of people with lived experience of mental illness (diagnosed or otherwise) as equal partners alongside other healthcare stakeholders, in the design and contribution to the protocol.

Information Governance (IG) refers to the way in which the NHS handles, stores and processes information, in particular personal and sensitive information relating to patients and employees. It was vital to ensure that IG individuals were happy with the privacy and storage features of the digital medicine system

Clinical Commissioning Groups (CCGs) are clinically led groups within the NHS that are responsible for the planning and commissioning of healthcare services for their local area.

Response Accepted No Further Action Needed

3. Goal is to examine acceptance and performance – these terms need to be defined. What defines acceptance?

Our Original Response:

We are particularly interested in assessing the acceptance of the digital medicine technology in individuals from different care settings. Acceptance will be assessed by study completion and feedback from subjects from patient satisfaction surveys. Furthermore, acceptance will also be evaluated by healthcare providers using the system; this will be assessed by how their clinical decisions altered whilst using the system and through HCP Utility questionnaire evaluations.

In respect to performance, the study will be assessing multiple hardware and software from a varied population. Based on operational feedback of different phones and OS and any technical troubleshooting that occurs, the study will be able to determine areas of the app that need to be enhanced to ensure that the app functions across multiple hardware and operating systems.

This has been added to the introduction.

Response Accepted No Further Action Needed

4. Details on the logic for the sample size of 60 patients was not clear. Nor why the investigators would expect a 25% discontinuation rate for such a short period?

Our Original Response:

The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed in the USA. The discontinuation rate is assumed based on similar discontinuations for other psychiatry studies and the fact that an actively clinical stable population is not being recruited. This has been added to the statistical analysis section.

Response Accepted No Further Action Needed

Minor

5. It is not conventional to end the abstract with a section referred to as discussion and ethics. The ethics part would be expected to be in the text and frankly would be expected to be obtained.

Our Original Response:

If required, this can be removed or relocated at the editor's discretion. Previous methodology papers have followed this format hence the reason for providing this.

Response Accepted No Further Action Needed

6. The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality; however, who these data are communicated to is not clear nor how are these data used.

Our Original Response:

The data is communicated to the psychiatrist that is connected to the patient on the MyCite platform. Additionally, should the patient choose to share their data, they are able to invite additional healthcare providers, carers and/or family or friends. Recipients of the data, through a web-based password protected platform, are able to view this data and assist the patient with their treatment plan. It is envisioned that HCPs will be able to use this data to make more informed clinical decisions such as whether individuals need dose adjustment, medication changes or conversations on lifestyle, adherence or other parameters. This has been added to the introduction.

Response Accepted No Further Action Needed

7. The paragraph that starts off 'In an open-label, 8-week study, 78% of patients and 72% of HCPs reported being somewhat satisfied, satisfied, or extremely satisfied with the DMS [24].' Does not seem to fit with the logic flow of the introduction. It also was not clear if these results pertain to the current study or a different one. The responses also seemed biased to agreement

Our Original Response:

These results pertain to a different study (Peters-Strickland et al., Neuropsychiatric Disease and Treatment, 2016) and have been included to highlight previous acceptance of digital medicine system in US population during early acceptability assessments. The inclusion of the specific sentences highlighted in this part of the paper is that it follows a general introduction on how digital tools have

been used to assist with schizophrenia management before a detailed overview of the digital medicine system that is being tested. This has been addressed in the introduction and the reference has been updated.

Response Accepted No Further Action Needed

8. Page 10 – what results were obtained from the focus groups?

Our Original Response:

The objective of the focus groups was to obtain feedback on the app technology and assess the completion of specific app tasks. The groups identified issues that may have prevented the completion of key tasks and whether greater explanation would be needed, for instance in ensuring the app could send notifications to patients. Furthermore, general feedback on colour and language was obtained. This has been added to the coproduction and patient involvement section.

Response Accepted No Further Action Needed

9. Page 11 – what constitutes dependable and robust internet or wireless connection?

Our Original Response:

Subjects should have WiFi at home and/or at work, or at the very least have access to free WiFi hot spots. Alternatively, subjects should have a sufficient data plan from their mobile provider and/or coverage on their phone. Such assessments are made during the screening of potential subjects.

This has been added to the inclusion and exclusion criteria in table 1.

Response Accepted No Further Action Needed

10. Please clarify if the participants enrolled constitute a stable clinical group?

Our Original Response:

The degree of clinical stability will be varied across participants that enroll. In short, a fully stable patient population will not be actively recruited, instead a range of clinical populations (crudely based on CGI-S) from different care settings will participate. This has been added to the patient selection section.

Response Accepted No Further Action Needed

11. How feasible is it that the HCPs will confirm proper patch application? Are these individuals nurses or psychiatrists?

Our Original Response:

HCPs will confirm proper patch application when patients commence their usage of the digital medicine system, so called on boarding. These individuals will either be psychiatrists or research assistants for the site. During time in-between the only required site visits at weeks 4 and 8, patients will perform patch changing themselves and be guided, if required, through videos contained within the app. There is a freephone technical support line to assist individuals should they wish. This has been added to the procedures section.

Response Accepted No Further Action Needed

12. Page 15 is the first time they mention caregivers. Would introduce the involvement and how earlier in the paper.

Our Original Response:

There may be some formatting errors since caregivers is mentioned 8 times prior to page 15. Caregivers are able to participate in the study, but of course requires the subject to confirm/endorse. Should caregivers participate there are consent forms that are required to be signed in terms of data privacy (since names will be collected to allow registration with the online platform) and indeed surveys to complete at the end to understand whether the system assisted them in engaging with their patient. This has been added to the introduction.

Response Accepted No Further Action Needed

13. Page 17 it is not clear how the inconsistency finding of mems to self-report necessarily one way or the other supports the use of DMS

Our Original Response:

Electronic medication bottle caps are used as the current gold-standard surrogate for ‘objective’ adherence data. Few reports in this space exist and the need for more robust objective adherence data is supported through this discrepancy and the limitations of electronic medication bottle caps as an ‘objective’ measure, given it only measures an intermediate step in the ingestion process. This has been added to the discussion.

Response Accepted No Further Action Needed

14. While hummingbirds are nice, the reference in the title is not clear.

Our Original Response:

This is the trial name. Digital medicine studies are being branded using bird names. We expect there to be a number of others arising in the future.

Response Accepted No Further Action Needed

15. There does not seem to be a reason to include all of the study measures.

Our Original Response:

Study is exploratory in nature, so we are assessing a range of measures and how they may or may not be affective by a digital medicine system.

Response Accepted No Further Action Needed

New Comments from Peer Reviewer

Reviewer: 1

Reviewer Name: hayden bosworth

Institution and Country: Duke University

Please state any competing interests or state ‘None declared’: Working on a grant funded by Otsuka to the VA conduct a trial to evaluate adherence among individuals with severe mental health illness

Please leave your comments for the authors below

line 69 define IG – noted – defined earlier in the text

line 83 type and suggest adding may outweigh - manuscript has been updated

line 85 - it was not clear how investigators know whether an individual is having adherence problems text has been clarified

line 94 - not sure what 'it' is in reference to here - antecedent to be defined properly

line 101 - these data are outdated Request for updated reference (ref 14, line 101-103) cannot be obtained. The reference cited, despite being 10y old is the most recent England specific costs of inpatient and medication for schizophrenia patients.

line 159 - delete out - manuscript has been updated

line 168 - relative to what? it is not clear what the comparison is? pre/post, users versus non-users? Text has been clarified

line 187 - CGIs since this is a general audience, it is important to spell out what this - manuscript has been updated

line 393 - remove meticulous - manuscript has been updated

Response to Reviewer #2 (Davide Papola– WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation; Department of Neuroscience, Biomedicine and Movement Sciences; Section of Psychiatry, University of Verona, Verona (Italy))

1. This is an exploratory study on the DMS, released on the market in November 2017 by Otsuka Pharmaceutical Company. A wealth of research existed in this area 1-5 exploring quite the same research questions as for the present manuscript. I am wondering what new, additional information this exploratory study will provide to the existing literature that can move our knowledge forward in the research area of adherence to pharmacological treatments?

Our Original Response:

Authors agree and have incorporated the following in response from Major 1, Reviewer 1 and Reviewer 2.

Given the level of unfamiliarity with digital medicine systems, conducting clinical trials in this space requires a higher level of stakeholder management and alignment, especially when the trial is being held in a new environment. Whether it's a new country, a new healthcare system, or a new set of investigators, formal buy-in and input is critical to participation. The protocol outlines one way of managing and aligning stakeholders in such an environment - the UK mental health system. Additionally, and increasingly important within mental health services and interventions in the UK, is the involvement of end–users, so called service users who have lived experience of mental health. The methods paper describes a robust engagement strategy using such individuals in mental health research.

Digital health interventions require significant clinician and patient engagement. The protocol describes an approach to ensure that service users of a digital medicine intervention can assist with protocol design and system input e.g. approach and appropriate language

New Peer Reviewer Reply to point 1.

Authors keep mentioning the stakeholders involvement, stressing the description of the robust engagement strategy they want to adopt to conduct the study. Of course patient involvement is fine. Anyway, the study outcomes are not related to this process of patient engagement. Put in other words. It is important to involve patient representatives in healthcare decision-making activities, but – as I can read from the protocol - the study will not dig on how this involvement could have an impact on the study's outcomes. This is because study outcomes are focused on the technical reliability of the device, just as much as previous studies that I cared to mention in the first round of comments. This is the reason why I continue to believe that – in its substance - this study is going to be not more than a mere restatement of the previous studies on the topic. It is conducted in the UK, it provides for patients coproduction, but hardly it will move the field forward.

Our follow-up response:

Previous studies conducted on Abilify MyCite in the United States focused on stakeholder engagement, but inherently, the difference between previous studies and the currently concluded UK study is testing patients on the system in a closed environment, National Health System (NHS) whereby patient care is less segmented and should follow a continuum of care inclusive of wrap-around services to enhance the care of a patient. In so doing, we sought to test previously known

challenges with Investigator and Care giver failing to become more involved by reviewing available objective measures (e.g. patient dashboard indicating medication ingestion or not) through a protocol requirement that said individuals must not only review the dashboard, but document whether their review of the patients objective measures led to any changes or decisions in treatment (e.g. change in medication dose, change of medication, or other interventions). Furthermore, this particularly study uses the co-encapsulation method, taking the sensor tablet and one of either 4 anti-psychotic medications, to assess the value of the technology in different anti-psychotics other than Abilify. For these reasons, we believe this study will actually continue to enrich the iterative dataset inclusive of stakeholder engagement that continues to be collected on the Digital Medicine System and patients who engage. Please note that such data mentioned above (e.g. review of dashboard and decision changes based on data) will be fully discussed and appraised in the full study publication.

Abstract:

2. Authors claim that “digital technology has shown success in schizophrenia assessment and treatment”. This sentence is way too generic and simplistic and could be misleading. So I would omit it, or at least I would move it to the introduction, with some references.

Our Original Response:

This statement has been removed from the abstract.

Response Accepted No Further Action Needed

Introduction:

3. Pg 7 Line 11. I would change “to manage schizophrenia” with “to help people with schizophrenia dealing with their disease” or something similar.

Our Original Response:

Suggested edits are acceptable to the authors and the introduction has been changed as suggested.

Response Accepted No Further Action Needed

4. Line 31. “The DMS also communicates data on patient activity and rest levels as well as subjective data on mood and rest quality”; this only can happen if patients are compliant with the use of the DMS and willing to constantly insert data in the application. Such a reflection brings us to introducing the “selection bias” issue.

Our Original Response:

The subjective data that the system captures is reliant on individuals being engaged with the system; however, other data (medication, activity, rest) is objectivity recorded via the patch, which of course does require engagement but potentially less so than active engagement with the app.

One of the purposes of the study will be to assess individuals engagement with the patch as assessed by the time they wear it – such participants in this study will be from a range of clinical severities, as assessed by CGI-S.

To address the reviewer's concerns the sentence has been revised:

"The DMS also enables patients to share data on… rest quality, which can be generated while the patient is engaged with the system."

Response Accepted No Further Action Needed

5. Line 41. "In an open-label, 8-week study, 78% of patients and 72% of HCPs reported..". Please report the satisfied patients/total number of patient ratio; in this case: 47/60 and 43/60, respectively. A better reference for [24] could be: Peters-Strickland T, Pestreich L, Hatch A, Rohatagi S, Baker RA, Docherty JP, Markovtsova L, Raja P, Weiden PJ, Walling DP. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594.

Our Original Response:

Both comments have been edited within the paper; namely the absolute and relative scores, and the reference change.

Response Accepted No Further Action Needed

6. Line 49. Same as above.

Our Original Response:

We have added the absolute number for the percentage of patients utilizing the call center and the number of schizophrenia patients included in the rate of ingestion adherence.

Response Accepted No Further Action Needed

Methods and analysis.

7. I suggest moving the inclusion and exclusion criteria paragraph after the study design.

Our Original Response:

This has been moved as requested.

Response Accepted No Further Action Needed

8. Pg 9 Line 17. Please make clear if HCPs can access the web portal with or without the patient consent.

Our Original Response:

We have included the following:

HCPs can only access the portal for a specific patient once he/she has consented to give them access to their information in the system.

Response Accepted No Further Action Needed

Outcomes:

9. Knowing that the DMS can detect and report medication ingestion with an accuracy ranging from 93.1% to 100%4, what is the use of exploring the main outcome (proportion of days with good patch coverage during the assessment defined as having ≥80% patch data available or IEMs detected within each day of the assessment period)? It could be argued that this is a rethorical question. This outcome has been already verified4. As we already know that DMS is reliable (change in performances of a tested digital system are unexpected) what is the sense of exploring it again?

Our Original Response:

Previous studies performed using the DMS were conducted in relatively stable individuals of schizophrenia. For this study, we have broadened out the inclusion criteria and will be assessing the technology in a range of clinical groups from different care settings, such as those individuals managed in the community or on specialized services such as Early Intervention in Psychosis services to determine the performance in these different environments. This has been added to the introduction.

New Peer Reviewer Reply to point 9.

My point still stands. Of course, to broaden the inclusion criteria is fine. But a DMS has already proven reliability in reporting medication ingestion with accuracy in relatively stable individuals, do we expect different results from a different cohort of patients? As the main outcome is “good patch coverage”, being stable or unstable from a psychopathological point of view will not make any difference.

Our follow-up response:

Whilst DMS has proven reliable in stable populations of schizophrenia, bipolar, and MDD patients in the United States, the system has never been “tested” in patients experiencing early episode psychosis nor has it been used in more acute patients with increased symptoms requiring more focused medication management and assurance of medication compliance. We presently do not know if the use of this system may challenge a patient with more psychotic symptoms or early engagement due to recent diagnosis of illness. Therefore, we set out to use the same previously established endpoint of good patch coverage to assess a different population of patients in a different healthcare system to understand viability with said population and system.

10. The secondary outcome is of poor clinical meaning for at least two reasons: 1) it is likely that this trial will suffer from some sort of selection bias, as only individuals motivated to participate in the study and willing to use such a device will enter the study. Furthermore, although participants must have a diagnosis of psychotic disorder, following the inclusion / exclusion criteria it's likely that only those with a relatively low level of impairment, good insight of disease and good functioning will be enrolled6. As a consequence, participants will be more likely to adhere to the treatment. Thus, this study might render an over emphasised view of the beneficial effects of the DMS. For this reason, the study is far from being considered "pragmatic" as claimed by authors in the abstract. If the study authors want to retain their statement about the pragmatism of the study, they should present a PRECIS-2 tool assessment in the protocol7.

Our Original Response:

Whilst the PRECIS-2 tool assessment was not completed during the design of the study, when it is designed to be conducted, a post assessment use of the tool confirms the use of the term pragmatic. For example, from the nine PRECIS-2 domains:

Eligibility: Would score 4 (out of 5) since those identified in the study would be those identified in usual care. The study does exclude inpatients, which in the "real world" could in theory participate but we felt the DMS intervention was of limited benefit in this setting since inpatients have observed adherence

Recruitment: would score 4-5 since recruitment is based simply on screening patient caseloads and assessment of patients who may need help with adherence measures. No advertisements have been conducted.

Setting: Would score 4-5 since the care settings used in the study are those in usual care. We have a range of participants from community and specialist mental health services

Organisation: Would likely score 3-4 since although the resource/expertise is largely similar to usual care, the study does use NHS research staff to assist with training and screening, as is commonplace with all clinical studies in the UK

Flexibility (delivery): Would score 3-4 since the study gives patients and HCPs the ability to follow standard of care but does require specific site visit at w4 and w8 (yet one could argue this would occur naturally since the w4 visit is to collect a new prescription (which would occur in the real world) and the w8 visit is the completion of the study. Patients do not experience any other "forced" visits.

Flexibility (adherence): Would score 3 since following enrolment if patients do not utilise the patch/app the site can contact the patient to found out why they are not engaging and try to encourage; however, this would be the same if the DMS was indeed normal practice; this is the intention of the tool to promote conversations between visits when individuals are not adherent.

Primary outcome: would score 3-4; whilst the outcome may not be obvious to patients, the outcome has been supported from conversations with HCPs and payers. The good patch coverage days are essential to provide insight into medication taking so again, if the intervention become standard, the metric would be used since it would determine whether objective and insightful data was being captured.

Primary analysis: Would score 4 since all individuals will be included in the analysis with all available data.

Based on the above, the average score is approx. 4 which equates to “Rather pragmatic”

The reason why the study is not the top score of 5 (Very pragmatic) is that the intervention itself does cause changes to current care but we are not stating how individuals should respond to these changes. They are free to decide for themselves.

Would the reviewer prefer if we include the above as a supplementary figure/text? Or is the above explanation sufficient?

New Peer Reviewer Reply to point 10.

It would be good to include the PRECIS evaluation as a supplementary figure/text.

Our follow-up response:

We have added to supplemental material the text above as a retrospective PRECIS-2 evaluation conducted on the protocol to confirm utilization of the pragmatic term.

11. 2) It has poor clinical meaning to make claims on adherence as proposed by the authors, namely without a control group composed of patients not using the DMS. I would be eager to read about a pragmatic trial with broad inclusion criteria, randomly allocating participant either to DMS or “per os” assumption, to assess if there are changes in outcomes like relapse episodes or hospital admissions (both compulsory and on a voluntary basis). This is not a study on treatment adherence, so much so that “ingestion adherence” outcome does not appears nor in the title nor in the abstract, nor in the conclusion. About the latter issue. The study’s outcomes are not presented in a consistent way through the manuscript: in the title and at the beginning of the abstract authors mention “acceptance” and “performance” of the DMS, at the end of the abstract the “proportion of days with good patch coverage” (is this the “performance”?) and “ingestion adherence”. In the methods again they talk about “proportion of days with good patch coverage” and “ingestion adherence”, but in the conclusion they state that “usability” and “acceptance” will be examined.

Our Original Response:

The study is not intended to measure and report or make any claims of adherence, but instead, to report the observed ingestions recorded by the DMS. Our goal is to look at the impact of patients improvements as a result of participation (e.g. reduced need for follow-up care, knowledge of adherence to medication to help physicians decide whether patients are medication compliant or

require a long acting injectable or other follow-up care) with the hypothesis that DMS will reduce overall healthcare utilization burden. This has been added to the introduction.

New Peer Reviewer Reply to point 11.

1) I appreciated what the authors added to the introduction with regards to this matter. Still, some degree of confusion remains. Authors state that “The study is not intended to measure and report or make any claims of adherence” but, in the text, the secondary endpoint is: “ingestion adherence, defined as …” (line 274). This could be misleading. Maybe authors should cancel “ingestion adherence” as the definition for the secondary endpoint and rephrasing the sentence as follows: “The secondary endpoint is the proportion of detected IEMs to the total expected IEMs ingested on the assessment days that showed good patch coverage”. This would be in line with what the authors stated above.

2) Authors hypothesize that “DMS will reduce overall healthcare utilization burden”, but no study outcome is intended to test that. Authors should characterize this claim more precisely.

Our follow-up response:

1) Whilst we agree this language could make the protocol and subsequent manuscript clearer, the study concluded enrollment in March 2019 and therefore we cannot make these changes. Within the protocol, we specifically define what our ingestion adherence metric means: whilst not identical to true adherence in the clinical sense, this metric is objective and has meaning, which is why we report it.

2) The study has pre and post 24-week data collection specific to use of the healthcare system. Our hypothesis is that there may be some impact on the frequency and engagement that patients have with the healthcare system as a result of DMS usage; however, we do not claim that the study will confirm nor deny this hypothesis but inform it. This is why there is no clearly defined endpoint relating to this but listed as “other data collected” and as an exploratory objective.

Statistical analysis

12. How has the sample size been determined?

Our Original Response:

The study described is a feasibility study with no comparisons and no formal power calculations. The sample size was chosen to contain roughly 20 patients per indication and align with historical studies performed in the USA. This has been added as requested by Reviewer 1 comment 4.

Response Accepted No Further Action Needed

Discussion

13. Pg 16 Line38: “Because it can be implemented discreetly, patients may feel destigmatized and assimilate back into society more readily”. Authors take a leap linking the use of DMS with patient recovery! This is totally misleading. This sentence could be good for an advertising campaign, but it’s amiss for a scientific paper. Please, remove it.

Our Original Response:

For the context of the reviewer: The emphasis behind the original statement was that the patch was “hidden” reducing any feelings of stigmatization that, say a visible wearable may bring.

The following has been added to the discussion for context. The DMS provides this feedback discreetly, through user-owned and operated applications and a patch that is not readily visible as it is worn on the torso underneath clothing, reducing any potential stigmatization if it (the patch) was visible.

Response Accepted No Further Action Needed

14. As the only limitations, in the study key points, the authors mention the short trial time-frame and the small sample size. No mention of any study limits are in the discussion. I think that the generalizability issue is as connected to selection bias as it is to the small sample size considered for the study. Authors should clarify this point. From my perspective, there are more possible limitations that should be considered. The first one is that this device may complicate the patient daily routine, as they should not only remember to take the medication but also deal with all the possible everyday setbacks related to the patch stuck on the chest, such as remembering to change it every week, adherence problems in case of sweating, and the possible need to depilate the skin for better adherence. Considering that patients with low illness insight often struggle to comply with relatively simple therapeutic regimes, how can they adhere to such a complex routine?

Our Original Response:

In addition, another limitation would be selecting a specific mental health population within the UK which may not generalize to other patient populations. Although the DMS does require the patient to engage more with their own care, the benefits of increasing their awareness of medication, activity, rest, and mood patters outweighs risks/burden for most patients. The DMS was not developed for all mental health patients, but for a subset of patients who have difficulty with adherence and want to improve their status by self-monitoring with potential for their HCP’s to make better clinical decisions based on objective data from the DMS. Patients with poor insight into their illness will likely be a better candidate for a long-acting injectable atypical antipsychotic than this DMS. We have added these additional limitations to the study in the limitations section.

New Peer Reviewer reply to point 14.

- I totally agree. This is crucial for putting the DMS into the correct perspective. DMS is not intended to help all patients with mental health conditions, but just “a subset” of them. I strongly recommend

making this clear in the inclusion criteria. Restricting the “P(opulation)” of the “PICO” (in this case the “PIO”, as the study is exploratory and doesn’t provide for a Comparison) from “people affected by schizophrenia, schizoaffective disorder, or first-episode psychosis” to “people affected by schizophrenia, schizoaffective disorder, or first-episode psychosis with good insight and willing to improve their status by self-monitoring with potential for their HCP’s to make better clinical decisions based on objective data from the DMS”.

- Then authors should rephrase (or delete) the sentence: “Poor insight into schizophrenia can increase risk of medication nonadherence” (line 99) as we agree on the fact that DMS is not thought to help patients with poor illness insight. For this reason the above-mentioned sentence is out of context.

- Finally, I would reconsider the fact that “patients with poor insight into their illness will likely be a better

candidate for a long-acting injectable atypical antipsychotic”, as it is not automatic that a patient with poor insight must take an antipsychotic. Maybe it would be best to end the sentence stressing the importance of strategies to improve the illness insight.

Our follow-up response:

Regarding point one, changes to the inclusion criteria can no longer be adjusted as the study completed enrollment in March 2019.

Regarding points two and three, it is the opinion of the authors, based on our view of the evidence, that these remain valid hypotheses, which we will continue to test through these studies. As we cite our reasons for our statements, we do not feel as though we are presenting pure conjectures and feel it appropriate to leave the text as is, given the readers will be able to form their own opinions on the evidence provided to support each statement.

15. Second, among reasons for refusing medications, perceived coercion and control is often reported and one may argue that this device may likely worsen these subjective feelings, particularly in patients with high levels of suspiciousness, paranoid thoughts and, most of all, passivity experiences and external control of thoughts or body functions. Paradoxically, only patients with good insight and adherence, who would probably not need electronic monitoring, are most likely to comply with all the requirements related to DMS. Third, it is not clear whether the function of the sensor in the pill can be somehow manipulated (for example, by melting the tablet in the water or other liquids)8. Authors must articulate a better dissertation on study limits. I deem pivotal a thorough discussion on selection bias.

Our Original Response:

The DMS was developed to facilitate patient-physician discussions about their medication adherence and overall health status; this system was not developed for “big brother” to spy on patients in between their physician/clinic visits. As with any new technology, the DMS may be used constructively to have a discussion based on objective evidence or destructively to tell the patient how bad they are behaving. In addition, literature suggests that patients with psychosis can and will engage with mobile technology tools if they perceive some benefit (i.e., connection with their doctor, management of voices, etc.) (Firth J, et al. Schizophr Bull. 2015;doi:10.1093/schbul/sbv132.). The

authors disagree that all patients with “good insight” would not benefit from the DMS. The DMS provides objective adherence information that even patients with good insight and intermittent adherence would find helpful to assist in managing their illness. Finally, the sensor has been tested by Proteus Digital Health and is not able to be manipulated or tricked. The ingestible sensor signal is activated to generate a small electrical signal once it is swallowed and comes into contact with stomach fluid; the electrical unique identifiable code signal is transmitted through the skin to the wearable sensor on the left torso. The signal is not transmitted out of the body (i.e., not RFID). Regarding selection bias for this study, the authors attempted to permit a wider range of patients with psychosis into the study to determine if they could benefit from the DMS (i.e., more sub-acute patients rather than completely stable as were done in previous pilot studies). The data collected in this study will indicate how useful or not the DMS may be to this particular UK mental health population.

New Peer Reviewer reply to point 15.

- “The authors disagree that all patients with “good insight” would not benefit from the DMS”. Now I see their point. I hope they can understand mine about the DMS not being thought for all patients diagnosed with schizophrenia, schizoaffective disorder, or first-episode psychosis, but only for a subset of them. And the need for making this clear throughout the manuscript.

- I thank the authors for their intention to broaden the range of patient with psychosis. This issue should be addressed in the discussion, along with a comment on selection bias and what can be done to prevent it.

Our follow-up response:

We appreciate the reviewer’s insight and alignment with the perspective that MyCite is not for all patients. For the purposes of the protocol manuscript, we make hypotheses and encourage application of less bias toward how these investigators should choose their patients for entry/enrollment. As such, we gave great leverage to the Principal Investigators who have now enrolled and completed this study to select patients based on our limited inclusion/exclusion criteria to ensure as much pragmatism as possible. When the data gathering is completed, and the study manuscript is published, we will comment in much further detail and reference back to this manuscript whether our hypotheses were upheld or whether the nature of the patients enrolled in the system provide us with a richer dataset upon which to infer new hypotheses.

16. To date, information on the cost of the DMS on a monthly basis is not available. This hampers the possibility to assess its cost-effectiveness. I would be pleased if the authors could add some information about this issue.

Our Original Response:

Cost of DMS will vary from market to market and it would be too early to speculate, and inappropriate, to share costs in markets where the system is not available. The study is not designed to make cost-effectiveness claims.

Response Accepted No Further Action Needed

17. Finally, 5 out of 7 of the authors are on the Otsuka payroll. This could lead to think that they are motivated to cast a bright light on the DMS.

Our Original Response:

We agree that 5 out of 7 authors are employees of Otsuka Pharmaceuticals. This is a protocol paper from an Otsuka sponsored study, hence the inclusion of Otsuka individuals who contributed to the design. The other two individuals on the author list are the PI and head of research from the lead site. Otsuka tries to execute studies and present data in an objective manner to move the field forward.

The paper emphasizes (or will enhance following the review of the manuscript) that the study is exploratory in nature and there are no comparisons being conducted or indeed powered statistics to make definitive claims. The Otsuka authors all meet the ICMJE criteria for authorship and it would be inappropriate to not include them as authors on this work.

New Peer reviewer reply to point 17.

I wonder what are the chances to come across a study funded by the company that invested in a new device, that encourages the reader not to use it.

This study is probably biased toward the use of DMS for the reasons I mentioned in the previous comments. In comparison to previous studies there are some differences (study context - UK instead of USA - and the involvement of patients in the study production) but outcomes are still quite the same. For this reason is likely that the main study results will repeat what is already known from other publications on the same topic: “DMS is safe, accepted and welcomed by patients”.

Our follow-up response:

We appreciate the reviewer’s perspective and have made extensive efforts to report observations rather than generate conclusions. Further, we take our responsibility as scientists to report facts seriously and believe we have upheld the highest of these standards and are among the groups being completely transparent with all regulatory authorities in this space with all statements we make. We do not believe this last comment warrants further action to this methodology publication.

Concluding remarks from Peer Reviewer #2

1) As long as the population considered for the study inclusion will remain “all” patients diagnosed with schizophrenia, schizoaffective disorder, or first-episode psychosis, the selection bias issue remains and must be carefully addressed in the manuscript. If the authors will opt for restricting the inclusion criteria to “a subset of people” affected by schizophrenia, schizoaffective disorder, or first-episode psychosis, then the selection bias issue will not be as pivotal anymore.

2) The important sentences the authors added at the end of the abstract/introduction should also be addressed in the discussion.

Our follow-up response:

From a study design perspective there is no selection bias; however, as the reviewer again infers, there may be selection bias on the part of the investigator determining which patients may be appropriate. Although this is actually in line with routine clinical practice, the reviewer appears to be referring to the issue of selection bias from a results interpretation perspective; as this is a methodology paper we are presenting and discussing the methods, not the results. We will be judicious in the main study paper to discuss this and welcome the reviewer to send correspondence on publication of the next manuscript but believe the reviewer's comments as they relate to this methods paper have been addressed.

Suggested list of references from Reviewer #2:

1. Kane, J. M.; Perlis, R. H.; DiCarlo, L. A.; Au-Yeung, K.; Duong, J.; Petrides, G., First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. The Journal of clinical psychiatry 2013, 74 (6), e533-40.

2. Rohatagi, S.; Profit, D.; Hatch, A.; Zhao, C.; Docherty, J. P.; Peters-Strickland, T. S., Optimization of a Digital Medicine System in Psychiatry. The Journal of clinical psychiatry 2016, 77 (9), e1101-e1107.

3. Kopelowicz, A.; Baker, R. A.; Zhao, C.; Brewer, C.; Lawson, E.; Peters-Strickland, T., A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. Neuropsychiatr Dis Treat 2017, 13, 2641-2651.

4. Profit, D.; Rohatagi, S.; Zhao, C.; Hatch, A.; Docherty, J. P.; Peters-Strickland, T. S., Developing a Digital Medicine System in Psychiatry: Ingestion Detection Rate and Latency Period. The Journal of clinical psychiatry 2016, 77 (9), e1095-e1100.

5. Peters-Strickland, T.; Pestreich, L.; Hatch, A.; Rohatagi, S.; Baker, R. A.; Docherty, J. P.; Markovtsova, L.; Raja, P.; Weiden, P. J.; Walling, D. P., Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat 2016, 12, 2587-2594.

6. Masand, P.; Han, C.; Pae, C. U., Will the Proteus sensor enhance adherence to aripiprazole or other antipsychotics? Expert review of neurotherapeutics 2017, 17 (4), 319-321.

7. Dal-Re, R.; Janiaud, P.; Ioannidis, J. P. A., Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC medicine 2018, 16 (1), 49.

8. Papola, D.; Gastaldon, C.; Ostuzzi, G., Can a digital medicine system improve adherence to antipsychotic treatment? Epidemiol Psychiatr Sci 2018, 27 (3), 227-229.

VERSION 3 - REVIEW

REVIEWER	Davide PApola WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation Department of Neuroscience, Biomedicine and Movement Sciences Section of Psychiatry, University of Verona. Italy
REVIEW RETURNED	26-May-2019

GENERAL COMMENTS	I have no further comments. I thank the editor and the study authors for this friutful exchanges of perspectives.