Author’s response to reviews

Title: Design and methods of the ‘Monitoring Outcomes of Psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol

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Version: 1 Date: 24 Oct 2018

Author’s response to reviews:

Response to Decision Letter

Dear editor,

Please find enclosed our revised manuscript “Design and methods of the ‘Monitoring Outcomes of psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol” (manuscript BHSR-D-18-00522). Below please find our point-by-point rebuttal to the Editor comments and the reviewers’ comments to our manuscript.

However, first we would like to express our gratitude to the reviewers and the Editorial Production Department for their thoughtful and constructive comments which helped us to improve our manuscript. We have responded to each of the reviewers’ comments and hope we have properly addressed the issues raised in this revised manuscript.
We hope this revised version will be published in BMC Health Services Research.

The authors

Technical Comments:

Editor Comments:

BMC Health Services Research operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:
Samantha Hollingworth (Reviewer 1): General. The MOPHAR program is commendable and clearly needed for the many people living with mental disorders with sub-optimal care. This is essentially a protocol paper but that it is not stated in either the title or abstract
Authors’ response: we added the term ‘study protocol’ to both the title and abstract:
Titlepage, page 1, line 1-2: ‘Design and methods of the ‘Monitoring Outcomes of psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol’
Abstract, page 2, line 11: ‘The implementation of a structured somatic monitoring program as part of routine clinical practice, as we describe in this study protocol, may be a solution.’

Title
Define your acronym for MOPHAR
Authors’ response: we added the definition of the acronym for MOPHAR in the title on the titlepage:
Titlepage, page 1, line 1-2: ‘Design and methods of the ‘Monitoring Outcomes of Psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol’

Introduction
P5 line 14 'drug use' Please be clear if this is for prescribed medicines or (illicit) drugs. Consider using the term medicines for prescription products?
Authors’ response: we agree that the term ‘drug use’ is not a clear definition in this paper. In this paper, ‘drug use’ is supposed to refer to both prescription and over-the-counter medication. We replaced ‘drug use’ with ‘medication use’ in our revised paper:
Background, page 5, line 6: ‘Furthermore, there may be considerable medication discrepancies between the medication overview at the psychiatric outpatient clinic and the actual drug medication use by the patient [12].’
Methods/design, page 15 line 21: ‘The physical exercise and lifestyle questionnaire (filled in by the nurse during a MOPHAR appointment) may also be repeated in the course of monitoring of psychotropic drug medication use.’
P5 line 33 could explain on the "introduction of new guidelines, consensus statements, education materials or (national) quality improvement programs". It seems they have not worked well. Why not? Authors’ response: we believe the introduction of such documents alone, without active implementation does not reach and/or activate mental health care professionals enough to improve monitoring practices. There may be several reasons for this lack of effectiveness. We added some of the potential reasons in our revised manuscript:

Background, page 5 line 16 and on: ‘There are several potential reasons for this lack of effectiveness of these strategies. For example, the documents or materials may not reach all relevant health care professionals in the expected time frame, awareness of the need for improvement of monitoring practices may be lacking, or resources for local implementation of the recommendations may be unavailable.

STaken together, structural support of mental health care professionals for data collection and follow-up testing at a local or regional level seems essential for improvement of monitoring practices in psychiatric outpatients.’

Methods

P6 line 33 It would help your readers to know the usual pathway of someone with mental illness. A) How do they end up at the outpatient clinic (by referral from whom)? B) Do they have a regular primary care doctor who would presumably have some information on existing comorbidities (also p13)? C) How often do they attend the outpatient clinic? D) Do they also have regular care from their primary care doctor? If they are referred to these clinics then surely there might have been a diagnosis and associated information collected at an earlier stage. Are there data already elsewhere that you can collate? E) What is your definition of a 'severe' mental illness?

Authors’ response:
Ad A) patients are usually referred to the mental health care outpatient department by their general practitioner or a mental health care treatment officer from another department or institution by means of a referral letter which may also contain information on existing co-morbidities.
Ad B)/D) In the Netherlands, all citizens have a regular care home physician who potentially but not necessarily has some information on somatic co-morbidity. Ideally, and in most cases, this information is provided by the document of the physician who refers the patient. Upon referral, the primary care physician transfers psychiatric but not somatic treatment to the psychiatric outpatient services when he refers the patient.
Ad C) Frequency of attendance ranges between once in three months and twice weekly, depending on factors such as stage and acuteness of illness, illness severity and intensity of treatment.
Ad E) We do not use a separate definition of ‘severe’ mental illness (SMI) in MOPHAR; we don’t select patients based on severe or any mental illness for inclusion. Rather, we adopt the international definition of SMI if relevant for research purposes.

We have added information on the elements of the setting asked about by the reviewer in our revised manuscript:
Methods, Page 9 line 15 and on: ‘Patients can be referred by their general practitioner or by a mental health care treatment officer from another department or institution. Any information on the psychiatric symptoms, co-morbidities and medication use that has been noted in the referral letter is incorporated in the available information for the initial visit for MOPHAR. After referral and initial visit at the outpatient clinic, regular mental health care at the general practitioner’s practice stops.’
Methods/Design, Page 11 line 16 and on: ‘Frequency of attendance ranges between once in three months and twice weekly, depending on factors such as stage and acuteness of illness, illness severity
and intensity of treatment; for MOPHAR they visit the clinic at least at initial visit and yearly, with additional (combined) visits if they (start to) use psychotropic medication.'

P7 line 2 Given the focus on medicines, you might want to comment about the contribution that could be made by having a pharmacist on the team! No mention of one at all.
Authors’ response: we agree with the reviewer that the participation of a pharmacist in the team is very important. We -in our opinion- already mentioned the responsibility of the pharmacist on the team on page 8, line 6-7. We added some emphasis on the pharmacist’s (potential) contribution with respect to the psychotropic pharmacotherapy in MOPHAR:
Methods, page 11 line 3 and on: ‘The pharmacist is responsible for training the MOPHAR nurses (e.g. medication reconciliation) and the quality assurance of the established (psychotropic drug-specific) monitoring protocols. In addition, the pharmacist can be consulted by the treatment team with medication-related questions.’

P7 line 7 What is a nursing specialist - are they different to the psychiatric nurse?
Authors’ response: a nursing specialist in psychiatry is a psychiatric nurse who has been additionally licenced (Master of Advanced Nursing Practice) in order to be able to independently treat mostly stable patients, whereas the psychiatrist usually treats the more complex patients or patients in which pharmacotherapy needs optimization. A nursing specialist is allowed by law to prescribe a limited set of medicines, in this case psychotropic drugs. We added this information to the revised manuscript:
Methods, P11, line 10 and on: ‘Because outpatients are simultaneously treated for their psychiatric disorder by different mental health care providers (e.g. a psychiatrist, psychologist, nursing specialist (nurse with a Master of Advanced Nursing Practice, allowed to treat patients independently or in some specialized settings under supervision of the psychiatrist) and/or psychiatric nurse), the appointments for a MOPHAR screening and the invitations to fill in online questionnaires are planned together as much as possible, shortly before the appointments with the mental health care provider(s).’

Give an indication of time involved in the process e.g. somatic screening at first appointment. What is the average time for a patient to complete the online questionnaire?
Authors’ response: we added the duration of the screening at first appointment, the yearly screening and the psychotropic drug-specific monitoring appointments and the average time for a patient to complete the online questionnaire:
Methods, page 11, line 23: ‘This general somatic screening (±45 minutes) serves to screen for existing somatic co-morbidities, side effects of drugs already in use (e.g. metabolic disturbances), and potential (additional) causes of the mental illness (e.g. thyroid dysfunction for depression).’
Methods, page 12, line 24: ‘This takes patients on average 60-90 minutes in total.’
Methods, page 15 lines 1-2 and line 9-10: ‘The general somatic screening at the first appointment is repeated yearly in all patients (±30 minutes), irrespective of psychiatric diagnosis or medication use. (...) In addition to the general somatic screenings at the first appointment and yearly thereafter, the MOPHAR nurse conducts additional screenings according to drug-specific monitoring protocols if a patient starts with or already uses one or more psychotropic drugs (±30 minutes per appointment).’

P8 line 31 Do all patients have access and skills in using the internet and online forms? What happens if they do not? Do you have a paper version they can complete? I imagine there might be quite a lot of missing data. Do you later try and get some of this missing information in the face to face appointment?
Authors’ response: this is an important remark. Not all patients may have access to and skills in using a computer and/or internet. Furthermore, during break-downs of the electronic medical records, the MOPHAR monitoring program should be able to continue. Therefore, we have a paper version that
patients can complete. Indeed, the nurse checks the filled in questionnaires for any missing data, so that information can be added during the screening appointment. Furthermore, and alternatively, extra computers are available at the outpatient services that patients can use to fill in the questionnaires, sometimes with the aid of the nurse. We added this information in our revised manuscript:

Methods, page 12, line 26 and on: ‘In case a patient does not have access to or skills in using a computer and/or internet or the electronic medical records are unavailable, a paper based version of the questionnaires can be completed. Eventually, the whole MOPHAR program can be implemented non-electronically. Furthermore, and alternatively, extra computers are available at the outpatient services that patients can use to fill in the questionnaires, sometimes with the aid of the nurse. The nurse checks whether all requested questionnaires have been filled in completely before the screening, so any missing information can be added during the appointment.’

P10 line 1 Please specify more clearly what the two questionnaires are: patients and family members? Two different surveys for the patients? Is this the same questionnaire the patient was asked to complete online?
Authors’ response: we have been unclear about this. One questionnaire concerns somatic disease history of the patient and first-degree family members, the other concerns the patient’s lifestyle, including physical exercise and diet. These questionnaires are different from the questionnaire that patients have been asked to complete online, which concerns psychiatric disease history only. These two questionnaires are filled in by the nurse while interviewing the patient (page 10, line 18-19). We have rephrased the sentence about the content of the questionnaires in our revised manuscript:

Methods, page 14 line 3 and on: ‘Third, two structured interviews: one regarding somatic disease history of somatic disease for the patient and first-degree family members and the other regarding the patient’s lifestyle, including physical exercise and diet.’

P10 Line 7 Why is the medication reconciliation not performed by a pharmacist? Is the nurse sufficiently trained in all aspects to fully perform this role? This seems a major issue.
Authors’ response: we agree that it seems logical to have the medication reconciliation performed by a pharmacist. However, during the treatment of their psychiatric disease, patients may see many different mental health care professionals at the same time or consecutively (e.g. a nurse, a psychologist, a psychiatrist, a psychotherapist, etc.). For some patients, it is difficult to adjust to all the different persons they visit to get treatment. Therefore, we believe it is more clear for the patient when all elements of the MOPHAR screening are performed by one person, i.e. the nurse. The MOPHAR nurse is thoroughly trained by the MOPHAR pharmacist to perform medication reconciliation, which we emphasized in our revised manuscript:

Methods, page 10, line 12 and on: ‘To this end, in a one-day session the psychiatric nurses are trained by the MOPHAR pharmacist in the logistics of the MOPHAR monitoring program and how to perform medication reconciliation, how to enter the medication use in the electronic prescribing system and how to register the MOPHAR screening results.’

Methods, page 11 line 3 and on: ‘The pharmacist is responsible for training the MOPHAR nurses (e.g. medication reconciliation) and the quality assurance of the established (psychotropic drug-specific) monitoring protocols.’

P10 line 45 How often do patients attend the clinic? Only once a year?
Authors’ response: frequency of attendance ranges between once in three months and twice weekly, depending on factors such as stage and acuteness of illness, illness severity and intensity of treatment; for MOPHAR they visit the clinic at least at initial visit and yearly, with additional (combined) visits if they (start to) use psychotropic medication. We added this information in the revised manuscript:

Methods, page 11 line 16 and on: ‘Frequency of attendance ranges between once in three months and
twice weekly, depending on factors such as stage and acuteness of illness, illness severity and intensity of treatment; for MOPHAR they visit the clinic at least at initial visit and yearly, with additional (combined) visits if they (start to) use psychotropic medication.’

This program seems rather time intensive for staff and patients. How does this fit into the usual workflow of staff? Are there resource implication (i.e. you need more staff or more time on these tasks)? Are you planning to measure costs of the program?
Authors’ response: since somatic monitoring is in part recommended in Dutch guidelines, we think it does fit in the usual workflow of the team. However, for training, supervision, implementation and support, extra resources are necessary. We may plan to measure cost(effectiveness), as mentioned in the general research objectives (page 14, line 18 and on). We added the information on the time investment for the team:
Methods, page 10 line 26 and on: ‘Since somatic monitoring is in part recommended in Dutch guidelines, MOPHAR is meant to be fitted into the usual workflow of the team. However, extra resources are needed for training, supervision, implementation and support.’

Discussion
Please comment on where that there are other published papers on similar monitoring programs. How is yours different? The same? You make little comment on the existing guidelines, etc. in The Netherlands.
Authors’ response: we added information on other published papers on similar monitoring programs in the revised manuscript:
MOPHAR current status and future perspectives, page 17, line 4 and on: ‘To the best of our knowledge, we are the first to describe a comprehensive monitoring program that actively supports mental health care professionals to implement guideline-concordant general somatic and psychotropic-specific monitoring of psychiatric patients in daily clinical practice, that is flexible to accommodate patients with any psychiatric diagnosis. Two monitoring programs have been described in the literature which, although with a similar level of active support, focused on psychotic patients only and/or on metabolic syndrome screening and monitoring [45, 46].’

As stated in the Methods/Design section (page 10, line 15 and on), the MOPHAR monitoring recommendations were based on the available relevant monitoring guidelines to start with. We used both the national and international guidelines or consensus documents available at the time that the protocols were written, which we clarified in our revised manuscript (see below). In 2015, the new guideline ‘Somatic screening of patients with a severe mental illness’ was published in The Netherlands, in which recommendations were described that were similar to the ones in the MOPHAR protocols. We added this information to our revised manuscript:
Methods, page 13, line 20 and on: ‘This protocol has been written in 2014 by a Dutch multidisciplinary working group, consisting of psychiatrists (including BD and HGR), (hospital) pharmacists (HM, MS) and a clinical chemist. The monitoring recommendations were based on the available national and international relevant monitoring guidelines to start with [27-31], but since there was a paucity thereof, the protocol was mostly based on clinical experience and expert opinion of the members of the working group. In 2015, the new guideline ‘Somatic screening of patients with a severe mental illness’ was published in The Netherlands, in which similar recommendations were described to those in the MOPHAR protocols [32].’

Fernanda Raphael Escobar Gimenes, PhD (Reviewer 2): The paper explores an important subject to the clinical practice and to the quality of care provided for psychiatric outpatients. However, the introduction, background, objectives, methods and conclusion require quite a work as it currently
doesn't present a clear structure and a logical flow. I offer the following advice and critique to enhance its overall clarity, quality and value to the readership and beyond.

Title: Please, indicate that this paper refers to a study protocol
Authors’ response: this valuable comment has also been made by reviewer 1. We added the term ‘study protocol’ to both the title and abstract:
Titlepage, page 1, line 1-2: ‘Design and methods of the ‘Monitoring Outcomes of psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol’

Background
Page 4, line 9: Please, consider the use of "adverse drug event" instead of "iatrogenic adverse effects".
Authors’ response: we replaced ‘iatrogenic adverse effects’ by ‘adverse drug effects’ in our revised manuscript:
Background, page 4 line 9: ‘In addition, the use of psychotropic drugs may cause and/or increase the vulnerability of psychiatric patients to somatic complications due to iatrogenic adverse drug effects [1, 6].’

Page 5, line 47: Please, capitalize "p" for "Monitoring Outcomes of psychiatric Pharmacotherapy"
Authors’ response: we capitalized “p” for "Monitoring Outcomes of psychiatric Pharmacotherapy" in our revised manuscript:
Title page, page 1, line 1-2: ‘Design and methods of the ‘Monitoring Outcomes of Psychiatric Pharmacotherapy’ (MOPHAR) monitoring program – a study protocol’
Abstract, page 2 line13-14: ‘In order to address these issues, we developed the innovative program ‘Monitoring Outcomes of Psychiatric Pharmacotherapy (MOPHAR)’.’
Introduction, page 5 line 24 and on: ‘In order to address these issues, we developed the innovative care path ‘Monitoring Outcomes of Psychiatric Pharmacotherapy (MOPHAR)’.’
List of abbreviations, page 21, line 8: ‘MOPHAR Monitoring Outcomes of Psychiatric Pharmacotherapy’

Methods/Design
Perhaps the objectives of your project could be described in a separate section named "Objectives of the study".
Authors’ response: we thank the reviewer for this suggestion. However, we respectfully decided to not put the objectives of MOPHAR in a separate section “Objectives of the study”, because there are two sets of objectives in this paper (the objectives of the monitoring program and the objectives of the research within the program) and we would like to prevent a mix-up. The objectives of MOPHAR are now in a separate, identically named section, the objectives of the MOPHAR studies are in the ‘MOPHAR research’ section. For clarity, we added a reference to the research objectives in the former section:
Methods/Design, page 9 line 9-11: ‘Secondary objective is to enable routine collection of longitudinal monitoring data of daily psychiatric practice for research purposes. The general research objectives have been discussed above.’

Target population and setting
Although you affirm that the MOPHAR monitoring program can be implemented at any mental health care outpatient clinic, it is unclear whether you will implement the program in other mental health institutions beyond the one where the program is already being implemented or if the proposed study will be conducted only at this large secondary community mental health care outpatient department. Please, clarify this issue.
Authors’ response: for this paper we focused on MHS Drenthe, but after that we will try to spread the MOPHAR concept including MOPHAR research to other mental health care institutions. We added this information in our revised manuscript:

MOPHAR current status and future perspectives, page 17, line 2-3: ‘After that, we aim to implement MOPHAR at other mental health care institutions and also include patients from these other centres in MOPHAR research.’

Please, add the exclusion criteria(s) for this study and specify the sample size.

Authors’ response: there are no general exclusion criteria for inclusion in the MOPHAR patient registry, because all patients referred to the outpatient services are included regardless of diagnosis or disease severity, as mentioned on page 15, line 23-24. There is no pre-specified sample size for the MOPHAR patient registry. Because all new patients are asked for informed consent to be included in MOPHAR, the sample size will increase in time. Per individual research question, the sample size will be calculated for the analyses. We added this information in the revised manuscript:

Methods/Design, page 7, line 4-5: ‘The sample sizes for analyses will be pre-specified per individual research question.’

The MOPHAR treatment team

Page 7, lines 21-33: You described how nurses conduct the medication reconciliation. I wonder if nurses have access to the medical prescription to enter the medications in the electronic prescribing system or if the nurses enter the information provided by the patients (verbally). If nurses have access to the medical prescription, I wonder if it is handwritten or electronic? I am concerned about the medication transcribing process because the literature shows that errors can occur during this process, especially if prescriptions are illegible. Would you, please, clarify the aspects of this process?

Authors’ response: the nurse requests a medication overview from the community pharmacy by fax as part of the preparation for the screening appointment. The medication overview entails a print of the pharmacy records, therefore it does not contain illegible prescriptions. At the screening appointment, the nurse reconciles the overview with the actual medication use by interviewing the patient. Combining pharmacy records and patient counselling is currently the gold standard for medication reconciliation. However, this transcription process is not ideal because errors may occur when copying the pharmacy information. Since in the Netherlands, it is yet technologically impossible to directly transfer the medication records from the community pharmacy to the electronic prescribing system, we believe this is the best possible practice. We clarified the issues raised by the reviewer in our revised manuscript:

Methods/Design, page 14, line 7 and on: ‘Last, medication reconciliation. This is performed by the nurse through a combination of the pharmacy records and patient counselling. In preparation of the screening appointment, the nurse requests a medication overview (including medication and allergies or intolerances) from the community pharmacy of the patient by fax. At the screening appointment, the nurse reconciles this overview with the actual medication use by interviewing the patient. Medication reconciliation provides an up-to-date and complete medication overview including all drugs currently in use and all medication allergies or intolerances that the nurse enters in the electronic prescribing system.’

Lines 28-33: According to this sentence "The team must identify a clear workflow regarding the communication of results with other relevant health care professionals", but I wonder if the setting where this program is already implemented has your own workflow of communication and how it happens. This is an important aspect of the program once gaps in communication during patient handovers is one of the major factors related to adverse events in healthcare settings.

Authors’ response: we added information on the workflow of communication at MHS Drenthe in our
At MHS Drenthe, the primary treatment officer sends a summary of the findings from the MOPHAR screenings to the general practitioner. The prescriptions are sent to the community pharmacy.

In addition, I wonder if only healthcare settings with electronic medical record can implement the MOPHAR program or if the program can be implemented in every healthcare settings regardless of whether they have electronic medical records or not.

Authors’ response: MOPHAR can also be implemented in healthcare settings without electronic medical records. All information will then be kept as paper files, which in MOPHAR will have the general drawbacks of non-electronic medical records. The questionnaires are also available as paper-based versions, as not all patients may have access to and skills in using a computer and/or internet. In addition, in case of a break-down of the electronic medical records, these will make it possible to continue with the MOPHAR program. We added this information in our revised manuscript:

Methods, page 12, line 26 and on: ‘In case a patient does not have access to or skills in using a computer and/or internet or the electronic medical records are unavailable, a paper based version of the questionnaires can be completed. Eventually, the whole MOPHAR program can be implemented non-electronically. Furthermore, and alternatively, extra computers are available at the outpatient services that patients can use to fill in the questionnaires, sometimes with the aid of the nurse.’

Online patient-filled questionnaires

You affirm that "after an invitation letter for the first appointment has being sent, patients are asked to fill in online questionnaires". I wonder if all patients have access to a computer and if not, how these questionnaires are filled? This information might interest the international audience, especially those countries with limited resources whose patients have no access to a computer.

Authors’ response: Please see also the comment of reviewer 1 on this issue. The questionnaires are also available as paper-based versions, as not all patients may have access to and skills in using a computer and/or internet. Furthermore, and alternatively, extra computers are available at the outpatient services that patients can use to fill in the questionnaires, sometimes with the aid of the nurse. We added this information in our revised manuscript:

Methods, page 12, line 26 and on: ‘In case a patient does not have access to or skills in using a computer and/or internet or the electronic medical records are unavailable, a paper based version of the questionnaires can be completed. Eventually, the whole MOPHAR program can be implemented non-electronically. Furthermore, and alternatively, extra computers are available at the outpatient services that patients can use to fill in the questionnaires, sometimes with the aid of the nurse. The nurse checks whether all requested questionnaires have been filled in completely before the screening, so any missing information can be added during the appointment.’

Screening appointment with MOPHAR nurse

You informed that "... patients from most teams are asked in the invitation for the appointment to go to the laboratory for blood withdrawal in the week before the screening." Many readers will not be familiar with the health care system in Netherlands. Perhaps it might be interesting to describe how the process of laboratory test occurs in this country as it might be different from other countries. For instance, in some countries, patients require a physician order for laboratory test samples.

Authors’ response: we added information on the process of laboratory measurements in our revised manuscript:

Methods/Design, page 13, line 13 and on: ‘Second, laboratory measurements. A nursing specialist or doctor orders the laboratory tests on a paper-based laboratory order form. The laboratory associated with MOPHAR has developed a dedicated laboratory order form for MOPHAR, on which the applicant
can order all test from one measurement moment with one check. The nurse can perform the
venepuncture, but patients from most teams are asked in the invitation for the appointment to go to the
laboratory for blood withdrawal in the week before the screening with the laboratory order form sent
along with the invitation.’

Page 13, lines 26-40: you described that "… the MOPHAR monitoring program also provides the
opportunity for a long-term (longitudinal) prospective observational cohort study. The large amount of
information collected in this patient-registry of MOPHAR can be used for research…", but what
questions do you wish to address in this paper?
Authors’ response: in the current paper, we wish to describe the methods and design of the MOPHAR
monitoring program and only the general research objectives (in addition to the objectives of the
MOPHAR monitoring program). We mention those in the Discussion (page 15, line 15 and on). More
specific research questions will be formulated per individual study within MOPHAR. For clarity, we
added this in our revised manuscript:
Methods/Design, page 7, line 24: More specific research questions will be formulated per individual
study within MOPHAR.

Page 14, lines 1-3: you affirmed that the (cost)effectiveness of the MOPHAR program will be accessed.
However, this aspect was not presented anywhere else. Why is this important? A brief overview should
be provided in the background section.
Authors’ response: Although it seems logical to perform somatic monitoring in psychiatric patients and
apply subsequent consequences (i.e. treatment of somatic complications, both by providing medication
and by providing life style programs that work), there is not yet an evidence base for somatic
monitoring of psychiatric patients and this is not yet routine clinical practice in the Netherlands. As the
implementation of somatic monitoring programs may thus warrant an investment without evidence
based benefits from clinical trials, establishing a cost-benefit ratio is necessary to basically support
broad implementation and reimbursement by health care insurance companies. We added this
information in our revised manuscript:
Background, page 6, line 8 and on: ‘Although it seems logical to monitor and treat known
complications of psychiatric disease and psychotropic medication, the evidence for benefits of
monitoring specific (sets of) parameters (and subsequent treatment if indicated) in terms of for example
less somatic complications, better quality of life or shorter treatment duration is lacking. The
(costo)effectiveness of monitoring of specific (sets of) parameters needs to be established to provide an
evidence base for investing in implementation of systematic monitoring programs and reimbursement
by health care insurance companies.’

Please, provide details on the definitions used in this study. For example, what do you call an adverse
event? (page 14, line 7) Along the whole text, you use different words for expressing the same term
(i.e. adverse effects, adverse events, adverse outcomes, etc). Please, consider the use of a theoretical
framework (for example, the International Classification for Patient Safety, from WHO) and provide
the definitions that will be adopted in this study.
It is not clear how you will access patient harm (adverse event) associated with the use of psychotropic
drugs.
Authors’ response: we agree that our use of different terms for adverse effects in this paper needs
clarification. We adopted the use of adverse effects throughout the paper:

Methods/Design, page 7 line 11 and on: ‘The general research objectives are:
1 To investigate the association between patient characteristics and outcomes (e.g.
(costo)effectiveness, adverse effects) of psychiatric pharmacotherapy. Amongst others the
association between pharmacogenetic determinants/biomarkers and the prevalence of adverse events effects of antidepressants will be investigated.

2 To investigate the association between the use of specific psychotropic drugs and adverse outcomes effects like metabolic abnormalities in selected samples and the unselected population (population-based research). In addition we will be able to set up intervention studies targeting such adverse outcomes effects.

Theoretical frameworks and specific definitions (e.g. from WHO) will be specified per individual study in MOPHAR research. We added this information to our revised manuscript:

Methods/Design, Page 7 line 24-25: ‘More specific research questions will be formulated per individual study within MOPHAR, along with theoretical frameworks and specific definitions, if applicable.’

The occurrence of adverse events will be registered though the questionnaires and measurements performed in MOPHAR. All of this information will be registered in the electronic medical records.

Informed consent

You affirmed that "all participants provided written informed consent", but I wonder about the new patients that will be included in this study. How will you address this ethical matter? What about the extra blood sample for future studies? Were the patients aware of this at the time they signed their consent form to participate in the MOPHAR program?

Authors’ response: we ask all eligible patients to participate in MOPHAR research and to provide written informed consent for use of their data and withdrawal of an extra blood sample for research purposes (please note that we state ‘all participants provide written informed consent’ (present tense)). Without written informed consent, patients will still receive regular treatment and somatic monitoring care in the context of MOPHAR. However, they cannot participate in MOPHAR research, which means their data will not be used for research purposes and no extra blood sample will be withdrawn for research purposes. For clarity, we added this information in our revised manuscript:

Declarations, page 19, line 4 and on: ‘The research aspects of MOPHAR were approved by the independent medical ethics committee (RTPO 928, rTPO Leeuwarden, The Netherlands). All participants in MOPHAR research provide written informed consent for use of their data and withdrawal of an extra blood sample for research purposes. Patients that do not provide informed consent for MOPHAR research, will still receive somatic monitoring care from the MOPHAR monitoring program (but their data will not be used nor will an extra blood sample be withdrawn for research purposes).’

The sequence of the topics covered in this paper is peculiar. Please consider revision so it can gain in clarity. For instance, you may present the topics following the sequence:

1. Introduction and background,
2. Aims/Objectives,
3. Methods: study design / participants and setting(s) / the intervention (MOPHAR program) / outcomes assessments / data collection / planned data analysis / ethical approval, and
4. Conclusion.

In addition, if you pretend to develop more than one study, perhaps you could describe each study separately.

Authors’ response: we agree that our manuscript can gain in clarity as a study protocol. We moved the study details from the Discussion to the Methods/Design section, so the research information (participants, outcomes, etc.) is presented before the details on the MOPHAR monitoring program. To
To accommodate this revision, we adjusted the text of the Background and Conclusion sections of the manuscript accordingly:

**Background, page 6 line 14 and on:** ‘This monitoring program added to standard psychiatric treatments, also provides the opportunity to build a patient registry for the conduct of research on topics such as physical complications, side effects of medication and monitoring care in psychiatric outpatients. (...) This paper describes the research aspects of the MOPHAR study as well as the objectives, target population, setting and the composition and roles of the treatment team process and measurements of the MOPHAR monitoring program and indicates what measurements are performed at which time points during outpatient treatment in the MOPHAR monitoring program as well as research aspects of this project.’

**Conclusion, page 19 line 7 and on:** ‘In addition, it provides the opportunity to establish a patient registry for research purposes. (...) Given our experience regarding implementation of the MOPHAR program, we expect that the MOPHAR program including the research aspects is feasible and beneficial for patients in any MHS organisation.’

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Authors’ response: no suggestions were done concerning improvements to the English language within our manuscript.

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- Ethics approval and consent to participate
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- Authors’ Information

Authors’ response: the Declarations section is in place; the ‘Authors’ Information’ subsection was added.

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