Towards tailoring of self-management for patients with chronic heart failure or chronic obstructive pulmonary disease: a protocol for an individual patient data meta-analysis

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ABSTRACT

Introduction: Self-management interventions in patients with chronic conditions have received increasing attention over the past few years, yet the meta-analyses encountered considerable heterogeneity in results. This suggests that the effectiveness of self-management interventions must be assessed in the context of which components are responsible for eliciting the effect and in which subgroups of patients the intervention works best. The aim of the present study is to identify condition-transcending determinants of success of self-management interventions in two parallel individual patient data meta-analyses of self-management trials in patients with congestive heart failure (CHF) and in patients with chronic obstructive pulmonary disease (COPD).

Methods and analysis: Investigators of 53 randomised trials (32 in CHF and 21 in COPD) will be requested to share their de-identified individual patient data. Data will be analysed using random effects models, taking clustering within studies into account. Effect modification by age, sex, disease severity, symptom status, comorbid conditions and level of education will be assessed. Sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination: The de-identified individual patient data are used only for the purpose for which they were originally collected and for which ethical approval has been obtained by the original investigators. Knowledge on the effective ingredients of self-management programmes and identification of subgroups of patients in which those interventions are most effective will guide the development of evidence-based personalised self-management interventions for patients with CHF and COPD as well as with other chronic diseases.

Trial registration number: PROSPERO: CRD42013004698.

Strengths and limitations of this study

This individual patient data (IPD) meta-analysis will evaluate the effects of self-management interventions across two chronic conditions: patients with chronic heart failure and patients with chronic obstructive pulmonary disease.

Embedding of the study in an international network and careful consideration of methodological challenges of the IPD approach have resulted in a robust design of data collection and analysis.

Retrieval bias might occur if not all the original investigators are willing or able to participate and not all individual patient data can be included.

INTRODUCTION

With the rising number of people suffering from one or more chronic conditions,1–3 interventions to support self-management have received increasing attention over the past few years. Such interventions aim to teach patients the skills to actively participate in the management of their chronic condition and generally comprise skills for symptom monitoring, management of medication use and changing health behaviours.3

The evidence presented so far in meta-analyses seems to favour self-management interventions for improving a range of outcomes in various patient groups.4–10 Yet several authors encountered considerable heterogeneity in the outcomes analysed,1,9 sometimes leading to contradictory findings.11,12 A recently published large randomised controlled trial (RCT) among patients with chronic obstructive pulmonary disease (COPD) even reported unexplained higher mortality rates among the patients in...
the intervention group, who received one group session and multiple individual sessions addressing problem-solving techniques and lifestyle changes, followed up by telephone contacts.\textsuperscript{13}

One explanation for those ambiguous findings might be the high variation across studies evaluating self-management interventions. Self-management interventions can be regarded as complex interventions.\textsuperscript{14} The intervention studies differ not only in procedural aspects such as content, duration and intensity,\textsuperscript{14} but also in the patient populations included and outcomes measured.\textsuperscript{15} The question whether self-management interventions are effective cannot be answered without considering which components are responsible for eliciting the effect and identifying in which subgroups of patients the intervention is most effective. Few attempts have been made to identify determinants of success across conditions,\textsuperscript{15} which is rather surprising since a majority of the patients with a chronic condition suffer from comorbidity.\textsuperscript{16,17} Individual trials in different chronic conditions have reported large proportions of non-complying and non-responding patients.\textsuperscript{3} Based on these results, the question arises if barriers to adhere to interventions and adopt self-management behaviour are disease-specific or transcend specific conditions.

The combination of studies in a meta-analysis or meta-regression might provide insight into which programme-specific components are likely to be effective. Intervention studies, however, may differ not only with regard to the intervention evaluated, but also with regard to characteristics of the population included. Comparisons of patient characteristics across studies based on aggregate data in a ‘classical’ meta-analysis may be subjective to ecological bias.\textsuperscript{18} A meta-analysis of individual patient data (IPD) overcomes this potential drawback and enables a straightforward analysis of both subgroups of patients in whom the intervention will be most effective and the effects of relevant components of the studied (complex) interventions.\textsuperscript{19} Sufficient power for analysing subgroups is warranted due to the larger numbers of patients included in the analyses, which overcomes the problems with limited power of subgroup analyses experienced in individual trials.\textsuperscript{19,20} An IPD meta-analysis therefore seems an attractive approach for unravelling the determinants of success of self-management interventions.

In order to discover the determinants of success of self-management interventions for chronic disease ‘at large’ (ie, condition-transcending), the present study will initiate two parallel IPD meta-analyses of self-management trials in two different chronic conditions: in patients with chronic heart failure (CHF) and in patients with COPD. The focus will be on patients with CHF or COPD because of the large number of patients confronted with either one or both of these conditions\textsuperscript{2,21} and the large number of available self-management trials. Although the management of these conditions differs considerably, both patient groups are confronted with daily adherence to a drug treatment and lifestyle advice and monitoring of signs and symptoms is important for the prevention or timely detection of exacerbations.\textsuperscript{21,22} This makes self-management an inevitable part of care for those patient groups.\textsuperscript{21,25} In both conditions, self-management interventions are extensively studied, but the outcomes of published studies are heterogeneous.\textsuperscript{6,11}

**Objectives**

The present paper provides a detailed description of the rationale and design for this IPD meta-analysis. The primary objective is to identify programme-specific and patient-specific determinants of the effect of self-management interventions on health-related quality of life (HRQoL), mortality, all-cause and disease-related hospital admissions and days in hospital in patients with CHF and patients with COPD.

In addition to two independent analyses for self-management trials in patients with CHF and patients with COPD, we will compare the results in both patient groups and investigate the similarities and differences in determinants. The secondary objective is to identify programme-specific and patient-specific determinants of successful self-management interventions in chronic disease ‘at large’, that is, condition-transcendent determinants.

**METHODS AND ANALYSIS**

**Identification of studies**

An extensive literature search has been conducted in the electronic databases of PubMed, EMBASE and Cochrane Central Register on Controlled Trials, PsycINFO and CINAHL from January 1985 to June 2013. Medical Subject Heading (MeSH) terms and key words used in the title and abstract were ‘chronic heart failure’, ‘chronic obstructive pulmonary disease’, ‘self-management’, ‘self-care’, ‘patient-education’, ‘randomized controlled trial’ and synonyms (see online supplementary appendix 1 for PubMed search strategy as an example of the complete search terms). Reference lists of relevant systematic reviews were hand-searched and experts in the domain were consulted to ensure a complete coverage of relevant studies.

**Included studies**

Studies included in this IPD meta-analysis are RCTs with concealed allocation to treatment. Inclusion criteria for patients are an established primary diagnosis of CHF or COPD according to the prevailing international clinical guidelines.\textsuperscript{21,23} This IPD meta-analysis aims to determine patient-specific effect modifiers; therefore, no exclusion criteria apply with regard to, for example, disease severity or comorbidities.

Since a gold standard of which essential elements constitute a self-management intervention is lacking,\textsuperscript{24} an extensive literature search was performed before an
international group of seven experts reached consensus during a conference meeting on essential components for defining ‘self-management intervention’. This resulted in inclusion criteria for interventions, with included interventions requiring a minimum of two of the following components: (1) active stimulation of symptom monitoring, (2) education in problem solving skills (ie, self-treatment such as managing acute exacerbations, resource utilisation and stress/symptom management) and enhancement of (3) medication adherence, (4) physical activity, (5) dietary intake or (6) smoking cessation. The intervention selection is schematically presented in figure 1.

Studies are included in the IPD meta-analysis if they (1) studied an intervention which fulfilled the requirements of the definition of self-management intervention, (2) compared the self-management intervention to usual care or another self-management intervention, (3) reported data on one or more of the relevant outcomes for this IPD meta-analysis (see below), (4) followed patients for at least 6 months and (5) were reported in English, Dutch, French, German, Italian, Portuguese or Spanish.

Methodological quality
Quality appraisal is performed by two independent researchers not involved in any of the primary studies. The methodological quality of the studies is assessed through three relevant criteria based on the ‘Risk of bias’ tool from the Cochrane Collaboration25:
1. Random concealed allocation to treatment;
2. Intention-to-treat analysis;
3. Other deviances (eg, discrepancies in baseline characteristics, high drop-out rates with unbalances between groups and risk of contamination).

Discrepancies between the two researchers are solved through discussion with a third researcher. Results of the quality appraisal will be applied in sensitivity analyses including only studies with a low risk of bias to assess the impact of studies of lower methodological quality.

Data collection
Fifty-three RCTs (32 in CHF patients, 21 in patients with COPD) have been selected for this IPD meta-analysis (see online supplementary appendix 2 for a list of included studies). The original investigators are requested to participate in this IPD meta-analysis through an invitation by email, written in English, Spanish, Portuguese or Dutch. Email addresses have been obtained through contact details of recent publications or retrieval of affiliations. A reminder is sent after several weeks if no response is received, after which other investigators of the original trial will be approached. Investigators will be asked to send their encrypted data, preferably electronically, only after written agreement, by creating encrypted files (in a WinZip file). Standardised data collection forms with the minimum required data items are provided to investigators, but they can send their data in any format most convenient for them (eg, SAS, SPSS and Microsoft Excel spreadsheet). Additionally, investigators are asked to check the extracted intervention characteristics from their studies to ensure a correct interpretation of interventions.

The data items to be collected are based on clinical relevance, previously reported meta-analyses (programme-specific determinants) and subgroup analyses in RCTs (patient-specific determinants). Table 1 presents the data items investigators are requested to share.

Figure 1 Inclusion criteria for interventions.
Data will be saved in the original format as sent by the investigator, and subsequently will be converted to a common SPSS format (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, V20.0 Armonyk, New York: IBM Corp) for data checking and recoding. Data of each trial will be checked with regard to the range of variables measured, extreme values, internal consistency, missing values and consistency with published reports. The details of the interventions as presented in table 2 are cross-checked with trial protocols and published reports. Discrepancies with published results, missing data or inconsistencies will be verified with the original investigators and any problems resolved by consensus.

Across studies, variables might be coded differently and recoding may be necessary to create uniform categories in the combined dataset. To ensure the correct interpretation of original categories and a correct recoding, new categories are only coded after consultation of interpretation of original categories and a correct recoding may be necessary to create uniform categories in the combined dataset. To ensure the correct interpretation of original categories and a correct recoding, new categories are only coded after consultation of the original investigators and any problems resolved by consensus.

### Project management

One of the major challenges in IPD meta-analyses is good communication across cultural and language barriers and careful management of and negotiation with collaborating investigators. For this IPD meta-analysis, an international collaborative study group is established, the Tailoring of Self-managementT and E-health Individual Patient Data (TASTE-IPD) study group. From each original trial, one representative becomes a member of the collaboration. Representatives of the trials will be invited to teleconferences (at least twice a year) and meetings scheduled during international

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### Table 1 Data items investigators are requested to share

<table>
<thead>
<tr>
<th>Study level</th>
<th>Study level</th>
<th>Patient level</th>
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</thead>
<tbody>
<tr>
<td>Methodology</td>
<td>Intervention</td>
<td>Characteristics at baseline</td>
<td>Intervention as implemented</td>
<td>Outcomes</td>
</tr>
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<td>▶ Mode(s) of delivery</td>
<td>▶ Sex</td>
<td>▶ Number of actual contacts with patient during intervention</td>
<td>▶ Health-related quality of life (score on instrument)</td>
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<td>▶ Content covered in intervention</td>
<td>▶ Age</td>
<td>▶ Content covered with individual patient</td>
<td>▶ Mortality (yes/no; time-to-event)</td>
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<tr>
<td>▶ Method of randomisation</td>
<td>▶ Number of planned contacts during intervention</td>
<td>▶ Years since diagnosis</td>
<td>▶ Targeted behaviour achieved</td>
<td>▶ All-cause hospital admissions (number; time-to-first-event)</td>
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<tr>
<td>▶ Blinding to group assignment</td>
<td>▶ Duration of the intervention</td>
<td>▶ Disease severity (CHF=LVEF; COPD=FEV1%, FEV1, FVC)</td>
<td>▶ Targeted behaviour achieved</td>
<td>▶ Disease-related hospital admissions (number; time-to-first-event)</td>
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<td>▶ Type of training given to interventionists</td>
<td>▶ Symptom status (CHF=NYHA class; COPD=dyspnoea)</td>
<td>▶ Loss-to-follow-up and reason</td>
<td>▶ All-cause days in hospital (total number of days)</td>
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<td>▶ Comorbid conditions</td>
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<td>▶ Smoking status</td>
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CHF, chronic/congestive heart failure; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FEV1%, predicted forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

### Table 2 Determinants to be analysed

<table>
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<td>Programme-specific</td>
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*Based on self-management literature.
†Based on social cognitive theory.
‡Based on behavioural techniques.
conferring (annually). Separate teleconferences/meetings will be held for the COPD and CHF trials. During those meetings, major methodological decisions and (preliminary) results will be discussed. Between meetings, members of the study group are updated on study progress through newsletters. Before submission of a manuscript for publication, a draft version will be circulated among investigators to allow for comments, revision and approval. Publications are authored with the names of the investigators where possible and on behalf of the collaboration as a whole with names of other participating investigators listed in the acknowledgements. During the project, the collaboration might decide on new research questions which can be answered through a re-analysis of the combined database.

The project management team will be responsible for management decisions within the collaboration and will organise communication with investigators through mailings, teleconferences and meetings. Its members carry the responsibility for the decisions with regard to daily management of the study, collection of the individual data, development of the core dataset and statistical analysis. The project management team is supported by expert members, who are self-management experts in the fields of either CHF or COPD.

Outcome measures
The present study will focus on various outcome measures. These include:

1. Change in HRQoL at 6 and at 12 months. A distinction is made between disease-specific and generic HRQoL to address the different assessment of HRQoL applied in the original studies;
2. Mortality (time-to-event, % death at 6 and at 12 months);
3. Hospitalised for any cause (time-to-event, % hospitalised at 6 and at 12 months);
4. Total number of days spent in hospital for any cause at 6 and at 12 months;
5. Hospitalised for resp. CHF or COPD (time-to-event, % hospitalised at 6 and at 12 months);
6. Total number of days spent in hospital for resp. CHF or COPD at 6 and at 12 months.

Statistical analyses
First, statistical analyses will be performed for CHF and COPD studies separately to meet the primary objective, but the analyses will be similar. To address the secondary objective, analyses will be repeated combining the data from both patient groups to assess whether effect determinants transcend the specific chronic condition. An additional covariate will be included in the models below to indicate the specific condition. All analyses will be performed in R for Windows V2.15.3 (R Development Core Team, Released 2013, Vienna, Austria: R Foundation for Statistical Computing), according to the intention-to-treat principle. Missing data in studies will be addressed by using multiple imputations by chained equations. Missing values will only be imputed within studies.

The IPD will be analysed using a one-stage approach, that is, simultaneously analysing all observations while accounting for clustering of observations within studies. For time-to-event data, the effects of self-management will be quantified by estimating HR and 95% CI. Cox proportional-hazard models will be used to analyse the data, including a cluster statement to allow inter study variability. For binary outcome data (mortality, all-cause and disease-related hospital admissions), risk ratios and 95% CI will be estimated using logistic mixed-effects models. Effects on continuous outcomes (HRQoL and days in hospital) will be quantified by mean differences and 95% CI and will be estimated using linear mixed effects models. In the log-binomial and linear mixed-effects models, random intercepts and random slopes will be included to take clustering within studies into account. Heterogeneity is assessed with the $I^2$ statistic.

Programme-specific determinants
To identify programme-specific determinants of self-management interventions, the aforementioned models are complemented with covariates for programme characteristics. Table 2 presents an overview of the potential programme-specific determinants to be studied. The programme-specific determinants are based on social cognitive theory, self-management literature and successful behavioural techniques. Additionally, the intensity and duration of interventions will be studied, since these have shown to be related to outcomes in behavioural interventions. Programme-specific determinants are considered significant if the p value is <0.05.

Patient-specific determinants
The aforementioned models will be extended to study effect modification by patient characteristics. Effect modification implies that the effect of the intervention on an outcome differs depending on the value of a third variable, the effect modifier. This can be studied by including the interaction terms in the models. An overview of potential effect modifiers is presented in table 2. This is a selection of clinically relevant variables, which can be expected to have been collected across the majority of trials in a comparable manner. Next to age, sex, disease severity and symptom status, the present study will focus on comorbid conditions (with specific attention to depression) and level of education, as those variables have been shown to be related to change in self-management behaviour in chronic patients. Since the amount of effect modifiers included in the models is restricted by the total number of patients included for analysis, the optional patient-specific effect modifiers will only be included if sufficient patient data are available.

To assess whether the effect of self-management is modified by prespecified patient characteristics, each...
model will include interaction terms of the patient characteristics in table 2. Hence, the independent variables in each model are the random intercepts and slopes for the individual studies, the self-management intervention, the specific patient characteristic and interaction terms (self-management by patient characteristics), with the outcome as a dependent variable. Coefficients of interaction terms will be presented with 95% CI.

Sensitivity analysis
Sensitivity analysis will be performed to assess the robustness of the findings. Inclusion of aggregate data of studies for which IPD are unavailable will be performed to test whether IPD are representative of all eligible studies. A complete-case analysis will be carried out to assess the effects of imputing missing data. In addition, inclusion of only studies with a low risk of bias will be performed to assess the impact of studies of lower methodological quality on the findings. Adaptations to the statistical analysis plan will be made only after the study group has been consulted and consensus has been reached.

ETHICS AND DISSEMINATION
The de-identified IPD are used only for the purpose for which they were originally collected and for which ethical approval has been obtained from the individual studies. In the case of re-analysis of de-identified patient data, informed consent is not deemed necessary. Data will be included in the IPD meta-analysis only after written agreement of the original investigator and after de-identification. Data will remain the property of the original investigators at all times, and they have the right to withdraw their data from the study. The shared datasets will not be used for purposes other than declared in the protocol without the permission of the original investigators. Data are considered confidential and will be stored on a secured location on the digital network of the UMC Utrecht that can only be accessed by the members of the project management team.

This project is embedded in the research line TASTE, which aims to enhance the effectiveness of self-management for chronic conditions. Consolation of generating high-quality scientific output is strengthened by collaboration with international universities, educational institutes and patient/provider organisations. Results of this IPD meta-analysis will be disseminated in international peer-reviewed journals and at international conferences.

DISCUSSION
To the best of our knowledge, the present study will be the first IPD meta-analysis on comprehensive self-management interventions to be conducted across two chronic conditions: CHF and COPD. We aim to identify in each patient group which programme-specific and patient-specific determinants modify the effects of self-management interventions on HRQoL, mortality and healthcare use. Our secondary aim is to identify which determinants transcend both conditions and are associated with better outcomes of self-management interventions in chronic disease ‘at large’. This is crucial information in view of the common approaches in self-management strategies across conditions and the rising number of patients with multiple chronic conditions.

A re-analysis of self-management trials on the level of individual patients is essential to study programme and patient characteristics as possible determinants of success. IPD meta-analyses are still quite rare in the field of complex interventions, even though the literature on the methodology of IPD meta-analyses is increasing. Substantial efforts have been made to carefully design the present IPD meta-analysis and anticipate the limitations of the IPD approach. Based on the lessons learnt from other IPD meta-analyses in this area, the important methodological considerations are met as shown in table 3. With our extensive search strategy, we have minimised the chance of missing relevant trials. Since self-management interventions are complex interventions, a clear definition of inclusion and exclusion criteria is essential for a transparent selection of studies included. We carefully discussed and documented the reasons underlying our choice of the required data items, statistical plan and preplanned sensitivity analyses to ensure that we collect the necessary information to assess the robustness of findings and minimise bias.

Despite our careful methodological considerations, some of our methodological choices can be discussed. First, the choice of inclusion date. The earliest study included in our selection dates back to 1995, resulting in a time span of nearly 20 years over which individual trials were conducted. To ensure completeness, we have chosen not to exclude the first self-management trials, although the ‘usual care’ provided to control groups in these studies will not be comparable to the usual care that is more recent. Second, for our primary analysis, we have chosen to impute missing data only within studies. With this approach, we will limit our analysis to the studies which have provided data on the selected effect modifiers, which might introduce bias if data are not missing completely at random. Another solution might be to impute missing data across studies. Yet, the multilevel methods required to achieve this are quite novel and multiple imputation is generally recommended for imputing sporadic missing values instead of systematically missing data. As non-collected data will be systematically missing in that specific study, we have chosen the conventional approach of multiple imputation within studies only. Third, the quality of our findings is highly dependent on the quality of the original design, the quality and completeness of the data and the level of detail provided by the original researchers. Retrieval bias may occur if not all the original investigators are willing or able to participate and we cannot obtain all
IPD. Therefore, sensitivity analyses are planned to assess the impact on our findings.

With this planned IPD meta-analysis, we aim to advance our understanding of effectiveness of self-management interventions. Knowledge on the effective ingredients of programmes contributes to the development of evidence-based personalised self-management interventions. By identifying subgroups of patients in which self-management interventions are most effective, we will be better able to tailor future interventions and personalise care for patients with chronic disease.

Table 3  Comparison of meta-analyses of individual patient data on self-monitoring/self-management

<table>
<thead>
<tr>
<th>Study</th>
<th>Farmer et al27</th>
<th>Heneghan et al38</th>
<th>Pickup et al39</th>
<th>TASTE-IPD Self-management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies approached and declined19 27</td>
<td>100% participation</td>
<td>52% participation</td>
<td>100% participation</td>
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<td>+</td>
<td>±</td>
<td>+</td>
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<tr>
<td>Intention-to-treat analysis27</td>
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<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Clustering within studies preserved in analysis19</td>
<td>Random intercepts in 1-stage model</td>
<td>2-stage model</td>
<td>Preservation in 1-stage model</td>
<td>Random intercepts in 1-stage model</td>
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<td>+/?</td>
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<tr>
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<td>+</td>
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<tr>
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<td>Sensitivity analysis</td>
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<td>No analysis</td>
<td>Sensitivity analysis</td>
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Ethics approval  This IPD meta-analysis has been exempted from the Medical Research Involving Human Subjects Act of the Netherlands by the Medical Ethics Research Committee of the University Medical Center Utrecht, the Netherlands.

Provenance and peer review  Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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