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Towards tailoring of self-management for patients with chronic heart failure or chronic obstructive pulmonary disease: rationale and design 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 last years, yet meta-analyses encountered considerable heterogeneity in results. This suggests that 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 randomized 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 robustness of 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 programs 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, but also with other chronic diseases. This protocol has been registered in 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 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,[1,2] interventions to support self-management have received increasing attention over the last 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,[4,9] sometimes leading to contradictory findings.[11,12] A recently published large randomised controlled trial 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.[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.[14] The intervention studies not only differ in procedural aspects such as content, duration and intensity,[14] but also in patient populations included and outcomes measured.[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,[15] which is rather surprising since a majority of the patients with a chronic condition suffers from comorbidity.[16,17] Individual trials in different chronic conditions have reported large proportions of non-complying and non-responding patients.[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.

Combination of studies in a meta-analysis or meta-regression might provide insight in which program-specific components are likely to be effective. Intervention studies, however, may not only differ 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.[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.[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.[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 determinants of success of self-management interventions for chronic disease ‘at large’ (i.e. 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[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.[21,22] This makes self-management an inevitable part of care for those patients groups.[21,23] In both conditions self-management interventions are extensively studied, but outcomes of published studies are heterogeneous.[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 both program- 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 program- and patient-specific determinants of successful self-management interventions in chronic disease 'at large', i.e. condition-transcendent determinants.

METHODS AND ANALYSIS

Identification of studies

An extensive literature search has been conducted in the electronic databases of PubMed, EMBASE, Cochrane Central Register on Controlled Trials, PsycINFO and CINAHL from January 1985 to April 2013. MeSH terms and key words in title and abstract used were "chronic heart failure", "chronic obstructive pulmonary disease", "self-management", "self-care", "patient-education", "randomised 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 randomised controlled trials (RCTs) with concealed allocation to treatment, conducted in patients with an established diagnosis of CHF or COPD according to the prevailing international clinical guidelines.[21,23] Since a gold standard of which essential elements constitute a self-management intervention is lacking,[24] an extensive literature search was performed before an international group of 7 experts reached consensus during a conference meeting on essential components for defining 'self-management intervention'. This resulted in a definition requiring inclusion of a minimum of two of the following components in the intervention: (1) active stimulation of symptom monitoring, (2) education in problem solving skills (i.e. self-treatment such as managing acute exacerbations, resource utilisation, 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 six 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. Methodological quality of the studies is assessed through three relevant criteria based on the 'Risk of bias' tool from the Cochrane Collaboration:[25]

1. Random concealed allocation to treatment;
2. Intention-to-treat analysis;
3. Other deviances (e.g. discrepancies in baseline characteristics, high drop-out rates with unbalances between groups, 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 COPD patients) have been selected for this IPD meta-analysis. The original investigators are requested to participate in this IPD meta-analysis through an invitation by e-mail, 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. Only after written agreement, investigators will be asked to send their encrypted data, preferably electronically 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 (e.g. SAS, SPSS, Microsoft Excel spread sheet). Additionally, investigators are asked to check the extracted intervention characteristics from their studies to ensure a correct interpretation of interventions.

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

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, V.20.0 Armonyk, New York: IBM Corp) for data checking and recoding. Data of each trial will be checked with regard to range of the 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 correct interpretation of original categories and a correct recoding, new categories are only coded after consultation of the original investigators. All datasets from individual trials will be assigned a unique trial ID before being merged into the central database.

Project management

One of the major challenges in IPD meta-analyses is good communication across cultural and language barriers, careful management of and negotiating with collaborating investigators.[20] For this IPD meta-analysis an international collaborative study group is established, the TASTE-IPD (Tailoring of Self-managemenT and E-health Individual Patient Data) 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 conferences (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 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 upon new research questions which can be answered through re-analysis of the combined database.

The collaboration contains a project management team responsible for management decisions within the collaboration, communication with investigators and organising 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 months 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 months and at 12 months);
3. Hospitalised for any cause (time-to-event, % hospitalised at 6 months and at 12 months);
4. Total number of days spent in hospital for any cause at 6 months and at 12 months;
5. Hospitalised for resp. CHF or COPD (time-to-event, % hospitalised at 6 months and at 12 months);
6. Total number of days spent in hospital for resp. CHF or COPD at 6 months and at 12 months.

Statistical analyses

First, statistical analyses will be performed for CHF and COPD studies separately to meet the primary objective, but 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 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 version 2.15.3 (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 imputation by chained equations.[26] Missing values will only be imputed within studies.

The IPD will be analysed using a one-stage approach, i.e. simultaneously analysing all observations while accounting for clustering of observations within studies.[27] For time-to-event data, effects of self-management will be quantified by estimating hazard ratios (HR) and 95% confidence interval (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 (RR) and 95% CI will be estimated using log-binomial 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.[28]

Program-specific determinants

To identify program-specific determinants of self-management interventions, the aforementioned models are complemented with covariates for program characteristics. Table 2 presents an overview of potential program-specific determinants to be studied. The program-specific determinants are based on social cognitive theory,[29] self-management literature[24,30,31] and successful behavioural techniques.[32] Additionally, intensity and duration of interventions will be studied, since these have shown to be related to outcomes in behavioural interventions.[33] Program-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 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.[34,35] 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 pre-specified patient characteristics, each model will include interaction terms for 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, specific patient characteristic, and interaction terms (self-management by patient characteristic), 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

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 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 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 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 other purposes than declared in the protocol without 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 TAiloring of Self-managemenT and E-health (TASTE), which aims to enhance the effectiveness of self-management for chronic conditions.[36] Consolidation 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 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 program-specific and patient-specific determinants modify the effects of self-management interventions on health-related quality of life, mortality and health care 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.[16,17]

A re-analysis of self-management trials on the level of individual patients is essential to study both program and patient characteristics as possible determinants of success.[18] IPD meta-analyses are still quite rare in the field of complex interventions,[37-39] even though the literature on methodology of IPD meta-analyses is increasing.[27] Substantial efforts have been made to carefully design the present IPD meta-analysis and anticipate on the limitations of the IPD approach. Based on lessons learned from other IPD meta-analyses in this area, the important methodological considerations are met as is shown in Table 3.[37-39] 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 in- 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 pre-planned 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 timespan of nearly twenty 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 usual care 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, required multilevel methods to achieve this are quite novel and multiple imputation is generally recommended for imputing sporadic missing values instead of systematically missing data.[40] 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 depended on the quality of the original design, the quality and completeness of the data, and the level of detail provided by the original researchers.[25] Retrieval bias may occur if not all 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 programs 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 1: Data items investigators are requested to share.

Study level *Methodology*	**Study level** *Intervention*	**Patient level** *Characteristics at baseline*	**Patient level** *Intervention as implemented*	**Patient level** *Outcomes*
• Year of recruitment • Location of recruitment • Method of randomisation • Blinding to group assignment	• Mode(s) of delivery • Content covered in intervention • Number of planned contacts during intervention • Duration of the intervention • Type of training given to interventionists	• Sex • Age • Years since diagnosis • Disease severity (CHF=LVEF; COPD=FEV1%, FEV1, FVC) • Symptom status (CHF = NYHA class; COPD = dyspnoea) • Comorbid conditions • Level of education • Ethnic minority • Living alone • Self-efficacy • Depression • Body mass index • Smoking status	• Number of actual contacts with patient during intervention • Content covered with individual patient • Targeted behaviour achieved • Loss-to-follow-up and reason	• Health-related quality of life (score on instrument) • Mortality (yes/no; time-to-event) • All-cause hospital admissions (#; time-to-first-event) • Disease-related hospital admissions (#; time-to-first-event) • All-cause days in hospital (total # days) • Disease-related days in hospital (total # days)

CHF = chronic/congestive heart failure; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FEV1% = predicted forced expiratory volume in 1 second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2: Determinants to be analysed.

	Determinants
Program-specific	• Number of planned contacts • Duration of the intervention • Training given to interventionists (standardised/heterogeneous)† • Group contact with peers (y/n)*† • Keeping diaries for symptom-monitoring (y/n)ǂ • Goal-setting skills (y/n)*† • Problem-solving skills (y/n)*† • Support allocation skills (y/n)†
Patient-specific	• Sex • Age • Disease severity • Symptom severity • Number of comorbid conditions • Depression • Level of education *Optional variables (only analysed if sufficient data available):* • *Recently diagnosed* • *Self-efficacy* • *Living status* • *Body Mass Index* • *Smoking status*

*based on social cognitive theory; †based on self-management literature; ǂbased on behavioural techniques.

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

Study	Farmer et al.[37] *Self-monitoring of blood glucose*	Heneghan et al.[38] *Self-monitoring of oral anticoagulation*	Pickup et al.[39] *Self-monitoring of blood glucose*	TASTE-IPD *Self-management*
# studies approached and declined[19,27]	100% participation	52% participation	100% participation	On-going
Systematic search[27]	+/- Limited syntax	+	+/- Limited syntax	+
Efforts to include non-published data[20]	+	+	-	-
Intention-to-treat analysis[27]	+	+	?	+
Clustering within studies preserved in analysis[19]	+ Random intercepts in 1-stage model	+ 2-stage model	+/- Preservation in 1-stage model unclear	+ Random intercepts in 1-stage model
Handling missing data within studies and impact on results[27]	+	? No information handling missing data	+/? No information impact missing data	+
Impact of missing trials on results[19,27]	NA	?	NA	+ Sensitivity analysis of aggregate data
Impact of quality assessment on results[19]	+ Sensitivity analysis	- No analysis	- No analysis	+ Sensitivity analysis

NA = not applicable; + = present in study; +/- = partly present in study; - = not present in study; ? = no information in publication.

AUTHORS' CONTRIBUTIONS

All authors participated in developing the study design. NHJ and HW selected the studies. NHJ wrote the first draft of this manuscript. HW, JCAT, RHHW, TWET, TT, JP, JB, TJ, AWH and MJS revised several versions of the manuscript. All authors approved the final version.

COMPETING INTERESTS

None.

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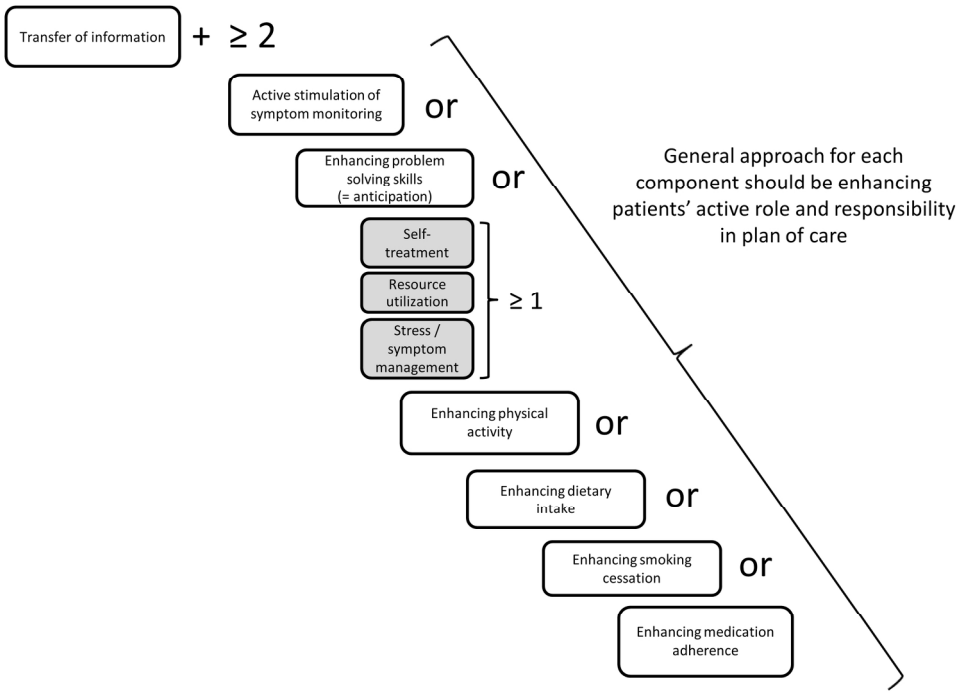
Figure 1: Inclusion criteria for interventions.



190x142mm (300 x 300 DPI)

APPENDIX 1: SEARCH STRATEGY FOR PUBMED

((“heart failure”[MeSH Terms] OR CHF[Title/Abstract] OR HF[Title/Abstract] OR “congestive heart failure”[Title/Abstract] OR “chronic heart failure”[Title/Abstract] OR “chronic cardiac failure” [Title/Abstract] OR “congestive cardiac failure”[Title/Abstract] OR “heart failure”[Title/Abstract] OR “cardiac failure”[Title/Abstract] OR “heart decompensation”[Title/Abstract])

OR (“pulmonary disease, chronic obstructive”[MeSH Terms] OR COPD[Title/Abstract] OR “chronic obstructive pulmonary disease”[Title/Abstract] OR “chronic obstructive airway disease”[Title/Abstract] OR “chronic airflow obstruction”[Title/Abstract] OR “chronic obstructive lung disease”[Title/Abstract] OR “chronic bronchitis”[Title/Abstract] OR bronchitis[Title/Abstract] OR emphysema[Title/Abstract] OR “lung emphysema”[Title/Abstract] OR “pulmonary emphysema”[Title/Abstract]))

AND (self-management[MeSH Terms] OR self-care[MeSH Terms] OR patient-education[MeSH Terms] OR “behavior therapy”[MeSH Terms] OR self-manag*[Title/Abstract] OR self-car*[Title/Abstract] OR self-monitor*[Title/Abstract] OR self-administration[Title/Abstract] OR self-medication[Title/Abstract] OR educate[Title/Abstract] OR educated[Title/Abstract] OR education[Title/Abstract] OR educating[Title/Abstract] OR educational[Title/Abstract] OR instructed[Title/Abstract] OR instruction[Title/Abstract] OR instructions[Title/Abstract] OR instructional[Title/Abstract] OR trained[Title/Abstract] OR “action plan*”[Title/Abstract] OR patient-educat*[Title/Abstract] OR patient-cent*[Title/Abstract] OR patient-focus*[Title/Abstract] OR “behavior therapy”[Title/Abstract] OR “behaviour therapy”[Title/Abstract] OR empowerment[Title/Abstract])

AND (“randomized controlled trial”[MeSH Terms] OR “randomised controlled trial”[MeSH Terms] OR “controlled clinical trial”[MeSH Terms] OR “random allocation”[MeSH Terms] OR “evaluation studies”[MeSH Terms] OR “intervention studies”[MeSH Terms] OR “randomized controlled trial”[Title/Abstract] OR “randomised controlled trial”[Title/Abstract] OR “controlled clinical trial”[Title/Abstract] OR “clinical trial”[Title/Abstract] OR “random allocation”[Title/Abstract] OR intervention[Title/Abstract] OR trial[Title/Abstract] OR trials[Title/Abstract] OR random[Title/Abstract] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR randomization[Title/Abstract] OR randomisation[Title/Abstract] OR randomizing[Title/Abstract] OR randomising[Title/Abstract] OR randomly[Title/Abstract] OR allocate[Title/Abstract] OR allocated[Title/Abstract] OR allocating[Title/Abstract] OR allocation[Title/Abstract])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS (Items not applicable, since manuscript is study protocol)			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION (Items not applicable, since manuscript is study protocol)			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

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Primary Subject Heading:	Patient-centred medicine
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Keywords:	individual patient data meta-analysis, self-management, chronic disease, chronic heart failure, COPD

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

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Word count: 3.393

ABSTRACT

Introduction: Self-management interventions in patients with chronic conditions have received increasing attention over the last years, yet meta-analyses encountered considerable heterogeneity in results. This suggests that 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 randomized 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 robustness of 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 programs 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, but also with other chronic diseases. This protocol has been registered in 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 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,[1,2] interventions to support self-management have received increasing attention over the last 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,[4,9] sometimes leading to contradictory findings.[11,12] A recently published large randomised controlled trial 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.[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.[14] The intervention studies not only differ in procedural aspects such as content, duration and intensity,[14] but also in patient populations included and outcomes measured.[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,[15] which is rather surprising since a majority of the patients with a chronic condition suffers from comorbidity.[16,17] Individual trials in different chronic conditions have reported large proportions of non-complying and non-responding patients.[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.

Combination of studies in a meta-analysis or meta-regression might provide insight in which program-specific components are likely to be effective. Intervention studies, however, may not only differ 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.[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.[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.[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 determinants of success of self-management interventions for chronic disease ‘at large’ (i.e. 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[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.[21,22] This makes self-management an inevitable part of care for those patients groups.[21,23] In both conditions self-management interventions are extensively studied, but outcomes of published studies are heterogeneous.[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 both program- 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 program- and patient-specific determinants of successful self-management interventions in chronic disease 'at large', i.e. condition-transcendent determinants.

METHODS AND ANALYSIS

Identification of studies

An extensive literature search has been conducted in the electronic databases of PubMed, EMBASE, Cochrane Central Register on Controlled Trials, PsycINFO and CINAHL from January 1985 to June 2013. MeSH terms and key words in title and abstract used were "chronic heart failure", "chronic obstructive pulmonary disease", "self-management", "self-care", "patient-education", "randomised 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 randomised controlled trials (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.[21,23] This IPD meta-analysis aims to determine patient-specific effect modifiers, therefore no exclusion criteria apply with regard to e.g. disease severity or comorbidities.

Since a gold standard of which essential elements constitute a self-management intervention is lacking,[24] an extensive literature search was performed before an international group of 7 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 (i.e. self-treatment such as managing acute exacerbations, resource utilisation, 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 six 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. Methodological quality of the studies is assessed through three relevant criteria based on the 'Risk of bias' tool from the Cochrane Collaboration:[25]

1. Random concealed allocation to treatment;
2. Intention-to-treat analysis;
3. Other deviances (e.g. discrepancies in baseline characteristics, high drop-out rates with unbalances between groups, 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 COPD patients) have been selected for this IPD meta-analysis. The original investigators are requested to participate in this IPD meta-analysis through an invitation by e-mail, 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. Only after written agreement, investigators will be asked to send their encrypted data, preferably electronically 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 (e.g. SAS, SPSS, Microsoft Excel spread sheet). Additionally, investigators are asked to check the extracted intervention characteristics from their studies to ensure a correct interpretation of interventions.

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

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, V.20.0 Armonyk, New York: IBM Corp) for data checking and recoding. Data of each trial will be checked with regard to range of the 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 correct interpretation of original categories and a correct recoding, new categories are only coded after consultation of the original investigators. All datasets from individual trials will be assigned a unique trial ID before being merged into the central database.

Project management

One of the major challenges in IPD meta-analyses is good communication across cultural and language barriers, careful management of and negotiating with collaborating investigators.[20] For this IPD meta-analysis an international collaborative study group is established, the TASTE-IPD (Tailoring of Self-managemenT and E-health Individual Patient Data) 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 conferences (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 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 upon new research questions which can be answered through re-analysis of the combined database.

The collaboration contains a project management team responsible for management decisions within the collaboration, communication with investigators and organising 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 months 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 months and at 12 months);
3. Hospitalised for any cause (time-to-event, % hospitalised at 6 months and at 12 months);
4. Total number of days spent in hospital for any cause at 6 months and at 12 months;
5. Hospitalised for resp. CHF or COPD (time-to-event, % hospitalised at 6 months and at 12 months);
6. Total number of days spent in hospital for resp. CHF or COPD at 6 months and at 12 months.

Statistical analyses

First, statistical analyses will be performed for CHF and COPD studies separately to meet the primary objective, but 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 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 version 2.15.3 (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 imputation by chained equations.[26] Missing values will only be imputed within studies.

The IPD will be analysed using a one-stage approach, i.e. simultaneously analysing all observations while accounting for clustering of observations within studies.[27] For time-to-event data, effects of self-management will be quantified by estimating hazard ratios (HR) and 95% confidence interval (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 (RR) and 95% CI will be estimated using log-binomial 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.[28]

Program-specific determinants

To identify program-specific determinants of self-management interventions, the aforementioned models are complemented with covariates for program characteristics. Table 2 presents an overview of potential program-specific determinants to be studied. The program-specific determinants are based on social cognitive theory,[29] self-management literature[24,30,31] and successful behavioural techniques.[32] Additionally, intensity and duration of interventions will be studied, since these have shown to be related to outcomes in behavioural interventions.[33] Program-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 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.[34,35] 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 pre-specified patient characteristics, each model will include interaction terms for 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, specific patient characteristic, and interaction terms (self-management by patient characteristic), 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

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 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 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 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 other purposes than declared in the protocol without 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 TAiloring of Self-managemenT and E-health (TASTE), which aims to enhance the effectiveness of self-management for chronic conditions.[36] Consolidation 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 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 program-specific and patient-specific determinants modify the effects of self-management interventions on health-related quality of life, mortality and health care 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.[16,17]

A re-analysis of self-management trials on the level of individual patients is essential to study both program and patient characteristics as possible determinants of success.[18] IPD meta-analyses are still quite rare in the field of complex interventions,[37-39] even though the literature on methodology of IPD meta-analyses is increasing.[27] Substantial efforts have been made to carefully design the present IPD meta-analysis and anticipate on the limitations of the IPD approach. Based on lessons learned from other IPD meta-analyses in this area, the important methodological considerations are met as is shown in Table 3.[37-39] 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 in- 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 pre-planned 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 timespan of nearly twenty 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 usual care 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, required multilevel methods to achieve this are quite novel and multiple imputation is generally recommended for imputing sporadic missing values instead of systematically missing data.[40] 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 depended on the quality of the original design, the quality and completeness of the data, and the level of detail provided by the original researchers.[25] Retrieval bias may occur if not all 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 programs 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 1: Data items investigators are requested to share.

Study level *Methodology*	**Study level** *Intervention*	**Patient level** *Characteristics at baseline*	**Patient level** *Intervention as implemented*	**Patient level** *Outcomes*
• Year of recruitment • Location of recruitment • Method of randomisation • Blinding to group assignment	• Mode(s) of delivery • Content covered in intervention • Number of planned contacts during intervention • Duration of the intervention • Type of training given to interventionists	• Sex • Age • Years since diagnosis • Disease severity (CHF=LVEF; COPD=FEV1%, FEV1, FVC) • Symptom status (CHF = NYHA class; COPD = dyspnoea) • Comorbid conditions • Level of education • Ethnic minority • Living alone • Self-efficacy • Depression • Body mass index • Smoking status	• Number of actual contacts with patient during intervention • Content covered with individual patient • Targeted behaviour achieved • Loss-to-follow-up and reason	• Health-related quality of life (score on instrument) • Mortality (yes/no; time-to-event) • All-cause hospital admissions (#; time-to-first-event) • Disease-related hospital admissions (#; time-to-first-event) • All-cause days in hospital (total # days) • Disease-related days in hospital (total # days)

CHF = chronic/congestive heart failure; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FEV1% = predicted forced expiratory volume in 1 second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2: Determinants to be analysed.

	Determinants
Program-specific	• Number of planned contacts • Duration of the intervention • Training given to interventionists (standardised/heterogeneous)† • Group contact with peers (y/n)*† • Keeping diaries for symptom-monitoring (y/n)ǂ • Goal-setting skills (y/n)*† • Problem-solving skills (y/n)*† • Support allocation skills (y/n)†
Patient-specific	• Sex • Age • Disease severity • Symptom severity • Number of comorbid conditions • Depression • Level of education *Optional variables (only analysed if sufficient data available):* • *Recently diagnosed* • *Self-efficacy* • *Living status* • *Body Mass Index* • *Smoking status*

*based on social cognitive theory; †based on self-management literature; ǂbased on behavioural techniques.

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

Study	Farmer et al.[37] *Self-monitoring of blood glucose*	Heneghan et al.[38] *Self-monitoring of oral anticoagulation*	Pickup et al.[39] *Self-monitoring of blood glucose*	TASTE-IPD *Self-management*
# studies approached and declined[19,27]	100% participation	52% participation	100% participation	On-going
Systematic search[27]	+/- Limited syntax	+	+/- Limited syntax	+
Efforts to include non-published data[20]	+	+	-	-
Intention-to-treat analysis[27]	+	+	?	+
Clustering within studies preserved in analysis[19]	+ Random intercepts in 1-stage model	+ 2-stage model	+/- Preservation in 1-stage model unclear	+ Random intercepts in 1-stage model
Handling missing data within studies and impact on results[27]	+	? No information handling missing data	+/? No information impact missing data	+
Impact of missing trials on results[19,27]	NA	?	NA	+ Sensitivity analysis of aggregate data
Impact of quality assessment on results[19]	+ Sensitivity analysis	- No analysis	- No analysis	+ Sensitivity analysis

NA = not applicable; + = present in study; +/- = partly present in study; - = not present in study; ? = no information in publication.

AUTHORS' CONTRIBUTIONS

All authors participated in developing the study design. NHJ and HW selected the studies. NHJ wrote the first draft of this manuscript. HW, JCAT, RHHW, TWET, TT, JP, JB, TJ, AWH and MJS revised several versions of the manuscript. All authors approved the final version.

COMPETING INTERESTS

None.

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Figure legend

Figure 1: Inclusion criteria for interventions.

Towards tailoring of self-management for patients with chronic heart failure or chronic obstructive pulmonary disease: ~~rationale and design~~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 last years, yet meta-analyses encountered considerable heterogeneity in results. This suggests that 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 randomized 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 robustness of 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 programs 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, but also with other chronic diseases. This protocol has been registered in 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 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,[1,2] interventions to support self-management have received increasing attention over the last 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,[4,9] sometimes leading to contradictory findings.[11,12] A recently published large randomised controlled trial 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.[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.[14] The intervention studies not only differ in procedural aspects such as content, duration and intensity,[14] but also in patient populations included and outcomes measured.[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,[15] which is rather surprising since a majority of the patients with a chronic condition suffers from comorbidity.[16,17] Individual trials in different chronic conditions have reported large proportions of non-complying and non-responding patients.[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.

Combination of studies in a meta-analysis or meta-regression might provide insight in which program-specific components are likely to be effective. Intervention studies, however, may not only differ 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.[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.[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.[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 determinants of success of self-management interventions for chronic disease ‘at large’ (i.e. 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[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.[21,22] This makes self-management an inevitable part of care for those patients groups.[21,23] In both conditions self-management interventions are extensively studied, but outcomes of published studies are heterogeneous.[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 both program- 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 program- and patient-specific determinants of successful self-management interventions in chronic disease 'at large', i.e. condition-transcendent determinants.

METHODS AND ANALYSIS

Identification of studies

An extensive literature search has been conducted in the electronic databases of PubMed, EMBASE, Cochrane Central Register on Controlled Trials, PsycINFO and CINAHL from January 1985 to June~~April~~ 2013. MeSH terms and key words in title and abstract used were "chronic heart failure", "chronic obstructive pulmonary disease", "self-management", "self-care", "patient-education", "randomised 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 randomised controlled trials (RCTs) with concealed allocation to treatment. Inclusion criteria for~~, conducted in~~ patients are ~~with~~ an established primary diagnosis of CHF or COPD according to the prevailing international clinical guidelines.[21,23] This IPD meta-analysis aims to determine patient-specific effect modifiers, therefore no exclusion criteria apply with regard to e.g. disease severity or comorbidities.

Since a gold standard of which essential elements constitute a self-management intervention is lacking,[24] an extensive literature search was performed before an international group of 7 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 ~~a definition~~ requiring ~~inclusion of~~ a minimum of two of the following components~~ in the intervention~~: (1) active stimulation of symptom monitoring, (2) education in problem solving skills (i.e. self-treatment such as managing acute

exacerbations, resource utilisation, 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 six 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. Methodological quality of the studies is assessed through three relevant criteria based on the 'Risk of bias' tool from the Cochrane Collaboration:[25]

1. Random concealed allocation to treatment;
2. Intention-to-treat analysis;
3. Other deviances (e.g. discrepancies in baseline characteristics, high drop-out rates with unbalances between groups, 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 COPD patients) have been selected for this IPD meta-analysis. The original investigators are requested to participate in this IPD meta-analysis through an invitation by e-mail, 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. Only after written agreement, investigators will be asked to send their encrypted data, preferably electronically 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 (e.g. SAS, SPSS, Microsoft Excel spread sheet). Additionally, investigators are asked to check the extracted intervention characteristics from their studies to ensure a correct interpretation of interventions.

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

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, V.20.0 Armonyk, New York: IBM Corp) for data checking and recoding. Data of each trial will be checked with regard to range of the 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 correct interpretation of original categories and a correct recoding, new categories are only coded after consultation of the original investigators. All datasets from individual trials will be assigned a unique trial ID before being merged into the central database.

Project management

One of the major challenges in IPD meta-analyses is good communication across cultural and language barriers, careful management of and negotiating with collaborating investigators.[20] For this IPD meta-analysis an international collaborative study group is established, the TASTE-IPD (Tailoring of Self-managemenT and E-health Individual Patient Data) 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 conferences (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 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 upon new research questions which can be answered through re-analysis of the combined database.

The collaboration contains a project management team responsible for management decisions within the collaboration, communication with investigators and organising 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 months 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 months and at 12 months);
3. Hospitalised for any cause (time-to-event, % hospitalised at 6 months and at 12 months);
4. Total number of days spent in hospital for any cause at 6 months and at 12 months;
5. Hospitalised for resp. CHF or COPD (time-to-event, % hospitalised at 6 months and at 12 months);
6. Total number of days spent in hospital for resp. CHF or COPD at 6 months and at 12 months.

Statistical analyses

First, statistical analyses will be performed for CHF and COPD studies separately to meet the primary objective, but 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 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 version 2.15.3 (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 imputation by chained equations.[26] Missing values will only be imputed within studies.

The IPD will be analysed using a one-stage approach, i.e. simultaneously analysing all observations while accounting for clustering of observations within studies.[27] For time-to-event data, effects of self-management will be quantified by estimating hazard ratios (HR) and 95% confidence interval (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 (RR) and 95% CI will be estimated using log-binomial 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.[28]

Program-specific determinants

To identify program-specific determinants of self-management interventions, the aforementioned models are complemented with covariates for program characteristics. Table 2 presents an overview of potential program-specific determinants to be studied. The program-specific determinants are based on social cognitive theory,[29] self-management literature[24,30,31] and successful behavioural techniques.[32] Additionally, intensity and duration of interventions will be studied, since these have shown to be related to outcomes in behavioural interventions.[33] Program-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 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.[34,35] 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 pre-specified patient characteristics, each model will include interaction terms for 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, specific patient characteristic, and interaction terms (self-management by patient characteristic), 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

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 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 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 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 other purposes than declared in the protocol without 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 TAiloring of Self-managemenT and E-health (TASTE), which aims to enhance the effectiveness of self-management for chronic conditions.[36] Consolidation 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 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 program-specific and patient-specific determinants modify the effects of self-management interventions on health-related quality of life, mortality and health care 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.[16,17]

A re-analysis of self-management trials on the level of individual patients is essential to study both program and patient characteristics as possible determinants of success.[18] IPD meta-analyses are still quite rare in the field of complex interventions,[37-39] even though the literature on methodology of IPD meta-analyses is increasing.[27] Substantial efforts have been made to carefully design the present IPD meta-analysis and anticipate on the limitations of the IPD approach. Based on lessons learned from other IPD meta-analyses in this area, the important methodological considerations are met as is shown in Table 3.[37-39] 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 in- 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 pre-planned 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 timespan of nearly twenty 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 usual care 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, required multilevel methods to achieve this are quite novel and multiple imputation is generally recommended for imputing sporadic missing values instead of systematically missing data.[40] 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 depended on the quality of the original design, the quality and completeness of the data, and the level of detail provided by the original researchers.[25] Retrieval bias may occur if not all 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 programs 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 1: Data items investigators are requested to share.

Study level *Methodology*	**Study level** *Intervention*	**Patient level** *Characteristics at baseline*	**Patient level** *Intervention as implemented*	**Patient level** *Outcomes*
• Year of recruitment • Location of recruitment • Method of randomisation • Blinding to group assignment	• Mode(s) of delivery • Content covered in intervention • Number of planned contacts during intervention • Duration of the intervention • Type of training given to interventionists	• Sex • Age • Years since diagnosis • Disease severity (CHF=LVEF; COPD=FEV1%, FEV1, FVC) • Symptom status (CHF = NYHA class; COPD = dyspnoea) • Comorbid conditions • Level of education • Ethnic minority • Living alone • Self-efficacy • Depression • Body mass index • Smoking status	• Number of actual contacts with patient during intervention • Content covered with individual patient • Targeted behaviour achieved • Loss-to-follow-up and reason	• Health-related quality of life (score on instrument) • Mortality (yes/no; time-to-event) • All-cause hospital admissions (#; time-to-first-event) • Disease-related hospital admissions (#; time-to-first-event) • All-cause days in hospital (total # days) • Disease-related days in hospital (total # days)

CHF = chronic/congestive heart failure; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; FEV1% = predicted forced expiratory volume in 1 second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2: Determinants to be analysed.

	Determinants
Program-specific	• Number of planned contacts • Duration of the intervention • Training given to interventionists (standardised/heterogeneous)† • Group contact with peers (y/n)*† • Keeping diaries for symptom-monitoring (y/n)ǂ • Goal-setting skills (y/n)*† • Problem-solving skills (y/n)*† • Support allocation skills (y/n)†
Patient-specific	• Sex • Age • Disease severity • Symptom severity • Number of comorbid conditions • Depression • Level of education *Optional variables (only analysed if sufficient data available):* • *Recently diagnosed* • *Self-efficacy* • *Living status* • *Body Mass Index* • *Smoking status*

*based on social cognitive theory; †based on self-management literature; ǂbased on behavioural techniques.

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

Study	Farmer et al.[37] *Self-monitoring of blood glucose*	Heneghan et al.[38] *Self-monitoring of oral anticoagulation*	Pickup et al.[39] *Self-monitoring of blood glucose*	TASTE-IPD *Self-management*
# studies approached and declined[19,27]	100% participation	52% participation	100% participation	On-going
Systematic search[27]	+/- Limited syntax	+	+/- Limited syntax	+
Efforts to include non-published data[20]	+	+	-	-
Intention-to-treat analysis[27]	+	+	?	+
Clustering within studies preserved in analysis[19]	+ Random intercepts in 1-stage model	+ 2-stage model	+/- Preservation in 1-stage model unclear	+ Random intercepts in 1-stage model
Handling missing data within studies and impact on results[27]	+	? No information handling missing data	+/? No information impact missing data	+
Impact of missing trials on results[19,27]	NA	?	NA	+ Sensitivity analysis of aggregate data
Impact of quality assessment on results[19]	+ Sensitivity analysis	- No analysis	- No analysis	+ Sensitivity analysis

NA = not applicable; + = present in study; +/- = partly present in study; - = not present in study; ? = no information in publication.

AUTHORS' CONTRIBUTIONS

All authors participated in developing the study design. NHJ and HW selected the studies. NHJ wrote the first draft of this manuscript. HW, JCAT, RHHW, TWET, TT, JP, JB, TJ, AWH and MJS revised several versions of the manuscript. All authors approved the final version.

COMPETING INTERESTS

None.

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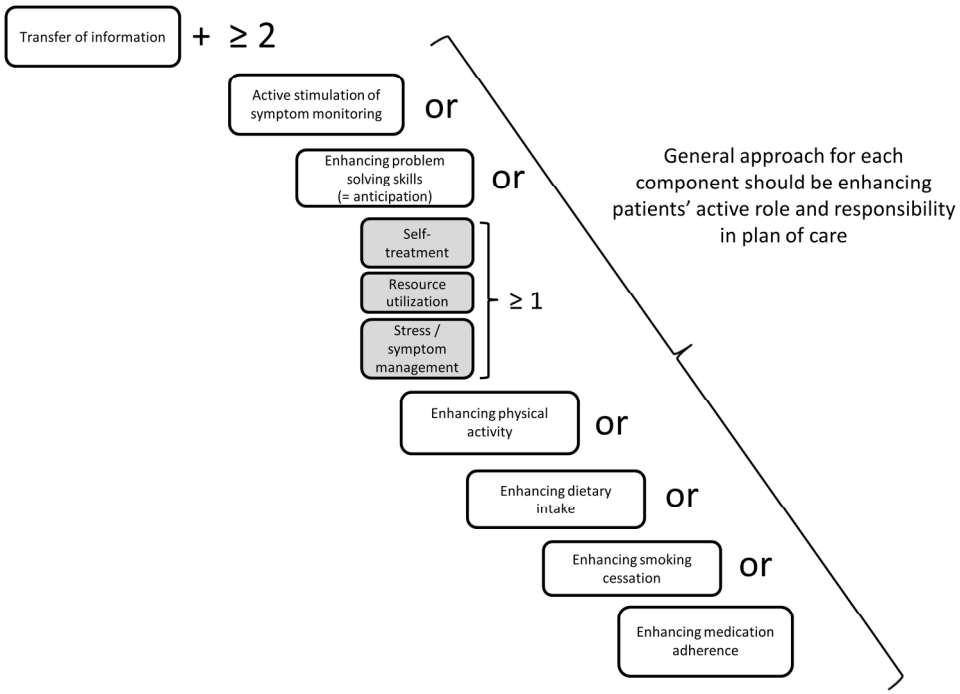
Figure 1: Inclusion criteria for interventions.



190x142mm (300 x 300 DPI)

APPENDIX 1: SEARCH STRATEGY FOR PUBMED

((“heart failure”[MeSH Terms] OR CHF[Title/Abstract] OR HF[Title/Abstract] OR “congestive heart failure”[Title/Abstract] OR “chronic heart failure”[Title/Abstract] OR “chronic cardiac failure” [Title/Abstract] OR “congestive cardiac failure”[Title/Abstract] OR “heart failure”[Title/Abstract] OR “cardiac failure”[Title/Abstract] OR “heart decompensation”[Title/Abstract])

OR (“pulmonary disease, chronic obstructive”[MeSH Terms] OR COPD[Title/Abstract] OR “chronic obstructive pulmonary disease”[Title/Abstract] OR “chronic obstructive airway disease”[Title/Abstract] OR “chronic airflow obstruction”[Title/Abstract] OR “chronic obstructive lung disease”[Title/Abstract] OR “chronic bronchitis”[Title/Abstract] OR bronchitis[Title/Abstract] OR emphysema[Title/Abstract] OR “lung emphysema”[Title/Abstract] OR “pulmonary emphysema”[Title/Abstract]))

AND (self-management[MeSH Terms] OR self-care[MeSH Terms] OR patient-education[MeSH Terms] OR “behavior therapy”[MeSH Terms] OR self-manag*[Title/Abstract] OR self-car*[Title/Abstract] OR self-monitor*[Title/Abstract] OR self-administration[Title/Abstract] OR self-medication[Title/Abstract] OR educate[Title/Abstract] OR educated[Title/Abstract] OR education[Title/Abstract] OR educating[Title/Abstract] OR educational[Title/Abstract] OR instructed[Title/Abstract] OR instruction[Title/Abstract] OR instructions[Title/Abstract] OR instructional[Title/Abstract] OR trained[Title/Abstract] OR “action plan*”[Title/Abstract] OR patient-educat*[Title/Abstract] OR patient-cent*[Title/Abstract] OR patient-focus*[Title/Abstract] OR “behavior therapy”[Title/Abstract] OR “behaviour therapy”[Title/Abstract] OR empowerment[Title/Abstract])

AND (“randomized controlled trial”[MeSH Terms] OR “randomised controlled trial”[MeSH Terms] OR “controlled clinical trial”[MeSH Terms] OR “random allocation”[MeSH Terms] OR “evaluation studies”[MeSH Terms] OR “intervention studies”[MeSH Terms] OR “randomized controlled trial”[Title/Abstract] OR “randomised controlled trial”[Title/Abstract] OR “controlled clinical trial”[Title/Abstract] OR “clinical trial”[Title/Abstract] OR “random allocation”[Title/Abstract] OR intervention[Title/Abstract] OR trial[Title/Abstract] OR trials[Title/Abstract] OR random[Title/Abstract] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR randomization[Title/Abstract] OR randomisation[Title/Abstract] OR randomizing[Title/Abstract] OR randomising[Title/Abstract] OR randomly[Title/Abstract] OR allocate[Title/Abstract] OR allocated[Title/Abstract] OR allocating[Title/Abstract] OR allocation[Title/Abstract])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6,9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS (Items not applicable, since manuscript is study protocol)			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION (Items not applicable, since manuscript is study protocol)			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENTARY FILE: LIST OF INCLUDED STUDIES

Included randomized trials in patients with chronic heart failure

1. Agren S, Evangelista LS, Hjelm C, et al. Dyads affected by chronic heart failure: a randomized study evaluating effects of education and psychosocial support to patients with heart failure and their partners. *J Card Fail* 2012;**18**:359-66.
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study of an outpatient inter-professional management programme for heart failure patients in Switzerland. *Swiss Med Wkly* 2011;**141**:w13171.
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