ESC Heart Failure

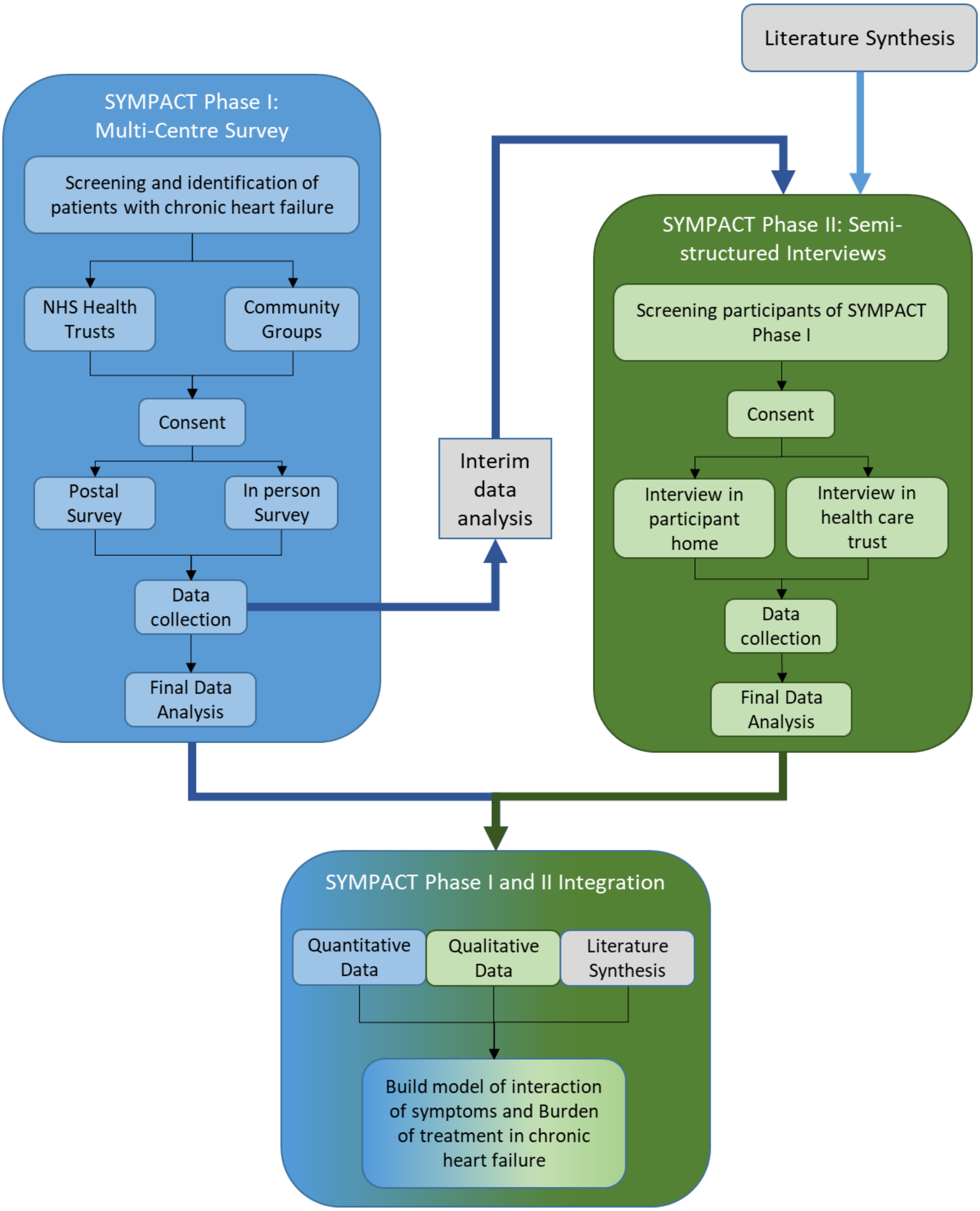
How SYMptoms and management tasks in chronic heart failure imPACT on a person’s life? Protocol for a Mixed Methods Study

--Manuscript Draft--

Manuscript Number:	ESCHF-20-00128R1
Full Title:	How SYMptoms and management tasks in chronic heart failure imPACT on a person’s life? Protocol for a Mixed Methods Study
Article Type:	Study Design
Corresponding Author:	Rosalynn C Austin University of Southampton Faculty of Health Sciences Portsmouth, Hampshire UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Southampton Faculty of Health Sciences
Corresponding Author's Secondary Institution:	
Corresponding Author E-Mail:	r.c.austin@soton.ac.uk
First Author:	Rosalynn C Austin
First Author Secondary Information:	
Order of Authors:	Rosalynn C Austin
	Lisette Schoonhoven
	Alison Richardson
	Paul R Kalra
	Carl R May
Order of Authors Secondary Information:	
Abstract:	Aims: Patients with chronic heart failure (CHF) struggle to follow self-care plans, which may lead to worsening illness and poor quality of life. Burden of Treatment (BoT) describes this workload and its impact on patients’ lives. It suggests the balance between a patient’s treatment workload and their capability to manage it is crucial. If BoT is reduced self-care engagement and quality of life may improve. This article describes the SYMPACT study design and methods used to explore how symptoms and management tasks impact on CHF patients’ lives. Methods: Using a sequential exploratory mixed methods design the interaction between symptoms and BoT in CHF patients’ will be investigated. Conclusions: If symptoms and BoT are intrinsically linked, then the high level of symptoms experienced by CHF patients may lead to increased treatment burden which likely decreases patients’ engagement with self-care plans. SYMPACT may identify modifiable factors to improve CHF patients’ experience.
Response to Reviewers:	See attached Revision response document for detailed response to reviewers as well as a list of changes made.
Author Comments:	I look forward to hearing from you soon in regards to a decision around publication NB: My affilation should be 'School of Health Sciences' not 'Faculty of Health Sciences'

Figure

Figure 1: SYMPACT study design overview: Flowchart illustrating the Phases of SYMPACT and how they inform each other



Cover letter

Title: How **SYM**ptoms and management tasks in chronic heart failure im**PACT** on a person's life (SYMPACT)? Protocol for a Mixed Methods Study

Authors: Rosalynn C Austin[1, 2, 3], Lisette Schoonhoven[1, 4], Alison Richardson[1,5], Paul R Kalra[2, 6], Carl May[7]

Institution work performed in: School of Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton, UK.

Author details[1]: RCA, Clinical Doctoral Research Fellow & Specialist Research Nurse[1,2], Portsmouth, UK. LS, Chair of Nursing Science[4], Utrecht, the Netherlands. AR, Clinical Professor of Cancer Nursing and End of Life Care & Director NIHR ARC Wessex[1,5], Southampton, UK. PRK, Consultant Cardiologist & Honorary Professor of Cardiology[2,6], Portsmouth, UK. CRM, Professor of Medical Sociology[7], London, UK.

Corresponding Author: Rosalynn C Austin; Queen Alexandra Hospital, Cardiology Research Nurses, C-Level, Southwick Hill, Cosham, Portsmouth, PO6 3LY.

R.C.Austin@soton.ac.uk Twitter: @RosalynnAustin

---

[1] 1: School of Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton.

2: Department of Cardiology. Portsmouth Hospitals NHS Trust.

3: National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Wessex. UK.

4: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University.

5: University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Health Sciences Clinical Academic Facility.

6*:* Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences. University of Glasgow and the University of Portsmouth.

7: Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine.

Abstract: *Aims:* Patients with chronic heart failure (CHF) struggle to follow self-care plans, which may lead to worsening illness and poor quality of life. Burden of Treatment (BoT) describes this workload and its impact on patients' lives. Suggesting the balance between a patient's treatment workload and their capability to manage it is crucial. If BoT is reduced self-care engagement and quality of life may improve. This article describes the SYMPACT study design and methods used to explore how symptoms and management tasks impact on CHF patients' lives. *Methods:* Using a sequential exploratory mixed method design the interaction between symptoms and BoT in CHF patients' will be investigated. *Conclusions:* If symptoms and BoT are intrinsically linked, then the high level of symptoms experienced by CHF patients may lead to increased treatment burden which likely decreases patients' engagement with self-care plans. SYMPACT may identify modifiable factors to improve CHF patients' experience.

Keywords: chronic heart failure, burden of treatment, symptom burden, self-care, mixed methods, study design

Word Count: (max 250): current 149

Introduction

Patients with chronic heart failure (CHF) often struggle to adhere to self-care expectations[1]. Non-compliance with self-care is suggested as a contributor to poor outcomes in CHF and is attributed to self-care that is neither sufficient nor effective[2]. Burden of Treatment (BoT) is comprised of dynamic states of workload (time and energy required to treat and manage a condition) and individual capacity (factors which alter ability to do work) [3-7]. Overwhelming treatment burden may be associated with adverse clinical outcomes [4,6]. Patient responsibility and engagement with self-care adding to BoT is not unique to CHF[7]. Clinical pathways and personal capacity appear to influence BoT in lung cancer and COPD[8]. BoT appears to be exacerbated by the level of support provided by healthcare systems and socioeconomic disadvantages in end-stage kidney disease[9]. How symptoms interact with burden of treatment has yet to be investigated.

CHF is a life-limiting syndrome and patients experience persistent, progressive, and debilitating symptoms such as breathlessness, fatigue, and oedema compromising their quality of life (QoL) despite optimized clinical treatment plans [10]. Complete elimination of symptoms is unlikely, yet there are likely treatment options that could help reduce symptoms. Lower symptom burden is associated with improved functional ability, and better self-care engagement [11]. While the theory of BoT acknowledges symptom burden it argues that symptoms are theoretically distinct. Examination of the literature, clinical observations, and patient and public involvement (PPI) suggests the symptoms in CHF may directly interact with BoT[12]. In this study, possible interactions between BoT and symptom burden will be measured quantitatively and explored qualitatively through interviews facilitating a deeper understanding of how patients with CHF experience burden of treatment. This paper outlines the design of the study: "How **SYM**ptoms and management tasks in chronic heart failure im**PACT** on a patient's life (SYMPACT)?" SYMPACT will examine and explore the interaction of symptoms experienced by patients with CHF with BoT. **Authors will test and explore the hypothesis (aims) that symptoms are intrinsically linked with BoT, i.e. patients with lower reported symptoms will report lower BoT and patients with higher reported symptoms will report higher BoT. This will be confirmed in how patients describe their experience.** The research questions are: (Phase I) Is there a relationship between quantitatively measured symptoms and BoT?; (Phase II) What is the perspective of patients with CHF on their experienced symptom burden and BoT?; and (Phase III) How do symptoms interact with BoT in CHF?

Study Design

SYMPACT is a sequential explanatory mixed method study (Figure 1); this methodology promotes the exploration of results in a quantitative study[13,14]. Qualitative results expand on insights derived from quantitative results[14] facilitating deeper explanations of observed statistical relationships. Combining the SYMPACT study results with a qualitative literature synthesis[15] enables the adductive analysis approach[16] to form a conceptual model of the interaction between BoT and symptom burden in CHF.

SYMPACT adheres to the Declaration of Helsinki and has been reviewed and approved by the University of Southampton Ethics Committee (ERGO: 41287) and the Nottingham HRA1 Research Ethic committee, Health Research Authority (MREC: 18/EM/0339, IRAS: 247773).

Phase I – Multi-centre survey of symptoms and BoT in CHF

Phase I of SYMPACT will test the following hypothesis: Symptom burden reported by CHF patients will be correlated with reported domains of BoT.

Design: Single time point survey using three validated questionnaires.

Participants: Multi-centre study across primary and secondary care NHS health trusts in the UK. English speaking adults with CHF (minimum of six months) and in the investigators’ opinion are not cognitively impaired, will be invited to complete the questionnaires. Patients with heart transplant or who are receiving palliative care will be excluded.

Methods: Following informed consent, health information will be collected: 1) demographics (age, gender, ethnicity, marital status, living situation), 2) CHF characteristics (diagnosis date, aetiology, New York Heart Association [NYHA] class, ejection fraction, clinical evaluations), and 3) personal health information (health issues, medications, hospitalisations).

Patients will be invited to complete 3 validated questionnaires: Heart Failure Symptom Survey (HFSS)[17], Minnesota Living with Heart Failure Questionnaire (MLHFQ)[18], and the Patient Experience of Treatment and Self-Care (PETS)[19].

a. HFSS is a reliable disease specific evaluation of heart failure signs and symptoms [17]. It measures the frequency, severity and impact of 14 symptoms; where the higher score equates to more severe experience.
b. MLHFQ captures key physical, emotional, social and mental dimensions of QoL in a brief questionnaire [20]. Lower scores on the MLHFQ relate to better health related QoL.
c. PETS describes the work of illness, facilitating tools, and exacerbating factors involved in self-care of generic chronic illness. It is a 48-item questionnaire quantifying the patient experience of BoT across nine domains[19].

Sample size: Sample size calculation is based on estimating the correlation between the above measures, to within a pre-specified precision (as defined by the 95% confidence interval [CI]). A width of 0.2 was chosen as a balance between the practical considerations and the ability to draw useful conclusions on the observed correlations. Pearson’s correlations power calculation formula[21], suggests a sample of size 350 will achieve this for any value of correlation.

Data analysis: Descriptive statistics will be used to summarize the study participants personal, CHF and health characteristics. Patients questionnaire responses will be described across gender, age, number of health issues and medications, NYHA class, and according to left ventricular ejection fraction.

A scatter plot will be used to visually assess relationship between reported symptom burden (measured by HFSS and MLHFQ) and BoT (measured by PETS); this will guide the choice of a suitable correlation tool (e.g. Pearson's or Spearman's) to summarize the relationship between the variables. Correlations will be presented with 95% confidence intervals.

An interim analysis will occur at about the halfway point. The results will be used to adapt the interview schedule, with specific probes to be used in Phase II.

***Limitations:* Limiting the sample to only three hospitals in a single county in the UK and patients who only speak English may reduce the generalizability of the results. Further, limiting the sample to CHF patients without heart transplants will ensure a focus to the generic lived experience of CHF. These limitations were thought to be reasonable due to limited availability of translated versions of the validated questionnaires and the aim of the project.**

Phase II – Semi-structured Interviews

CHF patients who complete Phase I, will be invited to take part in a semi-structured interview. The aim of this phase is to explore their experiences of living with CHF and elaborate on their questionnaire responses.

Design: Semi-structured interviews will be conducted either at a healthcare facility or the participant's home, according to patient choice. Using the interim results of the questionnaires as probes in the interview, should encourage in-depth description of experience of BoT, thereby substantiating the results from Phase I or providing explanation for differences observed.

Participants: Phase I patients are eligible to participate in Phase II. Phase II will begin after the completion of the interim analysis.

Sampling: Sample size will be defined by data saturation when three consecutive interviews do not generate any new information[22]. A maximum variation sampling technique will be used ensuring Phase II sample **is representative of** Phase I sample population.

Methods: Interviews will be audio recorded and the interviewer may take field notes.

SYMPACT Phase II interview schedule is based on previous interview questions developed by other researchers interested in BoT [5,23-26] and covers domains measured by PETS **[Supplemental material, *as per editor's choice*]**. Further probing questions developed from Phase I interim results will be added to the interview schedule. Following the interview, researcher reflections on the interview will be audio recorded, to promote transparency and reflexivity.

Data Analysis: All interviews and researcher reflections will be transcribed. Fieldnotes, where appropriate, converted into word documents. All participant identifiers in the interview data will be coded using their participant unique study number, assigned in Phase I.

Analysis of the interviews will follow an adapted form of Thomas and Harden's methods for thematic synthesis [27]. Using NVIVO (QRS Internationals), the interview transcripts and researcher notes will be examined line by line for symptom terminology. These will form the initial nodes. Coding credibility will be achieved through member checking (PPI, clinical expert, and co-authors)[28]. Each symptom node will be read in its context and a descriptive theme created. Finally, descriptive themes will be examined for similarities to the 'a priori' BoT framework. Constant comparison, reflexivity and discussion with co-researchers will increase rigor and trustworthiness[29].

The 'a priori' BoT framework incorporates the following: (1) *Workload*: involving the effort required to: enact tasks (technical and logistic); alter relationships (activate support and seek assistance); and evaluate outcomes of treatments (understanding and evaluation) [5,23]. (2) *Individual capacity*: encompassing an individual's abilities, their resources and their readiness to address the workload. Including consideration of a patient's physical function, cognitive function, emotional status, socioeconomic resources, social support networks, literacy, culture, and beliefs

[6]. (3) *Impact*: alterations to the patient's perception of self and their role. Including factors which make adhering to treatment plans more difficult[5,7].

Phase III – Data integration

Data integration for SYMPACT was planned in the study design. The validated questionnaires used were chosen according to theoretical similarities to BoT theory (detailed in table 1). The data from Phase I and Phase II will be integrated to inform the understanding of how symptoms interact with BoT in CHF. Symptom nodes and descriptive themes (Phase II) will be transformed through content analysis[30] and compared to the symptom burden scores (HFSS and MLHFQ) and BoT scores (PETS) from Phase I providing greater depth and insight to the patient experience. Through constantly comparing codes to the data[13] the descriptive themes will be refined and explored for points of interaction with the a priori BoT framework. This process should provide qualitative narratives to build on the statistical results from Phase I.

Patient and Public Involvement (PPI): The PPI group (members of the Patient Research Ambassadors' from the Queen Alexandra Hospital), **who are members of the public with a variety of chronic conditions, including carers of people with CHF.** They stated SYMPACT asks a valuable question which they identified as being important to their experience as patients and carer's. They **approved of** the study design as enabling would encourage participants to provide more in-depth information not covered by the questionnaires in this emerging field **which was of great importance to them, as they felt that often patient questionniares don't ask the questions that are important to them**. **They provided guidance around study design elements which helped to decrease the study burden for participants.** They assisted in the production of the participant and public facing documents **as well as refining and rephrasing interview questions for Phase II**. They agreed to help promote SYMPACT, perform credibility checks (**part of data analysis plan for Phase II)** and assist in results dissemination. **This group**

is and continues to be an integral part to this project and the primary authors PhD with regular meetings held to keep them appraised of progress and to encourage their input.

Discussion

Patients with CHF have high symptom burden and are expected to self-manage an illness with poor quality of life and high rates of morbidity and mortality. Despite marked progress with medical and device treatments readmission rates due to perceived non-adherence remain high and quality of life poor. CHF prevalence is expected to rise and the current demands on healthcare systems are already high. BoT **provides** a different perspective for examining the patient experience. It is thought that overwhelming treatment burden can lead to poor engagement with self-care which may contribute to poor outcomes. SYMPACT proposes a detailed measurement and exploration of treatment burden in patients with CHF. By exploring if symptoms interact with BoT, modifiable factors may be highlighted, providing the starting point for a patient focused intervention. Further as there are similarities in self-care expectations between CHF and other chronic illnesses this study may also offer transferable knowledge to the understanding of BoT across multiple chronic illnesses.

Acknowledgements

All authors read and approved the final manuscript. CRM, AR, and LS are the academic supervisors and PRK is the clinical supervisor for RA's PhD project. RA, AR, LS, PRK, and CM contributed to the conception and design of the study. RA drafted the article, with LS, PRK, AR and CM revising and editing for intellectual and clinical content. We thank Dr Sean Ewing for his statistical advice. Public and Patient Involvement provided by members of the Patient Research

Ambassadors **(Bill Ware, Carole King, Noreen Cole, Tim Coney, Anna Ganville-Hearson, Graham Edwards, and Chris Staples)** from Portsmouth Hospitals NHS Trust.

Funding

This work was completed as a part of a fully funded Clinical Academic Doctoral Fellowship at the University of Southampton, Portsmouth Health Trusts, and the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Wessex.

Declarations

Declarations: Ethics approval received from the UK Health Research Authority (MREC: 18/EM/0339) and University of Southampton (ERGO: 41287). ISRCTN11011943.

Professor Alison Richardson is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. Toukhsati SR, Driscoll A, Hare DL. Patient Self-management in Chronic Heart Failure – Establishing Concordance Between Guidelines and Practice. *Cardiac Failure Review.* 2015;1(2):128-131.
2. Gardetto NJ. Self-management in heart failure: where have we been and where should we go? *J Multidiscip Healthc.* 2011;4:39-51.
3. Gallacher K, Jani B, Morrison D, et al. Qualitative systematic reviews of treatment burden in stroke, heart failure and diabetes - Methodological challenges and solutions. *BioMed Central Medical Research Methodology.* 2013;13:1-10.
4. May CR, Eton DT, Boehmer K, et al. Rethinking the patient: using Burden of Treatment Theory to understand the changing dynamics of illness. *BMC Health Serv Res.* 2014.
5. Eton DT, Ramalho de Oliveira D, Egginton JS, et al. Building a measurement framework of burden of treatment in complex patients with chronic conditions: a qualitative study. *Patient Relat Outcome Meas.* 2012;3:39-49.
6. Shippee ND, Shah ND, May CR, Mair FS, Montori VM. Cumulative complexity: a functional, patient-centered model of patient complexity can improve research and practice. *J Clin Epidemiol.* 2012;65(10):1041-1051.

7. Demain S, Goncalves AC, Areia C, et al. Living with, managing and minimising treatment burden in long term conditions: a systematic review of qualitative research. *PLoS One.* 2015;10(5):e0125457.
8. Lippiett KA, Richardson A, Myall M, Cummings A, May CR. Patients and informal caregivers' experiences of burden of treatment in lung cancer and chronic obstructive pulmonary disease (COPD): a systematic review and synthesis of qualitative research. *BMJ Open.* 2019;9(2):e020515.
9. Roberti J, Cummings A, Myall M, et al. Work of being an adult patient with chronic kidney disease: a systematic review of qualitative studies. *BMJ Open.* 2018;8(9):e023507.
10. Zambroski CH, Moser DK, Bhat G, Ziegler C. Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. *Eur J Cardiovasc Nurs.* 2005;4(3):198-206.
11. Moser DK, Dickson V, Jaarsma T, Lee C, Stromberg A, Riegel B. Role of self-care in the patient with heart failure. *Curr Cardiol Rep.* 2012;14(3):265-275.
12. Austin R, Schoonhoven L, Kalra P, May C. Burden of Treatment in Chronic Heart Failure: Does symptom burden play a role. In:2018.
13. Creswell JW. *Research design : qualitative, quantitative, and mixed methods approaches.* Los Angeles; London : SAGE, 2014. 4th ed. International student edition.; 2014.
14. Creswell JW, Plano Clark VL. Chapter 4: Choosing a mixed methods design In: Creswell JW, Plano Clark VL, eds. *Designing and conducting mixed methods research.* Thousand Oaks, Calif: SAGE Publications; 2007:62-79.
15. Austin R, Kalra P, Schoonhoven L, May C. A qualitative systematic review of the experience of burden of treatment in those with chronic heart failure; exploring the presence and associations of symptom burden. In. Prospero2017.
16. Timmermans S, Tavory I. Theory Construction in Qualitative Research. *Sociological Theory.* 2012;30(3):167-186.
17. Pozehl B, Duncan K, Hertzog M. Heart Failure Symptom Survey: Validity and Reliability. *Journal of Cardiac Failure.* 2006;12(6):S100.
18. Rector T. Patient's self-assessment of their congestive heart failure: II. Content, reliability and validity of a new measure-The Minnesota Living with Heart Failure Questionnaire. *Heart failure.* 1987;3:198.
19. Eton DT, Yost KJ, Lai JS, et al. Development and validation of the Patient Experience with Treatment and Self-management (PETS): a patient-reported measure of treatment burden. *Qual Life Res.* 2017;26(2):489-503.
20. Rector TS. *Overview of the Minnesota Living with Heart Failre(R) Questionnaire.* 2005.
21. Loftus GR, Loftus EF. *Essence of statistics., 2nd ed.* New York, NY, US: Alfred A. Knopf; 1988.
22. Janice MM. The Significance of Saturation. *Qualitative Health Research.* 1995;5(2):147-149.
23. Gallacher K, May CR, Montori VM, Mair FS. Understanding patients' experiences of treatment burden in chronic heart failure using normalization process theory. *Ann Fam Med.* 2011;9(3):235-243.
24. Karamanidou C, Weinman J, Horne R. A qualitative study of treatment burden among haemodialysis recipients. *J Health Psychol.* 2014;19(4):556-569.

25. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC MEDICINE.* 2012;10.
26. Nordfonn OK, Morken IM, Bru LE, Husebo AML. Patients' experience with heart failure treatment and self-care-A qualitative study exploring the burden of treatment. *J Clin Nurs.* 2019;28(9-10):1782-1793.
27. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med Res Methodol.* 2008;8:45.
28. Thomas E, Magilvy JK. Qualitative rigor or research validity in qualitative research. *J Spec Pediatr Nurs.* 2011;16(2):151-155.
29. Elo S, Kääriäinen M, Kanste O, Pölkki T, Utriainen K, Kyngäs H. Qualitative Content Analysis. *SAGE Open.* 2014;4(1).
30. Bazeley P, Jackson K. Using coding queries to further analysis. In: *Qualitative Data Analysis with Nvivo.* 2nd ed.: Sage; 2013:242-269.

Table 1: Data integration overview for SYMPACT

A priori BoT Framework	**Phase I (Quantitative)**	**Phase II (Qualitative)**
	Variable measured	Question theme
Workload:		
Enact tasks	Clinical demand*	What tasks are performed in managing chronic heart failure? Does anyone help with this?
Alter relationships	PETS domains**	
Evaluate outcomes		
Individual Capacity:		
Individual’s ability	Clinical characteristics***	What makes managing chronic heart failure more difficult or easy?
Resources and readiness	Personal characteristics^	
	HFSS total score	
Impact:		
Alterations to self and role	MLHFQ total score	How does the work of managing chronic heart failure impact on their life?
Factors influencing adherence	HFSS interference scores^^	
	PETS domains**	

*Clinical demands: number of health issues, number of medications, hospitalisations within a year.

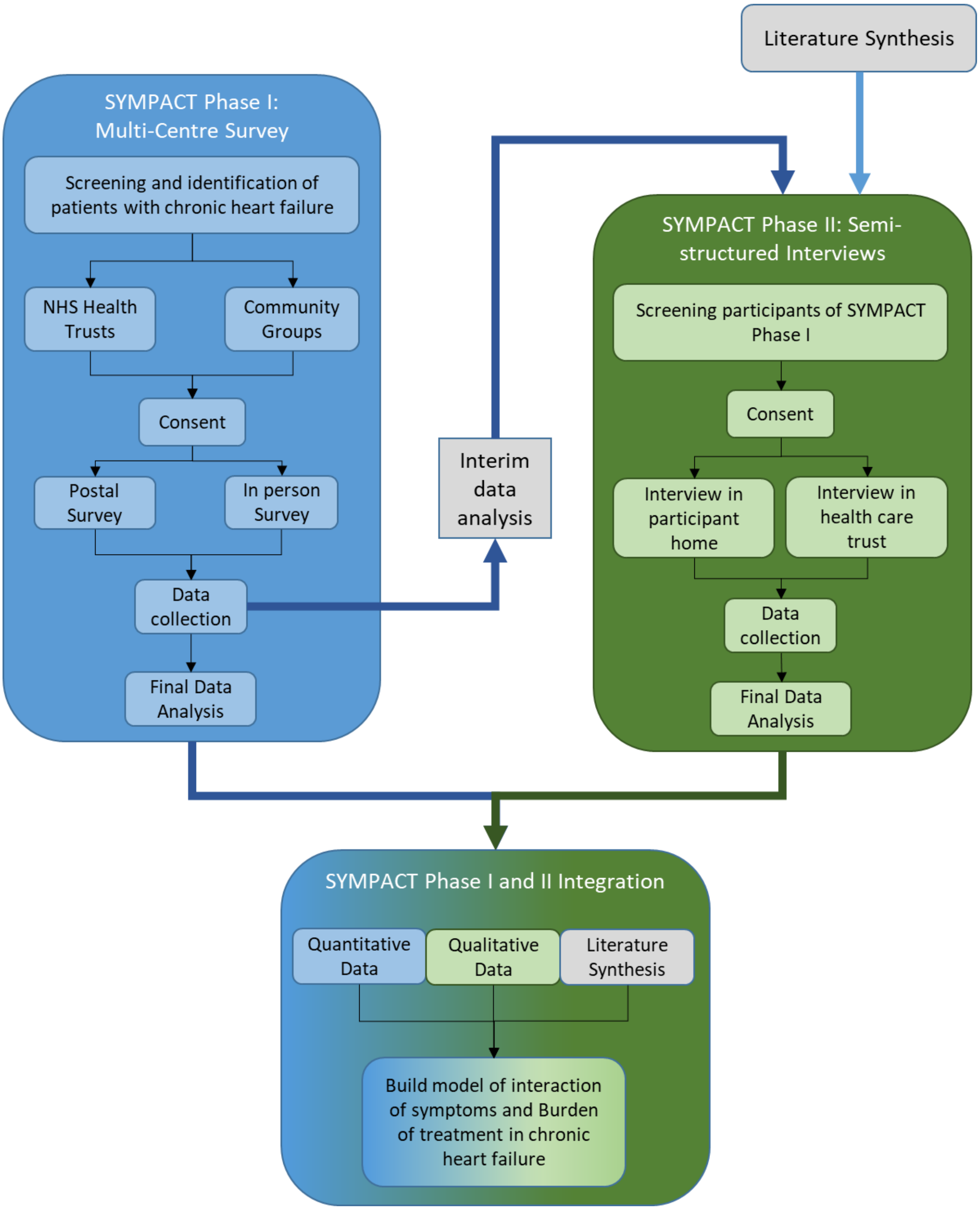
**PETS domains: sub-scores in PETS by work (e.g. medication management, attending appointment, etc), facilitating tools, and exacerbating factors involved in self-care.

***Clinical characteristics: NYHA classification, aetiology, ejection fraction, CHF type, and years since diagnosis.

^Personal Characteristics: age, gender, marital status, and living situation.

^^HFSS interference scores: sub-scale in HFSS that captures reported interference with physical activity and enjoyment of life.

Figure 1: SYMPACT study design overview: Flowchart illustrating the Phases of SYMPACT and how they inform each other



Ref.: Ms. No. ESCHF-20-00128
How SYMptoms and management tasks in chronic heart failure imPACT on a person's life? Protocol for a Mixed Methods Study
ESC Heart Failure

Dear Stephan von Haehling and M. Birhan Yilmaz,

Please find enclose a response to the reviewers' comments, as well as a list of changes made to the full manuscript. As requested, all changes made to the manuscript are in red and bold font.

Reviewers' comments:

Reviewer #3: Dear authors,
I'm happy to review this manuscript and would like to express how sorry I am about the current status of the study (due to the COVID19 situation). The paper outlines the study protocol nicely. The concept of the study is interesting, and more importantly needed on our field. The relationship between burden of treatment and different outcomes, more importantly from patients' prospective, need to be extensively investigated. As a process of reviewing I usually go through section by section and mark my suggestions to make it easier for the authors to follow up. However, this is a well written, concise and sandwishly-packed manuscript. Having said that, what is missing in the manuscript is the study's limitations for example: the selection of participants and the potential bias (English language speaking only, why are heart transplant patient are excluded) I'm quite sure that you do have an explanation but it would be nice if you include it for us readers.
Thank you

Stay well and safe

RESPONSE: Further explanation as to limitations in the study highlighted by Reviewer #3 have been made and can be found on pg. 6

Reviewer #4: The paper submitted by et al is a protocol for a study investigating the relationship between heart failure symptoms and 'burden of treatment' This seems a valuable study aim as heart failure patients are notoriously non-compliant with self management and any thing that can be done to improve this would be worthwhile.

The authors should be cautious however in their suggestion that lower burden of treatment leads to lowered symptoms, when it could be the other way around, i.e. that patients in the early stages of the disease have less symptoms and so require less BoT.

RESPONSE: The authors present the hypothesis that high levels of symptoms in CHF, may lead to higher BoT (abstract). On page 3 a generic statement on the overall hypothesis and aim of the study to help clarify this: "Authors will test and explore the hypothesis (aims) that symptoms are intrinsically linked with BoT, i.e. patients with lower reported symptoms will report lower BoT and patients with higher reported symptoms will report higher BoT. This will be confirmed in how patients describe their experience."

At this stage in the research the authors are not trying to examine this relationship in terms of disease progression, instead we are trying to explore these ideas in terms of the general CHF experience.

Is it worth including a measure of exercise capacity, i.e. six minute walk distance? this is commonly included in clinical practice and is much more objective a measure of functional class than subjective assessment clinic
At the very least I would expect to see it listed in the demographics if available

RESPONSE: This is an interesting idea. However, a six-minute walk test is not commonly included in current clinical practice in the hospitals where the data collection is planned; thus it was not included.

As this is a protocol paper it should explicitly list the interview questions referred to in phase ii.

RESPONSE: Interview questions have been provided to the journal to be published as supplemental material if they so wish.

Also the degree to which additional 'probing' questions (that are unstandardised) based on answers from phase I should be described, i.e.if more than 50% of interview questions are potentially different fro *each participant, how can one fairly assess the results? I may be trying to apply quantitative reasoning to a qualitative study here so I apologise if I'm missing the point.*

RESPONSE: Probing questions are an accepted technique in semi-structured interviews in qualitative research. Probes are not random, they are selected from a pre-set list of questions, based on the participant's response. The lines of questioning are not materially different across patients and they are consistently applied.

PPI- 'members of the patient research ambassadors at queen Alexandria hospital stated that SYMPACT asks valuable question' s, but were any of them people with heart failure? I hate to say it but this seems like a 'tick box' PPI and is far too generic. The authors should include specific feedback from actual patients with heart failure that has influenced the study design.

RESPONSE: Further details have been provided in the article around the role of the Patient Research Ambassador group has in this element of the primary authors PhD. The group have been integral to the authors PhD and have helped to refine the development of the project, providing opportunities for dissemination, and are looking forward to helping with the data analysis.

Overall this is an important study and I look forward to seeing it's findings

List of changes to the manuscript:

Location	Details	Reason
Pg. 3	'This' changed to 'The'	Grammatical change
Pg. 3	**"Authors will test and explore the hypothesis (aims) that symptoms are intrinsically linked with BoT, i.e. patients with lower reported symptoms will report lower BoT and patients with higher reported symptoms will report higher BoT. This will be confirmed in how patients describe their experience."**	Clarification for Reviewer #4 query.
Pg. 4	**SYMPACT adheres to the Declaration of Helsinki and has been reviewed and approved by the University of Southampton Ethics Committee (ERGO: 41287) and the Nottingham HRA1 Research Ethic committee, Health Research Authority (MREC: 18/EM/0339, IRAS: 247773).**	Ethics declaration
Pg. 6	***Limitations:* Limiting the sample to only three hospitals in a single county in the UK and patients who only speak English may reduce the generalizability of the results. Further, limiting the sample to CHF patients without heart transplants will ensure a focus to the generic lived experience of CHF. These limitations were thought to be reasonable due to limited availability of translated versions of the validated questionnaires and the aim of the project.**	Clarification for Reviewer #3 query
Pg. 6	'represents' changes to 'is representative of'	Grammatical change
Pg. 7	**[Supplemental material, *as per editor's choice*]. *Also authors are happy for this to be published within the article as a table.***	Clarification for Reviewer #4 query.
Pg. 8	**who are members of the public with a variety of chronic conditions, including carers of people with CHF.**	Clarification for Reviewer #4 query.

Pg. 8	‘regarded’ to ‘approved of’	Grammatical change
Pg. 8	‘would encourage’ to ‘enable’	Grammatical change
Pg. 8	**which was of great importance to them, as they felt that often patient questionniares don’t ask the questions that are important to them**. **They provided guidance around study design elements which helped to decrease the study burden for participants.**	Clarification for Reviewer #4 query.
Pg. 8	**as well as refining and rephrasing interview questions for Phase II**.	Clarification for Reviewer #4 query.
Pg. 9	(**part of data analysis plan for Phase II)** and assist in results dissemination. **This group is and continues to be an integral part to this project and the primary authors PhD with regular meetings held to keep them appraised of progress and to encourage their input.**	Clarification for Reviewer #4 query.
Pg. 9	‘is’ changed to ‘provides’	Word choice
Pg. 10	**(Bill Ware, Carole King, Noreen Cole, Tim Coney, Anna Ganville-Hearson, Graham Edwards, and Chris Staples)**	Acknowledgement of PRA members who contributed to protocol development.
Table 1	‘Tasks’ changed to ‘assigned’	Word choice

Interview schedule/guide

Click here to access/download

Supplementary Material

ESC_ProtocolPaper_supplemental_material_Interview_Schedule.docx

Table

Table 1: Data integration overview for SYMPACT

A priori BoT Framework	**Phase I (Quantitative)** Variable measured	**Phase II (Qualitative)** Question theme
Workload:		
Enact tasks	Clinical demands* PETS domains**	What tasks are performed in managing chronic heart failure? Does anyone help with this?
Alter relationships		
Evaluate outcomes		
Individual Capacity:		
Individual’s ability	Clinical characteristics*** Personal characteristics^ HFSS total score	What makes managing chronic heart failure more difficult or easy?
Resources and readiness		
Impact:		
Alterations to self and role	MLHFQ total score HFSS interference scores^^ PETS domains**	How does the work of managing chronic heart failure impact on their life?
Factors influencing adherence		

*Clinical demands: number of health issues, number of medications, hospitalisations within a year.

PETS domains: sub-scores in PETS by work **assigned (e.g. medication management, attending appointment, etc), facilitating tools, and exacerbating factors involved in self-care.

***Clinical characteristics: NYHA classification, aetiology, ejection fraction, CHF type, and years since diagnosis.

^Personal Characteristics: age, gender, marital status, and living situation.

^^HFSS interference scores: sub-scale in HFSS that captures reported interference with physical activity and enjoyment of life.