## 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---

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<td>How SYMptoms and management tasks in chronic heart failure imPACT on a person’s life? Protocol for a Mixed Methods Study</td>
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| Corresponding Author's Institution: | University of Southampton Faculty of Health Sciences |
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### 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 affiliation should be 'School of Health Sciences' not 'Faculty of Health Sciences'
Figure 1: SYMPACT study design overview: Flowchart illustrating the Phases of SYMPACT and how they inform each other.
Click here to access/download
Supplementary Material
CoverLetter_ESCHeartFailure.docx
Title: How SYMptoms and management tasks in chronic heart failure imPACT on a person’s life (SYMPACT)? Protocol for a Mixed Methods Study

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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. 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. 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). Overwhelming treatment burden may be associated with adverse clinical outcomes. Patient responsibility and engagement with self-care adding to BoT is not unique to CHF. Clinical pathways and personal capacity appear to influence BoT in lung cancer and COPD. BoT appears to be exacerbated by the level of support...
provided by healthcare systems and socioeconomic disadvantages in end-stage kidney disease\textsuperscript{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 \textsuperscript{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 \textsuperscript{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\textsuperscript{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 SYMptoms and management tasks in chronic heart failure imPACT 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?

\textbf{Study Design}
SYMPACT is a sequential explanatory mixed method study (Figure 1); this methodology promotes the exploration of results in a quantitative study\textsuperscript{13,14}. Qualitative results expand on insights derived from quantitative results\textsuperscript{14} facilitating deeper explanations of observed statistical relationships. Combining the SYMPACT study results with a qualitative literature synthesis\textsuperscript{15} enables the adductive analysis approach\textsuperscript{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.

\textit{Design:} Single time point survey using three validated questionnaires.

\textit{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.

\textit{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)\textsuperscript{17}, Minnesota Living with Heart Failure Questionnaire (MLHFQ)\textsuperscript{18}, and the Patient Experience of Treatment and Self-Care (PETS)\textsuperscript{19}.

- HFSS is a reliable disease specific evaluation of heart failure signs and symptoms\textsuperscript{17}. It measures the frequency, severity and impact of 14 symptoms; where the higher score equates to more severe experience.
- MLHFQ captures key physical, emotional, social and mental dimensions of QoL in a brief questionnaire\textsuperscript{20}. Lower scores on the MLHFQ relate to better health related QoL.
- 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\textsuperscript{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\textsuperscript{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. 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 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. 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). 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.

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). (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.
(3) **Impact:** alterations to the patient’s perception of self and their role. Including factors which make adhering to treatment plans more difficult

**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 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 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 questionnaires 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 apprised 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

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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

2. Gardetto NJ. Self-management in heart failure: where have we been and where should we go? J Multidiscip Healthc. 2011;4:39-51.


Table 1: Data integration overview for SYMPACT

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<td>PETS domains**</td>
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*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.
Dear Stephan von Haehling and M. Birhan Yilmaz,

Please find enclosed 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.

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 sandwichly-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 aplogise 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 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:

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Supplementary Material
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<td>PETS domains**</td>
<td></td>
</tr>
</tbody>
</table>

*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.