Author’s response to reviews

Title: Patient education in chronic heart failure in primary care (ETIC) and its impact on patient quality of life: design of a cluster randomised trial.

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Version: 3 Date: 20 November 2014

Author’s response to reviews: see over
Dear Dr Morawska

Please find enclosed the revised manuscript entitled:

‘Patient education in chronic heart failure in primary care (ETIC) and its impact on patient quality: design of a cluster randomised trial’

for consideration for publication in BMC Family Practice. Thank you for sending our paper out to review. We have revised our manuscript in light of the reviewers’ comments and we have employed a professional language editing service to improve the English. Below, we would like to present our detailed response to all your points. We have improved our manuscript accordingly. For your ease we highlighted all changes made in yellow.

If you have any questions or need more information, do not hesitate to contact us.

Yours sincerely

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on behalf of the authors
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Referee 1 : Carlos Brotons

Title : The study is very much focused on quality of life. Perhaps should be reflected in the title.

We added « quality of life » to the title.

Background :

It is mentioned that the aim is to improve CHF management, including.....effectiveness on quality of life. Reading this seems that the primary outcome it is expected to be some clinical parameter related with heart failure. This contrasts with the primary outcome stated (methods) which is patients' quality of life. Text in background should be modified.

We have modified the aim of the study as proposed (lines 113-114).
Methods:

All GPs who volunteered....' . 'potentially eligible practices are identified....' Should be clarified GPs/practice selection. It is a little confused talking about practices and GPs. It would be better to use only one term.

All GPs who volunteered were randomised. It was GPs that were randomised and not practices but to avoid contamination, GPs in a same practice were allocated to the same group. We have modified the section accordingly to clarify this and changes have been made to the “Practice recruitment and patient enrolment” section (lines 126-129, 172).

Who will train GPs?

We have detailed in the “GP’s training” section, who will train GPs (lines 202-204).

GPs are trained by experts: a nutritionist, an endocrinologist, a cardiologist, three GPs and a pharmacist, who are all patient education trainers and one has a Masters degree in patient education.

Secondary outcomes: How mortality and hospitalizations will be assessed and confirmed?:

We have detailed that GPs will assess and report mortality and hospitalisations in the case report form. At each planned visit, GP will report on enrolled patient events concerning death and/or hospitalisation with the corresponding dates (lines 169-170).

Sample size: Overall there will be 200 hundred patients in each group? Please specify.

We have specified that there will be 200 patients per group; 400 patients overall (lines 70-71, 257-259).

Discussion: Limitations of the study should be mentioned (bias of voluntary practices, probably lack of power to assess mortality and hospitalizations,...)
Lines 347-362. We have added in a section about the limitations of the study. Sample size estimation is only considered for the primary outcome, quality of life, defined by 2 tools SF-36 and MLHFQ. No estimation is performed for the secondary outcomes because most analyses of our parameters are exploratory and should have been underpowered. It is important not to focus just upon statistical significance, but also on the quality of the research within the study and the magnitude of improvement\(^1\). Therefore, according to the literature, sample size based on mortality would not seem to be feasible.

Level of interest:
An article of importance in its field

Quality of written English: Needs some language corrections before being published

The manuscript has been revised by a native English–speaking professional copy-editor with a background in the biomedical sciences.

Referee 2: Arno Hoes

Major compulsory revisions.

1. The inclusion criteria should be presented in more detail. I understand that if according to the cardiologist it is heart failure you consider it heart failure? How is this confirmed? From a hospital discharge letter? It would be good to ensure that patients really have heart failure and maybe include some of the criteria (notably echocardiographic criteria, also for diastolic dysfunction) included in the ESC guidelines. In addition, please include the terms universally applied in heart failure now: heart failure with reduced ejection fraction and with preserved ejection fraction (respectively HFrEF and HFpEF). Perhaps patients not receiving betablockers or ACE inhibitors should be excluded because they are unlikely to really have heart failure. I know the trial is ongoing, but some additional information on how the inclusion criteria are “operationalized” should be included.

Lines 135-141. We have modified this section and included terms: heart failure with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF). We have presented inclusion criteria in more detail: heart failure must be confirmed by the patient’s cardiologist in line with the European Society of Cardiology guidelines. When GPs recruit patients, patients’ cardiologists receive a letter to ask them to confirm heart failure according these guidelines. We agree with the reviewer that a discussion with the patient about their medication at the inclusion visit could be discussed. In fact, this information including betablocker and ACE inhibitor has been collected at baseline and at each GP visit. We will be able to follow-up with patients not receiving these treatments, though we anticipate though there will be very few. As proposed in the statistical considerations, treatment could be proposed as a covariate in a multivariate analyses.

2. There are a lot of secondary endpoints. Why so many? Especially the power for the mortality outcome is too low and this may also hold for hospitalizations. In my view it makes more sense to instead include the number of days in hospital as an outcome.
We agree there will be a lack of power for the mortality and hospitalisation outcomes. No sample size estimation is performed for secondary outcomes because most analyses of our parameters are exploratory and should have been underpowered. However, care must be taken to focus not only upon statistical significance, but also on the quality of the research within the study and the magnitude of improvement\(^1\). Also, concerning hospitalisation and mortality of patients, we want to be sure that the intervention does not seem to have a negative impact. We thank the reviewer for his helpful comment regarding number of days in hospital. This information was inadvertently omitted in our article but it is actually being reported by GPs at each patient visit. We have added this detail in our manuscript (lines 161-162).

3. The sample size calculation is not detailed enough. I cannot reproduce it now (or fail to understand how it is done). A difference of 12 points is chosen: why? Any rationale for this? Is this the absolute difference at 19 months (and thus is the baseline value ignored because of the randomization procedure?) or is it the difference in the delta (change)? Interestingly, the MLWHF outcome is dichotomized (see above), but in the sample size calculation this seems not to be taken into account. Please, improve the text of the sample size calculation so that it can be reproduced by others.

Lines 249-259. We agree that the sample size calculation should be more detailed. It is difficult to resume several simulations based on different values of intra-cluster correlation (ranged between 0.10 and 0.20) for each item of SF-36 and for MLHFQ. But, in line with the reviewer’s comment, we have added some details notably for the expected difference between randomised groups at M19. This primary analysis concerns the difference of SF-36 and MLHFQ at M19 and not the difference in the delta change. Due to lack information in the literature about SF-36 and MLHFQ on intervention studies targeting GPs\(^2\), the difference of 12 points was chosen using recommendations from Cohen\(^3\) where variability of the quality of life indicators is known\(^4\). Estimation of the effect size (ES) can be made based on a literature search, expert knowledge or using pilot studies. It is also possible to explore several scenarios using conventional effect sizes: small (ES = 0.2), medium (ES = 0.5) and high (ES = 0.8). Regardless of these considerations about effect size and difference observed in Brotons’ publication\(^2\), a difference of 12 points was considered for sample size estimation. A more complete formulation is added in our manuscript. The sample size
calculation is now more detailed and we feel that it is clearer and should now be reproducible by others.

<table>
<thead>
<tr>
<th>Standard-Deviation of SF-36 according to Leplège reference</th>
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<tbody>
<tr>
<td>Physical functioning</td>
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<tr>
<td>Vitality</td>
</tr>
<tr>
<td>Role physical</td>
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<tr>
<td>Bodily pain</td>
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<tr>
<td>Social functioning</td>
</tr>
<tr>
<td>Mental health</td>
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<tr>
<td>Role emotional</td>
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<tr>
<td>General health</td>
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</tbody>
</table>

Concerning the analysis of SF36 and MLHFQ, the analysis of delta change was not proposed. But, as suggested by Vickers and Altman, the baseline value is a covariate in a multivariate model. This aspect was proposed in the previous version of our paper.

Finally, we discuss in the methods section the possibility of categorising the MLHFQ (3 modalities). We agree with the reviewer that analysing categorized MLHFQ will be interesting but the sample size estimation based on this parameter seems difficult to determine due to 1) statistical power increase by categorical aspect and 2) lack of information about statistical distribution of studies on GPs. Nevertheless, we have added the analysis of this variable in the method section (lines 155-158).

4. Statistical analysis

See above: where is the dichotomized MLWHF outcome? What if there are baseline differences between the patients in the two groups. Will these differences be adjusted for and how? This should be dealt with.
According to the reviewer’s comment and previous answer, we have added the analysis of categorised MLHFQ to the method section (lines 155-158).

The initial comparability of the two arms will be assessed in the main characteristics of participants and potential factors associated with the primary outcome, as proposed in statistical considerations. The baseline difference between patients (or GPs) will be evaluated using clinical and statistical relevance\(^6\). (lines 264-266)

When appropriate, the statistical analysis plan includes multivariate analyses with an adjustment on these baseline characteristics. These aspects were mentioned on our text in the statistical section: “These models will include an interaction factor between both the randomisation group and the particular time point, and will be adjusted for baseline SF-36 scores, age, gender, diagnosis, smoking history, treatment and socioeconomic status.” (lines 274-277). We have also more clearly described this in the discussion (347-362).

**Minor essential revisions:**

1. Abstract: “The primary objective of this study is to improve chronic heart failure management in general practices by applying major elements of case management, including patient education to test the effectiveness on patient’s quality of life”. Please rephrase: the main aim seems to be to improve quality of life in heart failure patients though a complex intervention involving patient and GP education in primary care. The current wording is too complicated and unclear.

   *The main aim has been rephrased (lines 52-54).*

2. Abstract: The methods section of the abstract has a somewhat unusual contents in that some essential information is missing, while there is too much information on the sample size calculation. The latter need not be included in the abstract in my view (the number of patients or practices included should be
given), but other items, notably the inclusion and exclusion criteria should be mentioned here. In addition, some more information on the intervention would be helpful in the abstract.

*The methods section has been modified accordingly. (lines 56-67).*

Introduction

3. In the introduction, please spend some more words on the fact that there are only few studies assessing the effect of HF management programs in primary care and that more evidence is needed here, because the generalizability of hospital- or outpatient-based programs to primary care is limited. Also, refer to some studies that have been performed in primary care, such as a Belgian study (Dendale et al. TEMA-HF study, Eur J Heart Fail 2011) a few years ago and COACH-2 in the Netherlands (Luttik et al, Eur J Heart Fail 2014).

*Lines 101-108. We agree and have now described that more evidence is needed in primary care. We have added references you gave to us. However, the Dendale study was not exclusively in primary care because the patients were recruited at hospital and the intervention was performed partly by a nurse at hospital, with a telemonitoring follow-up and patients were asked to measure their body weight, blood pressure and heart rate daily, general practitioner and heart failure clinic were alerted by email and general practitioner was asked to adapt the treatment. As a consequence, there was no patient education in this intervention given by general practitioner. Concerning the Luttik study, as we understand, GPs were not specifically trained for this study and patient education was not carried out by them. Moreover, there was no quality of life assessment.*

4. Introduction: As in the abstract, the wording of the primary objective is not clear enough. Please rephrase.

*The primary objective has been rephrased. (lines 113-114).*

Methods
5. What is meant by “stratification on each of 4 areas”: randomization blocks?

The trial is carried out in the four administrative areas of the Auvergne region in France. To avoid the contamination bias and to ensure the randomisation balance (same number of GPs on intervention and control arms for each area of the Auvergne region), the design of this cluster randomised trial provides a stratification on Auvergne’s area. (Lines 126-130).

6. “All GPs who volunteered were randomized”; does this mean that while group practices were randomized, individual GPs with those practices could refuse to participate. If that is the case, this is unfortunate and this could induce bias (confounding) because of incomparability of the two groups.

GPs were randomised into two arms with GPs in the same practice allocated to the same group to avoid cross contamination. (lines 126-129).

7. Why include NYHA I patients, as they do not have complaints?

Because even if they are NYHA I, these patients suffer from heart failure and we are interested in their quality of life. We excluded NYHA IV patients because of their life expectancy. However, we will describe NYHA stages at baseline and at the end of follow-up and we can possibly compare symptomatic and asymptomatic patients.

8. Why assess the outcome (quality of life, QoL) at 7, 13 and 19 months and not at 6, 12 and 18 months?

These timings (7, 13 and 19 months) correspond to the patient education sessions. Figure 1. Lines 213-218.
9. The disease-specific QoL outcome MLWHF is dichotomized; I understand this is useful, but this also means that some information is lost. In the statistical analyses, however, the MLWHF outcome is analysed in a continuous fashion. Where is the dichotomization then?

This has been addressed in sections 3 and 4 in the major compulsory revisions (above).

10. Explain in more detail how “evaluation of their treatment” and “adherence to therapy” (how is the latter measured in the questionnaire?) is quantified.

Patients' treatment is reported at each GP visit in the case report form: we will be able to describe treatment at baseline and any modification during the follow-up. We will assess treatment reported by GPs at baseline and during the follow-up to guideline adherence to evidence-based pharmacotherapy. (lines 164-165).

Patient adherence to therapy is assessed with a self-administered questionnaire validated in French. Adherence will be assessed by patients themselves at baseline and at the end of follow-up. (lines 165-167).

11. Is there any evidence that the GP training program tested in this study is feasible? And has this approach been tested for any outcome before in France (or elsewhere)? It would be good to know that this is indeed a potentially useful program.

The GP training programme has not been tested before but this programme was validated by a grant from the French Ministry of Health and this study was funded in part using public funds because of this validation by regional health agencies and the French Ministry of Health. (lines 417-419).
12. I have the same question for the patient education intervention. Is there any evidence that this patient education program is feasible? It seems like a lot of work for the GP. It would be good to know that this is indeed a potentially useful program. In some countries this program would be best delivered by dedicated nurses.

The patient education intervention has not been tested, actually it is the aim of this study, to improve patient quality of life with heart failure though a complex intervention involving patient and GP education in primary care. But this programme has been validated by a grant from the French Ministry of Health, and this study was partly public funded because of this validation by regional health agencies and the French Ministry of Health. We agree with the reviewer, it is lot of work for the GP but actually we do not have dedicated nurses in France to involve in that kind of intervention and we want to know if it is effective to involve GPs in these kind of programmes.

Level of interest:

An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

The manuscript has been revised by a native English–speaking copy-editor with a background in the biomedical sciences.

1. Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Medical Research Methodology 2002; 2:8


Referee 3: Frank F Peters-Klimm

This study protocol is reporting a medium-size CRT on an educational Intervention in French GPs regarding heart failure care.

Major compulsory revisions

1. Description on interventional elements regarding time duration and how the fidelity of the implementation of the Intervention will be measurable.

*The interventional elements are described in the section “intervention group”. In order to know what GPs undertook with the patient regarding the intervention, at each GP visit, GPs report what they did and write in their case report form which topics they explored (Appendix 3). GPs have case report forms with written standardised instructions for the patient education sessions and to summarize each consultation and write personal patient objectives. (Lines 225-231).*

2. No comments regarding medical Treatment (pharmacotherapy) are being made. Will this outcome be measured - and, if, to what extent?

*Patients treatment is reported at each GP visit in the case report form: we will be able to describe treatment at baseline and any modification during the follow-up. (lines 163-167).*

3. The Researchers decided to first randomise the practices, then perform the Intervention. Ideally, GPs should first recruit Patients and make a baseline measurement of the outcome. This cannot be helped now anymore, but a (probable practical) reason should be given.

*The GP randomisation was done before patient recruitment. We felt that if patients were recruited after GPs received their training, the patients in the two groups*
might then be different because the training received by the GPs in the intervention group may make them feel more competent and therefore, they may recruit more severely ill patients as compared to the GPs in the control arm. To avoid this bias, we could have randomised GPs after they had included their patients, using the ‘Zelen’ method\(^1\). Unfortunately, this was not possible because the inclusion period lasts one year and the follow-up 19 months: given heart failure patients’ life expectancy, this was felt not to be appropriate. (lines 347-353).

It was GPs that were randomised and not practices but to avoid contamination, GPs in a same practice were randomised to the same group. We modified and detailed the cluster randomisation. This has been recorded in the Methods section (lines 126-128).

Minor essential revisions:

In the Background the authors move from international data on DMP to the French situation arguing that there is no literature for Primary care interventions. Actually there is some literature from Primary care in the Netherlands and Germany. The German examples are :
The German references have shown that the goal of improving Health related QoL in HF patients is an ambitious aim, even in more intense interventions (Peters-Klimm F, Campbell S, Hermann K, Kunz CU, Müller-Tasch T, Szecsenyi J. Case management for patients with chronic systolic heart failure in primary care: the HICMan exploratory randomised controlled trial. Trials 2010; 11:56. ) Some of the existing literature should be integrated in the Background section.

*Lines 101-108. We agree with you and have included more detail in the background literature for primary care interventions. We added the paper\(^2\) and some literature. However, for most of previous interventions, while patient recruitment was in primary*
care the intervention were not performed by GPs themselves (lines 105-106). In France, we do not have dedicated nurses or doctors’ assistants available to be involved in such intervention and we want to know how effective it will be to involve French GPs in these kinds of programmes. We do thank the reviewer for all these references because we will use them in the principle paper to discuss adherence to treatment and difficulties in improving the quality of life in heart failure patients with a complex intervention.

Level of interest:
An article of importance in its field

Quality of written English:
Needs some language corrections before being published.

The manuscript has been revised by a native English–speaking copy-editor with a background in the biomedical sciences.
