Author's response to reviews

Title: Individual Patient Data Meta-Analysis of Beta-Blockers in Heart Failure: Rationale and Design

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Author's response to reviews: see over
Individual Patient Data Meta-Analysis of Beta-Blockers in Heart Failure:

Rationale and Design

Response to reviewer’s comments

Reviewer: Lesley Stewart

Reviewer's comments in bold italics with authors’ response below.

This is a well planned methodologically sound research plan for an IPD meta-analysis.
The manuscript is clear and well written.

Minor comments on manuscript:
The submission has been made as a protocol, but the title of the submission describes an article on rationale and design rather than a protocol.

Apologies – the type of article has been changed to ‘Methodology’.

If I understand correctly, in addition to assessing the effectiveness of beta-blockers in heart failure, the authors also intent to use the data to develop a prognostic model to facilitate risk prediction. If so the second aim could usefully be added to the abstract.

The following has been added to the abstract:

Further, we aim to provide an assessment of economic benefit and develop a risk model for the prognosis of patients with chronic heart failure.

The project is limited to 11 major trials that include the majority of relevant information. It would be helpful to state the proportion of known randomised evidence that this includes (i.e. numbers of patients included/numbers of patients entered in all known randomised
trials which would other than size be eligible for inclusion).

Thank you for highlighting this important issue. The number of patients not included in this analysis is 838 (that would have been eligible if no minimum trial size was required).

The following has been modified in the Study Inclusion Criteria section:

By concentrating on the larger trials (which have enrolled 95.7% of all RCT participants), the project remains practical whilst the amount of data missed by not including the smaller trials is minimized.

For your information, the list of trials not included is presented in the table at the end of this document.

Please disclose what support from the four pharmaceutical companies comprised, noting any financial conflict of interest and stating their role and influence in data analysis, presentation and publication.

The Funding section has been modified:

The BB-HF project was investigator initiated. The BB-HF collaborative group extend their thanks to the four pharmaceutical companies that have supported this project. Menarini Farmaceutica Internazionale provided an unrestricted research grant to support administrative costs. None of the pharmaceutical groups have any role in data analysis or the drafting of manuscripts. Any additional funding received will be stipulated in future publications.

The intention to explore economic impact is not well developed.

The economic paragraph has been modified:
For the economic analysis, we propose to perform a cost analysis using standard published information to provide a representative spread of health economic scenarios. Costs of care will be derived from simple drivers like hospital length of stay, medications and other treatments and a cost effectiveness analysis will be carried out based on cost per event avoided (e.g. death or hospital admission). Modelling of cost effectiveness will be carried out based on specific subgroups such as age, gender and diabetes, in a number of different healthcare models (e.g. socialised care, private care and a mixed health care model), taking account of the different costs of beta-blockers. An overall population-based cost impact analysis will be derived assessing different levels of uptake of beta-blockers in heart failure with a view to estimating the cost savings of improving beta-blocker utilisation.

**Minor comments on data collection forms:**

The authors might have wanted to distinguish between what is unknown (i.e. missing at patient level) and what is unavailable (at trial level) and for some (conditional variables) what is not applicable. This can be helpful for analysis and interpretation of results.

The method of collecting data on hospital admission is quite complex and it might have been easier to collect as: type of admission: cv not hf; cv with hf; not cv; unknown; unavailable; not relevant (no admission) together with data of admission for each.

However, as most data have already been collected, I realise that even if the forms cannot be amended.

Thank you for this comment. We had two meetings of the Collaborative Group prior to extracting data so were aware of the types of data missing at a trial level. We did make an attempt at the patient level for determining missing data using the following coding sequence for categorical data; 0 = No, 1 = Yes, 9 = Unavailable. In general we are fortunate that the
trials, for the most part, were well executed and contain only a very small proportion of missing data for the majority of important variables. Regarding the type of hospital admission, these variables were based on the common data available in a few of the larger trials (data which were available to us prior to designing the extraction forms).

Additional amendments

The following section on author contributions has been added:

DK participated in the design of the study, manages the collaborative group and performs data management and statistical analysis. LM, GE, HK and MDF participated in the design and coordination of the study. DGA and NW participated in the design of the study and the statistical analysis. All authors read and approved the final manuscript.
Table of trials (<300 participants) not included in the analysis

<table>
<thead>
<tr>
<th>Citation</th>
<th>n</th>
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<tr>
<td>Bristow MR, O’Connel JB, Gilbert EM et al. Dose-response chronic-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Circulation 1994;89:1632-42.</td>
<td>139</td>
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<tr>
<td>Total</td>
<td>838</td>
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