Recommendations for managing missing data, attrition and response shift in palliative and end-of-life care research: Part of the MORECare research method guidance on statistical issues
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What is This?
Recommendations for managing missing data, attrition and response shift in palliative and end-of-life care research: Part of the MORECare research method guidance on statistical issues

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Abstract
Background: Statistical analysis in palliative and end-of-life care research can be problematic due to high levels of missing data, attrition and response shift as disease progresses.
Aim: To develop recommendations about managing missing data, attrition and response shift in palliative and end-of-life care research data.
Design: We used the MORECare Transparent Expert Consultation approach to conduct a consultation workshop with experts in statistical methods in palliative and end-of-life care research. Following presentations and discussion, nominal group techniques were used to produce recommendations about attrition, missing data and response shift. These were rated online by experts and analysed using descriptive statistics for consensus and importance.
Results: In total, 20 participants attended the workshop and 19 recommendations were subsequently ranked. There was broad agreement across recommendations. The top five recommendations were as follows:

1. A taxonomy should be devised to define types of attrition.
2. Types and amount of missing data should be reported with details of imputation methods.
3. The pattern of missing data should be investigated to inform the imputation approach.
4. A statistical analysis plan should be pre-specified in the protocol.
5. High rates of attrition should be assumed when planning studies and specifying analyses.

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The leading recommendation for response shift was for more research.

**Conclusions:** When designing studies in palliative and end-of-life care, it is recommended that high rates of attrition should not be seen as indicative of poor design and that a clear statistical analysis plan is in place to account for missing data and attrition.

**Keywords**
Statistics, research design, palliative care, consensus

**Background**

Palliative care studies often suffer from high levels of missing data and/or attrition (see Table 1 for definitions of missing data and attrition), often due to patients becoming unwell. It can be problematic to carry out statistical analysis of palliative and end-of-life care (P&EoLC) data because missing data are a potential source of bias in the analysis.³

Attrition can lead to censoring of data, as patients are no longer under observation. For example, this could be by not including data from patients in the treatment arm who have dropped out, so that the study population may no longer be representative of the target population. This can lead to overly optimistic results with the data showing poor outcomes censored. A major cause of attrition is death, and it is an expected outcome of many studies involving palliative care patients. There are no published systematic reviews of the rates of attrition in palliative care studies, but two key palliative care studies reported attrition rates of more than 60%.² ³ Indeed, in the seminal study by Temel et al., the sample size was increased due to attrition. Published recommendations on acceptable rates of attrition frequently refer to the '5-and-20' rule, which declares that attrition rates of less than 5% probably lead to little bias but those over 20% may lead to potentially serious threats to validity.⁵ Some journals will refuse to publish studies with attrition rates of more than 20%.⁶ So where does this leave palliative care research, which has potential for high levels of attrition?

‘Missing data’ refer to individual data that are not available due to non-response or incomplete collection. Where data are missing, one of the key questions is whether or not this occurred by chance. Missing data are categorised into completely missing at random (CMAR), missing at random (MAR) and missing not at random (MNAR) (see Table 1).⁷ There is likely to be a high level of missing data as patients completing a questionnaire might struggle to maintain concentration due to diminishing function. For studies involving P&EoLC patients, it is likely that the explanation for missing data is ‘MNAR’. This is likely to be as a result of the patient being too unwell to complete the questionnaire, which is not a random event. Table 1 shows the different types of missing data categories. Missing data can range from 0% to 100%, but as with attrition, we do not know the overall levels for missing data in P&EoLC studies, but we can assume that they are higher than for many other types of studies as they often include patients who could be actively dying. In one study with advanced breast cancer patients, 90% of their sample had missing datapoints.⁸

There are issues of how to design studies that allow for, or analysis that can appropriately compensate for, missing data and attrition.⁹ There are a variety of imputation techniques to compensate for missing data, but there is no one universally agreed method. The most commonly used method, last observation carried forward (LOCF), is probably unsuitable in research involving palliative care patients as their condition is likely to be progressing, and this would result in overly optimistic results. This article does not explicitly address imputation methods as there are many useful overview articles about imputation methods including one by the European Medicines Agency already published.

**Table 1.** Definitions for attrition, missing data and response shift.⁹

<table>
<thead>
<tr>
<th><strong>Attrition</strong></th>
<th><strong>Attrition can be defined as the loss of patients from the study, while missing data can more generally be defined as the absence of parts of patient’s data. Death represents one form of attrition.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Missing data</strong></td>
<td><strong>Missing data refers to individual records that are not available due to non-response or incomplete collection and can be a whole questionnaire (unit non-response) or the response to a particular question (item non-response). There can be different reasons for missing data and Rubin’s classification defines three types: missing at random (MAR) when missingness may depend on single variables, completely missing at random (CMAR) when missingness is not related to the specified variables and missing not at random (MNAR).</strong></td>
</tr>
<tr>
<td><strong>Response shift</strong></td>
<td><strong>Schwartz et al.¹⁰ defined response shift as a change in the meaning of an individual’s self-reported HRQOL, which can result from different processes:</strong></td>
</tr>
<tr>
<td></td>
<td>1. Recategorisation (i.e. a re-definition of HRQOL).</td>
</tr>
<tr>
<td></td>
<td>2. Re-prioritisation (i.e. a change in the importance attributed to component domains constituting HRQOL).</td>
</tr>
<tr>
<td></td>
<td>3. Recalibration (i.e. a change in a patient’s internal standards of measurements).</td>
</tr>
</tbody>
</table>

HRQOL: health-related quality of life.
Response shift poses a further challenge for P&EoLC research. One of the aims of palliative care is to help people adjust to their condition. As people begin to re-evaluate their physical or mental state in relation to their shortening lifespan, they may experience a ‘response shift’ in that what was once unbearable now becomes bearable. Schwartz et al.10 reported a patient, who exemplifies this:

During the radiotherapy I became more tired. At that time, I may have thought that I was tired. But now I say no I was not tired at all. Now I am tired. … So, now I may look differently upon that week, while at that time I may have thought that I was dead tired. (p. 714)

Response shift may be a desirable outcome in P&EoLC as patients come to terms with their situation and may reflect improved levels of coping. However, it may also introduce bias that affects the interpretation of results.

MORECare11 aims to identify, appraise and synthesise ‘best practice’ methods for the evaluation of end-of-life care, particularly focusing on complex service-delivery interventions and reconfigurations. Where there was a lack of published evidence, expert consultations were carried out. There were five consultations that looked at different topics:11 statistical considerations,12 ethical considerations,13 outcome measurement,13 the use of mixed methods14 and health economics.15 This article reports from the statistical considerations expert consultation that looked at missing data, attrition and response shift in relation to managing data from P&EoLC patients as there are no direct recommendations about how to manage such data.

**Table 2. Definitions for palliative and end-of-life care used for the recommendations.**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO17 definition of palliative care:</td>
<td>an approach which improves the quality of life of patients and their families facing life threatening illness, through the prevention, … assessment and treatment of pain and other problems, physical, psychosocial and spiritual.</td>
</tr>
<tr>
<td>End-of-life care definition from the United Kingdom’s Department of Health – The end of life care strategy18</td>
<td>The definition of the beginning of end of life care is variable according to individual person and professional perspectives. … For some the start may be at the time of diagnosis of a condition which usually carries a poor prognosis … For others it will be at a point when there is a deterioration in a chronic illness and it becomes apparent that the likely prognosis is measured in months or possibly a year or two … Alternatively, it could be an elderly person who is becoming increasingly frail.</td>
</tr>
</tbody>
</table>

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**Aim**

To develop recommendations about how to manage missing data, attrition and response shift in data arising from studies including P&EoLC patients.

**Methods**

We used the MORECare Transparent Expert Consultation (TEC)16 approach to conduct a consultation summit with experts in statistical methods in P&EoLC research. TEC is a combination of nominal group techniques and an online survey. The format of the consultation included presentations, discussion and nominal group techniques.

The MORECare workshop on statistical methods was organised by a team of senior academics who consulted with a medical statistician with experience in research involving palliative care patients. The group identified people with expertise in medical statistics, some, but not all, of whom had a background in palliative care research and others not. Palliative care researchers from the United Kingdom were also invited. We identified statisticians and researchers who had published in relevant areas such as missing data, attrition, response shift and statistical considerations in palliative care. Additional members who could not attend on the day due to other commitments were included in an online consultation.

At the beginning of the day, the definitions for P&EoLC were shared with the group (Table 2). The three main topics we chose to discuss on the day were attrition, missing data and response shift as there is a lack of published evidence in relation to palliative care. The following three presentations were made:

- Missing data (Professor Stephen Walters)
- Attrition (Professor Stephen Walters)
- Response shift (Professor Peter Fayers)

The presentations gave an overview of the topic as the participants had expertise in different areas.

Following each presentation, there was time for lengthy discussions where key points from the presentations could be addressed, clarified and discussed in relation to participants’ previous experiences. In the afternoon, the group members were assigned to three smaller groups to make recommendations about the three topics. The groups were organised using nominal group techniques and gave the opportunity for all participants to make a contribution:19

1. Each group had a facilitator and scribe.
2. Each participant was asked to write down recommendations individually on each topic area.
Table 3. Classification of recommendations.

<table>
<thead>
<tr>
<th>Rating</th>
<th>Median</th>
<th>Interquartile range</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong agreement/high consensus</td>
<td>≥8</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>Strong agreement/low consensus</td>
<td>≥8</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td>Moderate agreement/high consensus</td>
<td>&lt;8 to &gt;6</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>Moderate agreement/low consensus</td>
<td>&lt;8 to &gt;6</td>
<td>≥2</td>
<td></td>
</tr>
</tbody>
</table>

3. The recommendations were then shared with the small group and a list of original recommendations written up on a flip chart.

4. The recommendations were discussed for clarity and initial duplications removed.

5. The three groups came together and shared key recommendations, which were then discussed.

Following the summit, the core team of researchers (C.T., N.J.P., G.G. and V.S.) met to synthesise the recommendations from the three groups. Duplicate and similar suggestions were merged or removed. The team was trying to capture the recommendations that reflected the different discussions from the day. Recommendations that were applicable to research in general and were not particularly pertinent to research involving palliative care patients were also removed.

A final set of 19 recommendations were then put into an online consultation, which was sent to the summit participants and members of the project advisory group within 2 weeks of the summit. The MORECare project advisory group comprised senior representatives from academia, service providers, commissioners, the voluntary sector and lay members.

The participants from the online consensus were asked how much they agreed with each recommendation on a 9-point scale, where 1 was ‘strongly disagree’ and 9 ‘strongly agree’. They were able to make comments on each recommendation as well as enter general comments at the end of the consultation.

The median score and interquartile range (IQR) were calculated for each recommendation. The recommendations were then grouped into their level of agreement and level of consensus (see Table 3). This resulted in six potential levels of agreement ranging from ‘strong agreement’ with ‘high consensus’ to ‘no agreement’ with ‘low consensus’. Narrative comments were collated.

Ethics

The research was approved by the University of Manchester Research Ethics Committee (reference number 10328). All participants provided written informed consent.

Results

In total, 20 people attended the summit. This included eight medical statisticians and five palliative care researchers as well as seven members of the core research team. Between the three nominal groups, over 100 recommendations were made. These were reduced to 19 by the research team (N.J.P., C.T., V.S. and G.G.) for use in the online consultation. There was such a large reduction in recommendations because most recommendations were duplicated across the three groups and many were too generic. Where possible, the original wording of the recommendation was maintained. The online consultation was sent to members of the workshop and the project advisory group (n = 43), of which 18 people completed the online consultation (42%). Nearly all the responders had attended the summit and perhaps felt more able to complete the consultation because they had received the teaching on the day and had been involved in the discussions.

Some of the 19 recommendations grouped missing data and attrition (recommendations 2 and 12) although one is not synonymous with the other. This may have occurred because they are clearly linked and often occur in the same patient population. Indeed, attrition can be incorporated into missing data in some research articles.

Of the remaining 17 recommendations, 6 were about missing data, 5 on attrition and 6 on response shift. The participants broadly agreed with the 19 recommendations from the online survey (see Table 4 and Figure 1). The highest levels of agreement and consensus were around recommendations for attrition and missing data, with consensus for recommendations on response shift generally scoring lower. The five highest scoring recommendations are given in Table 5.

The recommendation for a clear statistical analysis plan was generic, but during the workshop discussion, it was clear that P&EOLC researchers did not routinely carry this out. It was rated high in this set of recommendations because researchers felt that this needed to be highlighted in palliative care where statistical analysis plans are not always in place.

Missing data (recommendations 2 and 9–13)

Participants in the online consultation agreed that studies should report missing data and the imputation method used to accommodate for them (recommendation 12). There was a great deal of discussion about the merits of different imputation methods but no universal method was identified, only that the method needed to take into account the study design (recommendation 10). This is in keeping with the general statistical literature on missing data. However, one recommendation that received broad agreement (recommendation 8) suggested using more than one imputation method in order to establish robust results. The aim of the day was not to develop recommendations about imputation methods, but the rating of these recommendations perhaps
indicates that there is a need to look at this area in greater detail in the future.

Recommendation 2 stated that the causes of missing data should be reported to help identify the correct imputation method. This might also help in the design of future studies, so that similar pitfalls could be avoided.

**Attrition (recommendations 1–3, 5–7 and 12)**

Recommendation 3 suggested that a taxonomy of the causes of attrition should be developed. This taxonomy was begun on the day but could be broadened. This is a novel idea that should help to rebut the idea that attrition is simply the sign of a poorly conducted trial. It would...
also support recommendation 1, which enforces the point that high rates of attrition do not imply a poorly conducted study. For longitudinal studies of P&EoLC, attrition (due to death or illness or incapacity) of participants is to be expected. It is very likely for this patient group that the mechanism for missing data is MNAR. There are no reported taxonomies of attrition, which could be identified in the literature, and to make a taxonomy of attrition would make an original contribution to recording trial data from studies involving P&EoLC patients, but also in studies not involving P&EoLC patients.

**Response shift (recommendations 4 and 14–19)**

There was less agreement around recommendations about response shift, which reflects this as a growing field of expertise where further work is required. At the meeting, it was agreed that response shift does occur and that this could be a desirable outcome of care. As people adjust to their situation, they may retrospectively re-evaluate their prior experience. One recommendation (18) that tried to account for this was to anchor responses. Anchoring responses against past experience may be a useful tool to employ in P&EoLC research when patient’s health can deteriorate quite rapidly. Recommendation 17 suggested exploring patients’ changing expectations and coping mechanisms as a way of exploring response shift.

Overall, participants felt that response shift, like missing data and attrition, requires further research before firmer recommendations can be made, which could tie in well to the ongoing work on patient-reported outcome measures (PROMS) in P&EoLC. However, none of the recommendations on response shift were in the top five.
Discussion

The summit gathered together individuals with expertise in this area and developed recommendations about how best to manage such data. These recommendations are underpinned by the assumption of the participants from the workshops that we need to carry out more research into these statistical issues. Recommendations for further research would be to conduct a systematic review of research involving P&EoLC patients to see exactly what the rates of attrition and missing data are and to see which imputation methods have been employed. This would also demonstrate how well this is reported in the published literature.

One of the recommendations from this study was that the standard norms in assessing study quality based upon rates of attrition should not apply to P&EoLC research, although in any investigation, the reporting of attrition is necessary to assess any potential bias. The recommendation to create a taxonomy of attrition could standardise how attrition is reported in a given study but would require further development. No other examples of taxonomies for attrition have been identified in the literature. Using secondary data analysis, we could test the taxonomy of attrition to see if this is possible. We would also welcome researchers to apply this taxonomy in future publications.

The recommendation to make a statistical analysis plan provides a structured way forward at the beginning of a study for how to manage missing data. This is recommended by the US Food and Drug Administration but deserves highlighting as good practice in palliative care research. Arguably, one recommendation that was implicit to the day was to involve a statistician in the design of research that requires statistical analysis, which also reflects good practice.

The imputation method should be predefined in the study protocol and fully reported. More research is required to identify which imputation method to use according to the data being analysed and the study design. There are useful websites about missing data, which researchers from the fields of social sciences and medicine can access. This is a rapidly developing field, with the number of citations for “multiple imputation” in article titles or abstracts increasing exponentially, covering both theoretical and applied studies, and the list of techniques and software for imputation is already long and growing. Further research is required to identify which imputation method to use according to the data being analysed, but there is a general agreement that no “universally applicable methods of handling missing values can be recommended.”

Many steps can be taken, which can help reduce missing data, such as reducing the burden of questionnaires. This has been tackled in greater detail at the MORECare summit on outcomes where overlapping issues such as burden and the use of proxies were explored. Designing studies in a realistic manner so that end points are readily achievable, in a timely manner, is another crucial issue.

The recommendation to anchor responses to minimise response shift was to compare oneself with how you felt at a previous time point. Formal anchoring is useful as research indicates that respondents do this themselves but may be using quite different anchors if this is not made explicit. Fayers et al. found that when a group of patients were asked to respond to the question, “How would you rate your overall quality of life?”, about 75% identified a single reference point with 22% thinking about how they were before they fell ill, 31% thinking about how they were a year ago and 22% had in mind reference to other people. Hence, an explicit reference point is useful. While this is useful, it may also prove problematic to patients who are asked to re-evaluate their status, as this may cause anxiety when they acknowledge their deteriorating health. Some measure of how people are coping with their change in health or well-being could be developed.

One of the limitations of this study was to include participants with limited statistical knowledge to comment upon the recommendations. We had wanted to include a broader sample of researchers and stakeholders to comment upon the recommendations, but they found this difficult to do without having listened to the basic lectures given at the summit. Some of the people who did not respond to the online survey contacted the research team directly to explain that this was because they did not feel they had sufficient expertise.

It could be argued that the presentations themselves led the participants to make recommendations; however, the presentations were made in an even-handed way and concentrated on teaching the broad issues involved and areas of disagreement rather than presenting either recommendations or solutions. Some bias may have arisen from the large group discussions; however, the nominal groups did allow people to make individual recommendations, and all ratings were done individually during the online sessions.

Some of their recommendations had multiple parts, and perhaps these should have been simplified where possible rather than maintaining the original wording. The attrition taxonomy was received well on the day; therefore, this was discussed as an integral way to report attrition, but it may have been better had it been reported on its own (recommendation 3). Indeed, this was the key recommendation for the day, which could be applied to any type of trial report beyond research involving P&EoLC participants.

The range in backgrounds of the people involved in making the recommendations is also a strength of the study. A genuine attempt was made to broaden the involvement of key stakeholders including patient or patient representatives. Ultimately, a group of recommendations have been developed, which could improve the quality of analysis and reporting of research in this area.

Conclusions

When designing research involving P&EoLC patients, high rates of attrition and missing data are to be expected and
should not necessarily be seen as indicative of poor design. It is recommended that a clear statistical analysis plan is in place, prior to the commencement of recruitment, which examines the patterns of missing data and attrition and takes these into account in the analysis of the data. For palliative care and end-of-life care studies, it is likely that data are MNAR since the likelihood of a patient of not responding to a quality-of-life (QoL) questionnaire at a particular time point is likely to depend on the unobserved values for their QoL at that time point. A taxonomy of attrition should also be applied to future studies to see whether it aids reporting. More research is required in statistical methods to assess these areas and also to develop the concepts of response shift in P&EOcLC.

Acknowledgements

We would like to thank the participants of the MORECare statistical recommendations workshop. MORECare aims to identify, appraise and synthesise ‘best practice’ methods to develop and evaluate palliative and end-of-life care, particularly focussing on complex service-delivery interventions and reconfigurations. Principal investigator: Irene J Higginson. Co-principal investigator: Chris Todd. The members of MORECare are as follows: co-investigators – Peter Fayers, Gunn Grande, Richard Harding, Matthew Hotopf, Penney Lewis, Paul McCrone, Scott Murray, Myfanwy Morgan; project advisory group – Massimo Costantini, Steve Dewar, John Ellershaw, Claire Henry, William Hollingworth, Philip Hurst, Tessa Inge, Jane Maher, Irene McGill, Elizabeth Murray, Ann Netten, Sheila Payne, Roland Petchey, Wendy Prentice, Deborah Tanner and Celia A Taylor; researchers – Hamid Benalia, Catherine J Evans, Marjolein Gysels, Nancy J Preston and Vicky Short.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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