

Executive summary

**Methods for the analysis of
quality-of-life and survival data in
health technology assessment**

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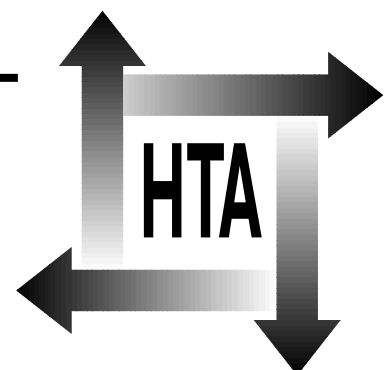
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**Health Technology Assessment
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Objectives

Quality of life has become an important issue in health care, especially in studies of chronic diseases. Substantial amounts of quality-of-life data are now being gathered in clinical trials, using a variety of instruments. In longitudinal studies of quality of life in which survival is also an endpoint, patients are generally severely ill and it is common for participants to drop out of the study because of illness or death. In such situations, the drop-out process may depend on the quality of life being experienced, rather than being random; hence the incomplete follow-up of patients is called informative drop-out. This must be appropriately accounted for in any analysis of the data to avoid the introduction of bias.

This study identifies and reviews critically the methods proposed for the analysis of quality-of-life and survival data in health technology assessment, particularly those that assess both these endpoints simultaneously. In this way methodology that requires wider dissemination can be identified together with areas requiring further research. It was not within the remit of this study to address issues related to the meaning, definition and measurement of quality of life.

Methods

The scientific and medical literature was searched for relevant methodological articles. Electronic searches were carried out systematically using Science Citation Index, Social Science Citation Index and the EMBASE database provided by BIDS (Bath Information and Data Service). The searches were supplemented by exploded references, personal collections and handsearching of the journal *Quality of Life Research*.

Results

Methods for analysing quality-of-life and survival data were found to fall into three broad categories, as described below, according to the research question underlying the study; this in turn depends on the disease and treatments under investigation.

Quality-of-life analysis in the presence of informative drop-out

The use of standard methods for the analysis of longitudinal data is discussed in terms of their application to longitudinal quality-of-life data. All methods, from simple descriptive analysis to complex modelling techniques, will give biased results when informative drop-out is present in the data. Standard methods should therefore be used with caution when analysing longitudinal quality-of-life data. Modelling techniques that deal with informative drop-out have been developed and their application to quality-of-life data is discussed.

Analysis of survival data adjusting for quality of life

In comparing treatments in terms of survival, it is often necessary to adjust for other patient-related factors, known as covariates, that could potentially affect the survival time of a patient. In some situations the survival analysis may need to adjust for baseline measures of quality of life (fixed covariates), while in others, allowance for changing quality of life over time may be required (time-dependent covariates). If assessments of quality of life are infrequent or data are missing for reasons other than death, then it may be difficult to adjust for changes in quality of life with any degree of accuracy. Modelling quality of life and survival as two simultaneous processes may improve the analysis in this situation.

Simultaneous analysis of quality-of-life and survival data

In studies in which quality of life and survival are both important endpoints, it may be advantageous to assess health technologies in terms of these endpoints simultaneously. Three different approaches can be used to achieve this:

- combining quality and quantity of life into a single endpoint and using quality-adjusted survival analysis methods to compare treatments
- using multistate models to model the movement of patients between various health states, defined by levels of quality of life and by death, and exploring how treatments differ in terms of these movements

- considering quality of life and survival as two simultaneous processes and describing the data in terms of two interlinked models.

Quality and quantity of life can be combined into a single endpoint by weighting periods of survival time according to the quality of life experienced. The resulting outcome measures are generally referred to as QALYs (quality-adjusted life years) with special forms known as TWiST (time spent without symptoms of disease and toxicity of treatment) and Q-TWiST (quality-adjusted TWiST). The use of standard survival analysis techniques on the QALY endpoint will generally give biased results because individuals with a worse quality of life will be censored earlier than those with a good quality of life, resulting in informative censoring. Methods of overcoming this problem, including partitioned survival analysis, are discussed. Quality-adjusted survival analysis overcomes problems of informative drop-out due to death and has the potential to be extended to deal with other disease- or treatment-related reasons for drop-out.

Multistate models are defined by categorising the period of follow-up of patients in a trial into a number of different health states defined in terms of levels of quality of life and death. The movement between health states is described by transition rates, which are modelled using the transition times for patients. Various modelling approaches are discussed. The inclusion of death as a health state in the model enables the analysis to deal with informative drop-out due to death and the inclusion of a 'drop-out' state could cover other reasons.

The most recently developed, and potentially most powerful, approach to analysing quality-of-life and survival data is to model the longitudinal quality-of-life data and the drop-out process, which includes drop-out due to death, as two simultaneous processes. Such an approach has the advantage of allowing quality-of-life data to be assessed longitudinally while adjusting for informative drop-out. In addition, the inter-relationship between the two can be explored.

Conclusions and recommendations

Obtaining appropriate data

- The method of analysis needs to be decided at the design stage of a study so that appropriate quality-of-life data can be collected. Issues to consider are:
 - the quality-of-life instrument to be used

- the frequency and timing of quality-of-life assessments
- the need to minimise non-compliance
- the collection of additional information, such as reason for drop-out
- the sample size required.

Choosing the appropriate method

- The choice of method should be based on the research question that the study aims to answer. The advantages and disadvantages of each method should be considered carefully together with the relevance and interpretability of the results to clinicians and patients.
- Methods used to analyse longitudinal quality-of-life data must allow for informative drop-out.

Reporting the analysis

- Methods used should be reported clearly, with details of definitions and assumptions used in the analysis.
- A sensitivity analysis should be carried out to assess the robustness of conclusions to any critical assumptions made in the analysis.

Recommendations for further research

- Further experience in the application of quality-adjusted survival analysis techniques to quality-of-life data is needed to enable a proper evaluation of such methods.
- Further research is needed in order to develop hierarchical models, multistate models and simultaneous modelling methods in their practical application to quality-of-life and survival data using both classical and Bayesian approaches. Consideration should be given to how methods could deal with the multi-variate nature of the quality-of-life endpoint.
- A full review of available software for methods that simultaneously analyse quality-of-life and survival data is needed to highlight areas requiring further development.
- Progress in the most rapidly developing areas of multistate survival analysis and simultaneous modelling should be monitored, together with parallel areas of methodological development such as in the field of AIDS research.

Publication

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

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The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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