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Economic Evaluation and Quality of Life Assessments in Cancer Clinical Trials: The CHART Trial

Jenny Morris and Maria Goddard

Arguments are being made more frequently to incorporate economic evaluations and quality of life assessments into clinical trials. Using a randomised, multicentre, phase 3 cancer clinical trial as an example, this paper outlines the importance of including such assessments; the practical considerations associated with the design of such trials; the methods for collecting such data; and, how such data can be used. Finally, it is emphasised that the anticipated benefits of collecting data relating to resource use and quality of life should outweigh the associated costs to research funding organisations.
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INTRODUCTION

IN RECENT years there has been considerable growth in the number of economic evaluations being integrated into clinical trials, especially phase 3 trials. Perhaps one of the most important reasons for such development is the recognition that the diffusion of many medical interventions takes place rapidly, prior to the assessment of associated costs and benefits [1]. The incorporation of economic analysis at an early stage can provide useful information to assist in the rational diffusion of technologies in the health care system [2]. Resources for health care can be used more efficiently, providing maximum patient benefit at minimum cost to the health service only if systematic evidence relating to the costs and benefits of interventions is available.

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Cancer therapies are often resource intensive and the potential patient population likely to receive the therapy may be large. Thus economic evaluations, integrated into cancer clinical trials may indicate in advance, the resource consequence of widespread adoption of new interventions.

In general, clinical assessments in phase 2 and 3 cancer trials focus on the physical domain, relying upon data obtained from the WHO performance status scale, for example, or the Karnofsky performance status scale, and from assessments of the side-effects of treatment, namely levels of toxicity. Such a focus excludes psychological and social functioning and, perhaps more importantly, the patients' perception of the effects of treatment; that is an assessment of the impact of treatment upon quality of life.

Most quality of life instruments are designed to cover four core domains: physical functioning, psychological functioning, social interaction, and disease and treatment-related symptoms. Given the toxicity and morbidity associated with the main modes of treatment for cancer, and the relatively limited survival associated with many cancers, consideration should be given to the inclusion of quality of life assessments into some phase 2 or 3 cancer clinical trials.

Assessments of patients' quality of life can, and should:

(i) clarify the views of patients, clinicians and purchasers when making decisions about treatment, especially when there are major differences between two treatments in the quality of patients' lives without any significant improvement in survival or local tumour control;
(ii) provide information to which patients can relate about the likely consequences of treatment;
(iii) quantify the extent to which levels of psychosocial morbidity vary according to the treatment regimes, and thus provide a focus for investigating ways in which such morbidity could be reduced; and
(iv) together with cost information, help determine the relative cost-effectiveness of different methods of treatment.

INCLUSION OF ECONOMIC EVALUATION AND QUALITY OF LIFE ASSESSMENT

Ideally, data on quality of life should be included in comparative trials of treatment regimes which are likely to have a significant impact upon patients' physical, psychological or social functioning, and/or if there is likely to be a trade-off between quantity and quality of life. These might include trials of treatment versus no treatment; trials which compare treatment modalities or treatments of varying intensity and/or duration; and trials of treatment in which survival is expected to be equivalent, but the quality of life different [3].

The advantages and disadvantages of incorporating economic analysis into clinical trials have been considered by others [4], and criteria for judging the appropriateness of doing so have been proposed [5].

In addition to consideration of the potential overall impact on resources, economic evaluation can also be used where the resource impact on different agencies such as the hospital sector, community sector and the patients and relatives is expected to differ between the alternatives being assessed. This is important as treatments which are cost-effective for one sector, such as the hospital, may not necessarily be cost-effective when considered from a wider viewpoint such as the community health services or society.

However, if it can be predicted that quality of life differences are likely to be small, or the unit cost difference between alternatives is likely to be small or where the therapy will be relevant only for small numbers of patients, then the costs of collecting the data will probably outweigh the benefits. Secondly, such assessments should be excluded when the treatment of the comparison group is so atypical that generalisations to normal practice could not be made; and also, when the nature of the patient group is such that collecting quality of life data over a period of time would not be possible.

THE CHART TRIAL (CONTINUOUS, HYPERFRACTIONATED, ACCELERATED RADIOTHERAPY)

Conventional radiotherapy given with curative intent, is commonly delivered over a period of up to 7 weeks, often consisting of daily treatment with breaks at weekends. However, scientific evidence suggests that tumour cells can proliferate during the course of treatment, causing problems with tumour control which can ultimately be a major reason for treatment failure; a shorter treatment duration has been shown to be beneficial in terms of tumour control. In addition, research has also shown that giving radiotherapy in many small doses, rather than in fewer larger doses, can reduce the incidence of late radiation damage [6].

The CHART regime offers an alternative mode of delivery aimed at achieving both these objectives. The treatment is continuous (given without interruption over weekends), hyperfractionated (small doses given three times daily), and accelerated (given over a period of 12 consecutive days). Pilot studies of the CHART regime for head and neck as well as bronchus patients have shown good results in terms of tumour response, and limited late normal tissue damage [7, 8]. The multi-centre randomised controlled trial is testing these results by comparing the CHART regime with conventional radiotherapy for patients with head and neck cancer and non-small cell carcinoma of the bronchus.

The trial of CHART and conventional radiotherapy raises important resource and quality of life issues as well as those related to tumour control, survival and morbidity. The CHART treatment involves a radical departure from the normal practice in radiotherapy departments, involving weekend and out of hours work which may have significant resource implications, especially in terms of overtime payments to radiographers and technicians. Secondly, conventional therapy is usually given on an out-patient basis, except where the patient lives too far away to travel daily, or where old age or sickness necessitates an in-patient stay. However, patients in the CHART arm will normally be in-patients for the duration of their treatment (sometimes accommodated in a hostel ward which is clearly less expensive than a fully staffed ward), except in the unusual circumstances where they live near enough to visit the centre three times daily, and/or do not wish to receive treatment as an in-patient. These differences will have resource implications for the hospital in terms of the provision of beds and will also affect resources for travel. Hospitalisation immediately post-treatment due to side-effects of treatment may also vary. Pilot studies have indicated that CHART might reduce the extent of late radiation changes, and a lower incidence of necrosis may also reduce the need for salvage surgery after treatment [7, 8]. Finally, variations between arms in the incidence and severity of side-effects may influence the use of community health services such as general practitioners and district nurses. The overall difference in resource use will depend upon the direction and magnitude of all the above factors.

The relative effectiveness of the alternative radiotherapy regimes is being assessed in terms of disease-free survival, local tumour control and morbidity. However, this does not encompass the psychological and social effects of treatment on the patient, nor the patients' perception of the severity of treatment side-effects. For example, there may be variations in the psychological reactions to the radiotherapy regimes followed; for some, the short regime may be preferable to undergoing more protracted therapy necessitating many visits; for others the strain of receiving treatment three times daily may be great. Furthermore, the effects on mood due to side-effects such as oesophagitis and mucositis needed to be quantified. Finally, salvage surgery may be required for those patients with head and neck cancers where radiotherapy has failed. It is important, therefore, to document the impact that such treatment may have upon the quality of life of these patients about which comparatively little is known [9, 10].

PRACTICAL CONSIDERATIONS

If economic evaluations and quality of life assessments are to be incorporated into clinical trials, this should be decided at the outset to ensure that the design of the trial meets the requirements of the different methodologies used.

As the CHART trial is being undertaken in 10 centres in the U.K., the decision had to be made as to whether resource and quality of life data should be collected from patients in all 10 centres, or whether the focus should be upon a subsample of the centres. It was finally decided to collect information from all the centres as a targeted subsample would not have been representative of the 10 centres for the following reasons:

- the recruitment of patients into both trials at each centre was limited (on average, 50 patients per centre, per annum for both trials);
- the centres varied in terms of whether they stood alone as oncology units or whether they were situated within a district general hospital;
- the size of the radiotherapy departments varied between centres.

The data collectors were either radiographers or nurses, and only a few had research experience. An attempt was made, therefore, to ensure that the same member of staff at each centre was responsible for data collection throughout the study period. Visits were made to all centres to ensure that the rationale for collecting such information was clear to the staff, and that they understood how the various forms should be completed. Such visits have continued on an annual basis throughout the study and have resulted in a high level of co-operation between the data collectors and the study co-ordinators in York.

METHODS OF DATA COLLECTION

One of the possible drawbacks of adding an economic analysis to clinical trials is the potential to exacerbate the already complicated data collection process. In choosing the method of data collection it is, therefore, important to limit the amount of data collected whilst ensuring that the main variations in resource use will be covered. Failure to recognise the burden imposed on the data collectors may result in the collection of large quantities of data only at the expense of quality.

The clinical pilot studies of CHART were used to highlight the areas of potential differences in resource use as indicated earlier. Data collection forms were designed to collect information relating only to activity or the quantity of resources used—for example, numbers of treatments, hospital days, miles of travel, etc. In order to estimate the resources used, the "unit costs" of these activities are obtained in a separate exercise involving the clinicians, accountants, radiographers, estate management officers and other sources. This was undertaken by staff at York as the data collectors cannot be expected to access and validate cost data.

Information on some of the forms can be easily obtained by data collection staff from the patient records, e.g. days of hospitalisation, times of treatment; other information may be obtained directly from patients, e.g. distances travelled, methods of transport.

The use of community health and social services is being assessed from two sources—the patients and their general practitioners. The latter have been asked to provide information relating to surgery and home visits and also referrals to other services such as district nursing and home helps. The same questions were asked of the patients and part of the analysis will be to investigate variation in reported use of services.

Information on the travel and personal costs to the visitors of the patients is also being gathered from a sample of patients. The need to limit the quantity of data collected prevented this from being incorporated into the trial for all patients, but will provide a useful source of additional information.

There are two main methods of obtaining quality of life data: (i) by interviews, and (ii) by using questionnaires. Within the context of multicentre clinical trials, it would be extremely costly to undertake interviews. This, together with the fact that quality of life assessments were not the primary focus of the CHART trial, led to the decision to use questionnaires. Self-report, rather than observer-rated, questionnaires were used as it has been shown that there are significant differences between a patient's assessment of his or her quality of life, and that made by the doctor or the patient's relatives [11]. Self-report questionnaires designed for use with cancer patients were examined for item coverage, time to complete, ease of scoring, use in other trials, and the recommendations of experts [12]. Consequently, the decision was made to use the Hospital Anxiety and Depression Scale [13] as a measure of psychological state, and the Rotterdam Symptom Checklist [14] to provide an assessment of performance status, physical and psychological complaints. Generic health status measures were considered inappropriate as the items contained in such instruments would not be sufficiently sensitive to detect changes in functioning in the patients in the CHART trials.

Both the quality of life assessments and resource data collection were planned to coincide with the collection of the clinical data (during patients' visits to hospital for either treatment or follow-up), but are limited to the first 2 years of follow-up. Events which have a significant economic or quality of life input (such as salvage surgery) will be captured adequately in this time scale.

QUALITY ASSURANCE

Data collection staff were in contact by telephone in between visits by the research team from York. Additionally, a workshop to explain the aims of the economic and quality of life elements of the trial was organised for the data collectors and provided useful background information about the clinical trial, as well as the economic and quality of life elements.

Meetings were also held regularly with the staff at the Cancer Trials Office to ensure that there were minimal problems with the coding and processing of the data. Such meetings and visits

are essential to ensure a high standard of data collection and processing, and should be allowed for in the design of studies which aim to collect resource and quality of life data.

It should be acknowledged that not all clinicians participating in a trial will be familiar with resource and quality of life information so such areas of investigation are not likely to be their primary focus of interest. It is essential, therefore, to ensure a two-way flow of information in the form of reports, and active participation on the trial steering committee.

Finally, and perhaps most importantly, at the outset of a trial, it should be recognised that the endpoints of the clinical trial and the resource and quality of life trial may differ. This has implications for the timing of data analyses and preparation of material for publication. This reiterates the need for collaboration on the design and timeframe of the trial at an early stage.

APPLICATIONS OF THE DATA

Collecting data on the resources required by the CHART and conventional regimes, together with quality of life data, will provide important additional information to that yielded from the clinical trial.

If the clinical results are unequivocally in favour of CHART, then the resource and quality of life data will be important in adding to the debate about which treatment is the most cost-effective. This will be a significant issue given the limited resources available for radiotherapy treatment. However, the complexity of the resource use issues in the CHART trial means that it is unlikely to be appropriate to summarise the results in terms of a single cost-effectiveness ratio. This is because data relating to costs are being collected along a number of dimensions: treatment costs, community costs, costs to patients, and so on, and similarly the effectiveness data in terms of quality of life are also multidimensional: anxiety, depression, physical and psychological complaints.

If the clinical data are equivocal, and there are also resource and quality of life differences, then the data could aid the decision about which method of treatment is the most cost-effective, and also less burdensome to patients.

Data can be presented to decision makers in a variety of ways. Cost information along each dimension could be combined with a single measure of effectiveness such as life years gained. Additionally, patients could be classified according to scores on the quality of life instruments and costs of care could be estimated for each sub-group of patients.

CONCLUSIONS

This paper has outlined some of the practical issues involved in the planning and organisation of a phase 3 clinical trial in which economic and quality of life components are incorporated. The main issues can be summarised as follows:

(i) It is clear that only some clinical trials will provide a suitable vehicle for economic and quality of life elements. There are both advantages and disadvantages to incorporating such assessments, and these should be weighed up when considering the design of the trial.

(ii) It is essential that economists and those involved with quality of life assessments are involved in the detailed design of the clinical trial. This allows the data collection points for the economic and quality of life analyses to be scheduled to coincide with the collection of clinical data.

(iii) It is vital that all those involved in the trial are aware from the outset that the timeframes for each element of the trial may differ. For instance in many cancer trials, the analysis of the clinical data may not be completed until the death of all patients in the trial, and/or after a sufficiently long follow-up period (say 5 years). However, it is likely that data about resource use and quality of life could be analysed at a much earlier stage in the trial. This raises the issue of whether such data could be published before the final clinical report is prepared, at an appropriate stage to be decided by the trial steering committee. For example, in the CHART trial, an interim clinical analysis will be undertaken at the end of the recruitment period. At this stage a preliminary report on the economic and quality of life aspects will be prepared, with a subsequent input into the final clinical report.

(iv) The choice of methods for data collection needs to take into account the staff available and the practical issues involved in the collection of a large volume of data. The implications of getting large amounts of low quality data should be considered when designing the trial.

(v) The need to ensure as high a standard as possible, namely in data collection is essential if the trial is to be successful in achieving its objectives. In instances where the data collection staff are unfamiliar with resource and quality of life issues, training will need to be provided either on a group or individual basis. Regular contact with staff maintains the quality of the data collection process throughout the trial, and also ensures a good relationship between the data collectors and study co-ordinators.

(vi) Finally, the resource implications of integrating additional elements into the clinical trial must be recognised. The benefits of including such assessments must outweigh the costs.

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APPENDIX: PARTICIPATING CENTRES AND PRINCIPAL CO-OPERATING CLINICAL ONCOLOGISTS

The Beatson Oncology Centre, Glasgow (Professor A. Barrett, Dr Canney, Dr MacBeth, Dr Robertson, Dr R.P. Symonds and Dr H. Yosef). Mount Vernon Centre, Northwood (Professor S. Dische and Dr M.I. Saunders). St Mary's Hospital, Portsmouth (Dr V. Svoboda). The Royal Infirmary, Bristol (Dr H. Newman). Mersey Regional Centre, Clatterbridge (Dr B. Cottier). The General Hospital, Nottingham (Dr D. Morgan). The Cookridge Hospital, Leeds (Dr I. Rothwell). The Royal Marsden Hospital, London (Dr J. Henk). Weston Park Hospital, Sheffield (Dr M. Whipp). The Velindre Hospital, Cardiff (Dr C. Gaffney). The Radiologische Klinik, Dresden (Dr T. Hermann). University Hospital, Umea (Dr B. Littbrand).

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Adjuvant Treatment in the Curative Management of Rectal Cancer: a Critical Review of the Results of Clinical Randomised Trials

J.F. Bosset and J.C. Horiot

A critical analysis of the results of randomised studies on adjuvant rectal cancer led to a different interpretation than given by the 1990 National Institutes of Health (NIH) conference which concluded that combined postoperative chemotherapy and radiotherapy resulted in increased local control and survival in stage II and III patients. We think there is not as yet indisputable evidence for the use of such combination postoperatively. Furthermore, this approach resulted in increased toxicity and was only consistent with moderate compliance. Conversely, preoperative radiotherapy, which was not even mentioned in the conclusions and recommendations of the NIH consensus conference, definitely increases local control and should now be proposed as standard initial treatment in T3T4 resectable rectal cancer. Moreover, preoperative concomitant chemotherapy is an attractive area for clinical trials.
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INTRODUCTION

THE OUTCOME of resectable rectal cancer treated with surgery alone is associated in some groups of patients with a high risk of local failure (LF) and distant metastasis (DM) [1–3]. Due to the extreme disability caused by LF, a gain in local pelvic control represents a major end-point of adjuvant treatments. Adjuvant radiotherapy has been shown to decrease LF without any effect on survival. Lately, studies have suggested an improved survival in high risk patients when chemotherapy and irradiation were used in combination postoperatively [4, 5]. In 1989, a U.S. National Institutes of Health (NIH) Consensus Conference stated that postoperative pelvic irradiation and chemotherapy should be regarded as standard treatment for stage II and III rectal cancer patients [6]. The aim of this review is to analyse the published results of randomised adjuvant trials, which in part enabled the consensus conference analysis, to discuss its conclusions and finally to suggest some areas for clinical research in this disease.

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RESULTS WITH SURGERY ALONE

After curative resection, the prognosis of rectal cancer is correlated with the depth of tumoral extension through the bowel wall, the nodal involvement and the number of involved nodes [1–3]. The 5-year survival ranges from 44 to 76% in stage B2 Astler-Coller's patients, and drops to 10–40% when regional nodes are involved [2, 7, 8]. In all stages, local recurrence is a major reason for failure as a consequence of the mode of spread of the tumour, with direct invasion of the extra-peritoneal fat and of the neighbouring structures. Other difficulties include surgical access to the deep pelvis and the surgeon's ability to clear the mesorectal fat [9, 10]. Inadequate surgical clearance of the radial margin appears to be the first cause of LF in rectal cancer [11, 12]. LF rate ranges from 5% in a few selected series to 40% in most reports [2, 9, 13]. In randomised trials on adjuvant treatments, the control group with surgery alone is associated with a 23–44% 2 to 5-year LF rate in Astler-Coller's B and C patients (Tables 1–3). These data are in accordance with those reported in the Gastrointestinal Tumour Registry of Côte-d'Or in France [14]. The 5-year LF rate may reach the astonishing figure of 75% when using proper pathological staging reflecting the degree of extension beyond the wall and when giving an actuarial estimate of the risk instead of crude figures [11]. The risk of DM is also strongly correlated with the locoregional extension of the disease [1–3].