The value of health-related quality of life assessment in cancer clinical trials
Efficace, F.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS
INTRODUCTION

Cancer clinical trials

Cancer clinical trials are studies conducted with patients and are generally designed to evaluate the safety and effectiveness of a new oncology therapy or to optimize different therapeutic approaches. Clinical trials, particularly randomized controlled trials, play a key role in cancer research as they provide the scientific evidence needed to adopt the best treatment for all cancer patients [1]. The provision of quality care depends on the ability to make choices from robust scientific data. Historically, the main purpose of cancer clinical trials has been to help establish improved survival rates but they also serve as vehicles to provide other important information which might be indicative of improved clinical response such as disease-free survival, progression-free survival or tumor response. These are still common endpoints to evaluate when examining the effectiveness of a potentially valuable new treatment. Whilst these traditional biomedical endpoints remain important, the scientific community has also recognized the necessity to go beyond the “biomedical model” given it confines attention to physical aspects without taking into account overall health conditions and how the patient is affected by illness [2].

Health-Related Quality of Life (HRQOL)

Documenting outcomes in clinical research has become a priority and now also includes the evaluation of other endpoints relating to the broader psychological and social domains of cancer patients. Within this changing paradigm in healthcare research, measuring the construct of HRQOL has become an essential aspect in cancer research. The World Health Organization points out that the main goal of cancer control is “a reduction in the incidence of the disease and of the associated morbidity and mortality, as well as improved quality of life for cancer patients and their families” [3].

Whilst some concerns still challenge researchers when trying to define and to measure the construct of HRQOL [4], there are many researchers who agree that it refers to some key areas such as physical functioning and psychological and social wellbeing [5,6]. In addition, there is also reasonable agreement that HRQOL is a multidimensional and dynamic construct that may change over time, due to patients’ health conditions [7]. Another important aspect researchers have already agreed upon is that HRQOL is best assessed by patients themselves [8-10]. While patient self-reporting HRQOL has been widely acknowledged, it is also important to take into account situations in which the ability to complete a questionnaire can be compromised for various reasons. In this respect, recent evidence suggests that healthcare providers and significant others can be “reasonably accurate” in evaluating several aspects of patient’s HRQOL [11].
The relevance of HRQOL measurement in cancer clinical trials

One of the fundamental questions regarding the use of HRQOL as an outcome indicator is: *why should it be used?* Regardless of the survival improvements achieved by cancer research in some specific areas, such as non-metastatic breast cancer or Hodgkin lymphoma [3], many patients still cannot be cured and treatments often heavily impact on the patient’s life. Very few other diseases have treatments as toxic as common cytotoxic agents frequently used with cancer patients and adverse treatment effects, such as fatigue, hair loss, and severe nausea and vomiting often have a major impact on the patient’s HRQOL [12]. HRQOL has now become a relevant outcome measure in cancer research and the proportion of trials including such an evaluation is increasing [13]. As an example of the key role played by HRQOL in cancer research, it is worthy of note that the U.S. Food and Drug Administration has supported its use as an outcome measure in the evaluation of new anticancer drugs for more than a decade [14] and more recently, similar recommendations have also been made by the American Society of Clinical Oncology [15].

Given the increasing cost of clinical research, the issue of the cost of *not* assessing HRQOL in a particular trial was also raised [12], particularly for large international clinical trials, which are unlikely to be repeated. Not including HRQOL as at least a secondary endpoint might considerably diminish the amount of information that could be available to help understand the global impact of the therapy [12]. A careful evaluation of the possible inclusion of HRQOL assessment into a given cancer clinical trial should always be taken into consideration. As an example, the Clinical Trials Group of the National Cancer Institute of Canada has a policy requiring that HRQOL be included into every randomized controlled trial unless there is a clear reason stated in the protocol why measuring it would not be appropriate [16]. Incorporating HRQOL in cancer research, to supplement traditional clinical endpoints, can provide a comprehensive picture of the whole treatment’s effectiveness.

The need to collect HRQOL data in a clinical trial setting can be more pronounced in specific trial contexts. For example, when the prognosis of the patients under study is unfavourable, when the expected impact on clinical effectiveness is small, or also when the expected impact on HRQOL is large. HRQOL can also be the main endpoint in equivalence studies when the treatments are expected to be equivalent in clinical efficacy, in this case, a new treatment would be deemed preferable if it confers some HRQOL benefit [17]. Even when two treatments do not show differences in terms of HRQOL this information can still be useful.

Although some methodological aspects still challenge researchers in this field of research, the inclusion of HRQOL evaluation in cancer clinical trials has been informative, providing useful additional information for example in brain, breast pancreatic and prostate cancer patients [18-21]. The issue of different choices in oncology therapies challenges health-care managers to provide patients with the best options available. Examples of useful information derived from HRQOL evaluation in cancer research have also been highlighted [22].

Whilst the importance of assessing HRQOL has been widely proven to be of use when evaluating the whole treatment effectiveness of a given trial, a number of methodological issues have to be considered when writing the protocol or reporting results [23-26]. These issues need to be addressed in order to rely on valid and robust outcomes hence strongly support and inform clinical decision-making. Methodological constraints of cancer clinical trials having HRQOL as an endpoint have also been reported as a limiting factor for oncology drugs approval [27].
Aim of the thesis

The aim of the thesis is to address some important questions related to the reporting and the use of HRQOL outcomes in the context of cancer clinical trials. In particular, the following key issues will be evaluated:

1) What is the current methodological quality of HRQOL assessment?

This question is addressed in Chapters 2 and 3 where the accuracy of HRQOL reporting in two common malignancies, prostate and colorectal cancer, is systematically reviewed. Chapter 2 provides a detailed investigation of the methodology used to assess HRQOL in randomized controlled clinical trials with prostate cancer patients, while Chapter 3 investigates the same issue in colorectal cancer. Measuring HRQOL in clinical trials requires making a number of decisions concerning the methodology of measurement related to several issues including the design of the study, the specific cancer population being evaluated, the most suitable measure to assess HRQOL for that given target population as well as the timing of measurements. Given this multifaceted issue, Chapters 2 and 3 try to identify the reported methodological quality of HRQOL assessment in a trial setting and suggest ways to avoid some methodological constraints when reporting future studies.

2) How can we better inform clinical decision-making and raise the standard of HRQOL reporting? To what extent do HRQOL outcomes currently support clinical decision-making?

These questions are the focus of Chapters 4 and 5. Chapter 4 deals with the issue of how to bridge the gap between HRQOL research and clinical practice. As bridging the gap between HRQOL research and clinical practice is still an immediate challenge [28], in Chapter 4 a HRQOL checklist is devised to help researchers in interpreting the reliability and robustness of HRQOL reported outcomes from a given cancer clinical trial and also to help raise the standard of HRQOL reporting in cancer research. Furthermore, the proposed HRQOL checklist is also used to estimate to what extent the randomized controlled trials that have included a HRQOL evaluation in prostate cancer so far, are likely to affect clinical decision-making.

Chapter 5 reports a longitudinal analysis examining the HRQOL aspects of patients with metastatic breast cancer receiving first line chemotherapy. These women were treated with either a standard chemotherapy regimen of doxorubicin and cyclophosphamide or the newer combination of doxorubicin and paclitaxel. The main aim of this study is to evaluate short-term HRQOL, trying to give additional information for the planning of future treatments. In order to maximize the robustness of the HRQOL outcomes, hence providing a strong support for clinical decision-making, study results are reported according to the HRQOL checklist previously devised in Chapter 4.
3) **What is the prognostic value of baseline HRQOL parameters? Do they predict survival both in loco-regional and metastatic disease?**

Some recent evidence suggests that multidimensional measures of HRQOL may independently predict survival in cancer patients. Chapters 6 and 7 investigate this issue, using HRQOL data previously collected in two randomized controlled clinical trials with breast cancer patients and explore the possible predictive role of HRQOL parameters. The rationale for this exploration is that while the independent value of HRQOL in predicting survival has been shown by using different questionnaires, the reason for this association is still not clear, given different methodologies have hindered comparisons. Furthermore, contradictory evidence exists as to whether HRQOL is predictive for patients with both early and very advanced disease stage. Hence, in order to further explore this issue Chapter 6 investigates the possible predictive role of HRQOL parameters in a metastatic breast cancer population and Chapter 7 focuses on the same issue in a breast cancer population with loco-regional disease.

The final section of the thesis, Chapter 8, provides a summary of results of the previous Chapters, some conclusions aimed at answering the above reported questions as well as discussing some implications for future research.

**REFERENCES**


