The value of health-related quality of life assessment in cancer clinical trials
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CHAPTER 8

SUMMARY AND GENERAL DISCUSSION
SUMMARY OF RESULTS

This thesis aims to provide insight into the use and interpretation of Health-Related Quality of Life (HRQOL) data in cancer clinical trials. The first part of this thesis (Chapters 2, 3) deals with methodological issues when assessing HRQOL in cancer research. The second part (Chapters 4, 5) addresses the issue of the added clinical value of HRQOL in clinical trials and its impact on clinical decision-making. The third part (Chapters 6, 7) explores the role of HRQOL parameters in predicting survival in metastatic and non-metastatic disease. The following paragraphs include a summary of the main findings of each chapter.

Chapter 1 provided a general view of the HRQOL assessment in cancer research and describes the general outline of the thesis.

Chapter 2 systematically investigated the methodological aspects of HRQOL assessment in Randomized Controlled Trials (RCTs) of prostate cancer patients that were published between 1980-2001. Articles were mainly identified in a number of relevant medical databases (including MedLine and the Cochrane Controlled Trials Register). Given that there is no gold standard regarding how to conduct and report on HRQOL in cancer clinical trials, these studies were evaluated using the available literature on good practice for conducting HRQOL assessment. Based on this literature, a reviewer protocol for evaluating the studies was developed. The protocol consisted of four main categories: Demographics, Trial design, HRQOL assessment methodology and Methods of analysis and results (Tables 1-4, Chapter 2). Each of these broad categories was then further divided into subtopics to evaluate the trials. Overall, each trial was independently evaluated by two reviewers on a set of 28 criteria reported in the reviewer protocol. Twenty-five RCTs, involving 8015 patients were identified. Though searches were initiated from 1980, no trials were published before 1993. HRQOL was used as a primary endpoint in six (24%) of these RCTs. Nearly all of the studies used a previously validated HRQOL questionnaire, thus, ensuring valid outcomes in terms of questionnaire choice. With the exception of one trial, all trials reported details on timing of HRQOL assessments. The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was the questionnaire most often used to assess patients’ HRQOL and was employed in eight (32%) trials. However, some trials were found to have methodological limitations in terms of HRQOL reporting. Only 11 (44%) of the studies clearly reported the percentage or the absolute number of patients who completed the HRQOL questionnaire before commencing the trial (namely, baseline compliance). The rationale for selecting a specific HRQOL questionnaire was also reported in 11 (44%) studies reviewed. Further limitations were the lack of detail regarding the reporting of missing HRQOL data during the trial in 13 (52%) RCTs and the omission to report a priori hypotheses, concerning the HRQOL primary endpoint, in 21 (84%) trials. In addition, the clinical significance of the HRQOL outcomes was only addressed in 4 (16%) RCTs.

Chapter 3 systematically investigated the methodological aspects of HRQOL in RCTs of colorectal cancer (CRC). This study followed the same systematic approach to the critical evaluation of the trials as reported in Chapter 2. All RCTs with CRC
patients were included in the systematic review, if they had a HRQOL evaluation and were published between 1980-2003. Thirty-one studies involving 9683 CRC patients were identified and subsequently evaluated on the same schema as adopted in Chapter 2. Each study was independently evaluated by four reviewers on the grounds of the protocol previously devised in Chapter 2. Twenty-two (71%) of the studies were published after 1997 and the remaining nine (29%) were published between 1994 and 1997. HRQOL was used as a primary endpoint in nine (29%) studies. The most common HRQOL questionnaire used was the EORTC QLQ-C30, as it was employed in 15 (48%) of these RCTs. All the studies used previously validated HRQOL questionnaires and provided details on the HRQOL timing of assessment during the trial. However, some HRQOL methodological drawbacks were also evident. Twelve (39%) of the RCTs did not provide HRQOL baseline compliance and 16 (52%) failed to provide any details regarding HRQOL missing data during the trial. Only eight (26%) trials explicitly stated an a priori hypothesis on HRQOL. The rationale for selecting a HRQOL questionnaire was reported in three (10%) of the studies reviewed and in only four (13%) of the studies did researchers investigate clinical significance of the HRQOL results.

Chapter 4 aimed at evaluating whether the inclusion of HRQOL, as a part of the trial design in RCTs of prostate cancer, has supported clinical decision-making for the planning of future medical treatments. In order to address this issue, the Minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials was developed. This checklist consists of eleven key HRQOL issues and was devised to evaluate the adequacy of HRQOL reporting of any cancer site in any clinical trial. It enables a quick review of a HRQOL trial report, by allocating a score ranging from 0 to 11. The higher the number of issues addressed, the higher the quality of the reported HRQOL outcomes. The checklist has been devised to address only the basic and essential criteria that a given trial should report to warrant valid and reliable HRQOL outcomes. It can also be considered as a minimum guideline to help investigators when writing the HRQOL report. The eleven items are grouped into four sections: Conceptual, Measurement, Methodology and Interpretation. The content of the checklist was based on authors' consensus about the most important HRQOL items to be reported in a trial report. However, as it was clear that the checklist items might have different relative importance, an ad-hoc panel of thirty HRQOL experts was asked to prioritise the eleven key issues. Once developed, the checklist was then employed to estimate the robustness of HRQOL outcomes of studies conducted in prostate cancer (previously identified in Chapter 2). The key question was: are the results robust enough to have a possible impact on planning future treatments and to support clinical decision-making? In this respect, both HRQOL and traditional clinical outcomes were systematically analyzed in each trial. Each study was then scored according to the checklist. This evaluation was aimed at identifying the RCTs with robust HRQOL outcomes. It was concluded that 33% (8 out of the 24 studies evaluated) had robust HRQOL outcomes, thus providing reliable HRQOL evidence that could be used to support clinical decision-making. Six of the eight robust RCTs found significant HRQOL differences between treatment arms. The added value of the HRQOL information was particularly important, given that seven, out of the eight of these methodologically robust studies, provided limited or no evidence of survival differences between treatment arms. All the eight higher-quality HRQOL trial reports
were published in or after 1998. This suggests that there has been a learning curve in the adoption of a more robust methodological approach to conducting and reporting of HRQOL in RCTs.

Chapter 5 compared HRQOL in a RCT which enrolled 275 patients with metastatic breast cancer receiving the combination of doxorubicin and paclitaxel (AT) or doxorubicin and cyclophosphamide (AC) as first-line chemotherapy treatment. The aim of the study was focused on investigating the short-term HRQOL outcomes. Assessments were planned at baseline and at the start of cycles two, four and six. A final assessment was planned three months after the last cycle. Two validated questionnaires were used to evaluate HRQOL: the EORTC QLQ-C30 and the breast cancer module (EORTC QLQ-BR23) both of which have proven robust psychometric properties [1,2]. Five key scales were selected a priori for HRQOL analysis, namely: global quality of life, fatigue, nausea and vomiting, upset by hair loss and systemic therapy side effects. Other HRQOL variables were then examined on an exploratory basis. In order to maximize the outcomes’ interpretability, results were reported according to the Minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials, (as reported in Chapter 4). Based on work by Osoba and colleagues [3], differences of at least 10-points (on a 0-100 scale) were classified as the minimum clinically meaningful change in a HRQOL parameter. For example, an increase by ≥10 points on a functional scale would mean a moderate improvement, whereas a decrease by ≥10 points would be interpreted as a moderate worsening. Changes of <10 effect points were considered as no change, or of small minor clinical relevance. Changes >20 were classified as large effects. Compliance at baseline was 79.6% (219 patients) and overall compliance for the first four assessment times was 66%, no significant differences between arms were evident. On the five scales selected a priori, no statistically significant differences between the two groups were seen at any time point. In both groups, these selected domains were impaired over time. Using the aforementioned criterion for clinically significant changes [3], fatigue increased in both arms by the second assessment then dropped in the AC arm to levels comparable with baseline, but remained moderately clinically meaningful in the AT arm. In both groups moderate clinically significant increases in systemic therapy side effects were seen, occurring at cycle two and continuing over the subsequent assessments. This became a large clinically meaningful effect in the AT arm at the last cycle. However, the global quality of life score showed no or little change during the entire study in both groups. The HRQOL information derived from this study is therefore useful when advising metastatic breast cancer patients of the expected HRQOL consequences of these treatment regimens.

Chapter 6 investigated the prognostic value of HRQOL parameters for survival in metastatic breast cancer patients. The study explored the relationship, using the baseline HRQOL data of the RCT reported in Chapter 5. The following HRQOL variables from the EORTC QLQ-C30 were studied: physical, role, emotional, cognitive, social functioning, fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss and global health status. In addition, pre-selected variables from the EORTC QLQ-BR23 were used for this analysis: systemic therapy side effects and future perspective as they were believed to possibly impact on predicting survival. The
research also controlled for important clinical variables including performance status, number of sites involved and disease free-interval. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. The univariate analysis found the following clinical variables predicting poor survival: low performance status, increased number of sites involved and multiple sites of visceral disease. Physical, social and role functioning as well as pain, fatigue, dyspnoea and appetite loss were also predictors of survival. After a stepwise selection, the final multivariate model retained one clinical variable and one HRQOL variable as independent prognostic factors, namely, performance status and appetite loss. Patients with a normal performance status (ECOG 0) had a median survival of 26.4 months as compared with patients with worse performance status (ECOG 1 and ECOG 2) who had a median survival of 20.5 and 11.1, respectively. In the final model, appetite loss (as reported by patients themselves) was the strongest independent HRQOL prognostic factor of survival. Patients with better appetite had a median survival of 25.2 months as compared with patients who had less appetite with a median survival of 16.2 months. This finding is consistent with previous research.

Chapter 7 investigated the predictive value of HRQOL parameters in a non-metastatic breast cancer population. The overall sample consisted of 448 locally advanced breast cancer patients who had been enrolled in an international RCT throughout Canada, Europe, Russia and South Africa. HRQOL baseline scores were assessed using the EORTC QLQ-C30. The selection criterion for including HRQOL variables was based on previous literature of similar studies that used the EORTC QLQ-C30. The following HRQOL variables were therefore pre-selected for this analysis: physical, emotional, role and social functioning as well as fatigue, pain, global health status/QL and appetite loss. The analysis also controlled for important clinical variables. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. In addition, a bootstrap re-sampling technique was used to assess the stability of the outcomes. In the univariate analysis, none of the HRQOL variables were associated with longer survival and the only clinical factor predicting poor survival was the diagnosis of inflammatory breast cancer. The final multivariate model retained inflammatory breast cancer as the only factor predicting overall survival (OS). The presence of inflammatory breast cancer shortens the median survival time from 6.6 years to 4.2 years (36% reduction). The present study suggests that baseline HRQOL parameters are not predictive of OS in non-metastatic breast cancer patients. Given the disease stage of the sample, the impact of HRQOL data on disease-free survival (DFS) was also explored. However, there were no significant relationships. Furthermore, a secondary exploratory analysis, including all the HRQOL variables of the EORTC QLQ-C30, was also conducted and resulted in similar findings, with none of the HRQOL variables being prognostic, and only TNM stage significantly predicting survival. It is possible to conclude that baseline HRQOL data do not have predictive value in breast cancer patients with no distant metastasis. This finding is compatible with some previous research conducted in early stage breast cancer.
GENERAL DISCUSSION

It is evident from this thesis that the number of RCTs incorporating a HRQOL evaluation has substantially increased in recent years, especially large multinational studies. HRQOL is now widely recognized as an important factor that provides insight into the optimal treatment approach for the patient, particularly in cancer clinical trials with expected short survival duration [4,5]. Interestingly, nearly all of the trials reviewed in Chapters 2 and 3 have dealt with advanced metastatic cancer patients.

Overall, this thesis has also highlighted a number of methodological challenges which investigators commonly face when assessing HRQOL in a clinical trial context. This could be expected, given the fact that HRQOL in cancer research is still regarded as a relatively new scientific discipline. Given the results of the thesis, the following paragraphs will draw some conclusions regarding the three key questions posed in the introduction section.

What is the current methodological quality of HRQOL assessment?

Previous works have focused on the adequacy of HRQOL measurement in clinical trials [6,7]. Some others were focused more on the issue of reporting on HRQOL in RCTs [8] but were restricted to only investigating response rates and presentation of results without giving details of the whole process of assessing HRQOL. Furthermore, they did not specifically focus on oncology but also took into account other diseases.

One of the aims of this thesis was the systematic evaluation of the entire methodological process of assessing and reporting HRQOL in cancer clinical trials. Actually, inadequate or poorly designed and reported HRQOL investigations in the context of RCTs can mislead clinical decision making, as it will hamper a clear appraisal of the validity of the outcomes. A systematic evaluation of the methodology used to assess HRQOL was therefore a necessary step towards investigating the state of the art of such an assessment. Particularly, the thesis investigated this issue in two of the most frequent malignancies, namely prostate and colorectal cancer.

Based on the recent literature dealing with good practice when conducting HRQOL assessment in cancer clinical trials, a detailed reviewer protocol was devised to analyze systematically several methodological issues related to the whole process of assessing HRQOL, from the rationale of doing such an assessment to the presentation and interpretation of the results.

Overall, more than seventy percent of the RCTs that included a HRQOL evaluation were published after 1996. The same trend has also been noted in other RCTs with different disease sites such as breast, lung or primary brain cancer [9-11]. Given this recent trend, it is not surprising that clinicians were challenged by a number of methodological issues when incorporating and interpreting HRQOL into a clinical trial setting. Measuring HRQOL in a clinical trial, in fact, requires making a number of decisions, with regard to the questionnaire selection, methods of administration and data collection as well as statistical analysis. Most of these decisions are also tightly interwoven. For example, the selection of a HRQOL questionnaire should be primarily based on the HRQOL hypothesis being tested in the trial, hence, it should be verified that domains explored by an instrument reflect those that are expected to change in the
study. Additionally, the frequency of the number of HRQOL assessments should not only take into account, for example, the course and severity of the disease, or the length of the trial, but also patient burden. Too much burden could result in an increasing number of missing data.

At present, a large number of validated questionnaires are available to assess HRQOL in cancer patients. These include generic cancer instruments, which can be used for different cancer populations, or cancer-site specific instruments to assess HRQOL in specific cancer disease-sites [12]. Nearly all of the RCTs identified in this work have used a validated questionnaire, covering at least, the main domains relevant to a generic cancer population. The most frequently used HRQOL measure was the EORTC QLQ-C30. Very few RCTs reviewed in this thesis have used ad hoc, non- previously validated questionnaires. Recent works have highlighted that among 123 RCTs, published after 1980 and conducted in different cancer disease sites (including brain, breast, colorectal, lung, ovarian and prostate cancer) very few (11%) used non- validated HRQOL questionnaires; and overall, the EORTC QLQ-C30 was the instrument most frequently used, being employed in 40% of these studies [13]. Actually, selecting the ‘right’ questionnaire is a fundamental step in designing and conducting a HRQOL clinical trial and needs careful evaluation of various aspects. Questions need to be asked, such as: is the content of the questionnaire appropriate to the research question? Does the questionnaire possess robust psychometric properties (in terms of validity, reliability and responsiveness)? How interpretable are the scores? Is the questionnaire easy to administer? Besides these issues, the cultural validity of the questionnaire has also to be verified, in case it is not validated for the same population under study. Detailed guidelines on how to make this choice from the array of available HRQOL measures have recently been published and will assist investigators when designing future studies [14]. Nevertheless, the choice of the instrument to be used is only one aspect of the multi-faceted process of obtaining valid and reliable HRQOL outcomes in a clinical trial setting. In this respect, the thesis has also highlighted a number of areas needing improvement when reporting HRQOL.

For example, in order to limit the risk of underpowering the study, which could lead to a non significant difference between treatment groups, stating an a priori hypothesis is necessary to identify the main HRQOL endpoint for which the required sample size is calculated. In this respect, this thesis highlighted that the proportion of studies reporting such a statement was small, both in prostate and colorectal RCTs, being respectively, 16% and 26%. Other systematic reviews in RCTs of breast and lung cancer found slightly higher percentages as 31% of these studies addressed this issue [9,10]. In any case, reporting a priori hypothesis emerged as a critical area which needs to be addressed in future studies.

HRQOL data are collected by administering HRQOL questionnaire at different time points during the course of the study and missing HRQOL forms at different scheduled assessments are unavoidable, mainly, due to patients’ health conditions. Furthermore, HRQOL data can also be missing more frequently than other medical data because it relies on the completion of several items [15], which can then result in an extra burden for patients. Given that HRQOL forms are usually not missing at random, and as such cannot be ignored without introducing bias in outcome interpretation, investigators are therefore challenged to address some key questions such as: is it possible to prevent or minimize the number of HRQOL forms? Which is the best statistical approach of handling HRQOL missing data during the course of the trial? At present, there is no uniformly accepted way of dealing with HRQOL missing data and
different statistical approaches might need to be pursued. Recent works have addressed handling missing data in a comprehensive way, and are likely to assist investigators when exploring this issue [16,17] This thesis identified the documentation of missing data as a possible limitation, as only approximately 50% of the studies conducted in prostate and colorectal cancer reported the proportion of patients who dropped out during the course of the trial. This aspect was however addressed in 79% of the RCTs in lung cancer [9] and in 47% of the RCTs in breast cancer [10]. Overall, 57% of 123 RCTs conducted in different cancer disease sites since 1980, reported HRQOL missing data during the course of the study [13].

Interpreting HRQOL outcomes also requires careful attention. Actually, using HRQOL as an outcome measure in a clinical trial poses unique problems inherent to the construct being measured. For example, what is the meaning of a given statistically significant difference in terms of HRQOL from a patient’s perspective? Does a statistically significant difference in a HRQOL domain, between treatment arms necessarily reflect a subjectively meaningful difference perceived by patients? Basically, the challenging issue is how to evaluate “a tangible benefit (improvement in health) with an intangible construct (HRQOL)” [18]. Especially in large trials enrolling hundreds of patients it is possible to find a statistically significant $p$ value that can only reflects for example, a 2 or 3 points shift on a 0 to 100 HRQOL scale. The key issue is whether these 2 or 3 points turn out to discriminate between patients with different health conditions. There are a number of methods, broadly divided into anchor-based and distribution-based approaches to addressing clinical significance, but at present there are no standards to address this topic [18]. As an example, the minimal clinically important difference (MCID) (which is an anchor-based approach) is one of the most quoted methodologies to evaluate HRQOL clinical significance and previous works, which have investigated this issue, are likely to help researchers when addressing this aspect related to the interpretability of the outcomes [3]. In this respect, this thesis has also highlighted room for improvement, as 16% of the RCTs in prostate cancer and 13% of the RCTs in colorectal cancer addressed the clinical significance of the HRQOL outcomes. Interestingly this limitation was also found in other RCTs of breast and lung cancer, which only addressed this issue in 16% and 21% respectively [9-10].

Whilst published guidelines are now available to help researchers to incorporate HRQOL assessments into cancer clinical trials [19-24], there are no gold standards or internationally agreed guidelines for reporting HRQOL in cancer clinical trials [25]. Nevertheless, considering that the Consolidated Standard of Reporting Trials (CONSORT), which is now the international gold standard for reporting a RCT, was only published in 1996 [26]; it is quite conceivable that the same level of agreement will be reached in the area of HRQOL research. It is worthy of note, that some of the methodological drawbacks identified in this thesis, particularly those related to dealing with missing data and assessing clinical significance have also been cited as reasons for the Food and Drug Administration (FDA) to withhold approval of oncology drugs based on HRQOL assessments [27]. Given the methodological shortcomings identified in this thesis, investigators are fervently encouraged to address these, in order to better support and inform clinical decision-making. At present, a number of guidelines are available to address some of the key issues identified in this thesis and these are expected to help when including HRQOL in a clinical trial protocol and reporting outcomes.
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?

Information about side effects, symptoms and treatment options are very important to cancer patients as they enable them to make treatment decisions. Cancer patients require information not only related to survival estimates, but also regarding HRQOL issues [28]. Providing patients with such information, from a methodologically sound research basis, is therefore of paramount importance. Thus, including HRQOL as an endpoint in a RCT setting could provide invaluable information related to treatment side-effects from the patients’ perspective. In this respect, the HRQOL findings reported in Chapter 5 are likely to help metastatic breast cancer patients make informed decisions between two different treatment modalities.

In an editorial entitled “Beyond the development of quality of life instruments: where do we go from here?” which appeared in May 2002 in the official journal of the American Society of Clinical Oncology (ASCO), the Journal of Clinical Oncology, Mark N. Levine and Patricia A. Ganz [29] stated that it is “disappointing” that, despite the fact that thousands of patients have been enrolled in cancer clinical trials with a HRQOL component, “there are relatively few examples of formal quality of life measurement that have influenced individual patient decision-making or treatment policies”. This represents a challenging issue for all investigators involved in HRQOL cancer research, as it leads one to question: what is the proportion of studies that have been conducted so far, whose HRQOL findings are likely to be applied in clinical practice? This is also a pertinent question that a part of this thesis has tried to address. Actually, whilst the number of studies including HRQOL is constantly increasing, there is at present no estimation regarding the possible impact of these on clinical decision-making. As has been recently highlighted: “a crucial task for clinicians in interpreting trial-based QOL results is to determine how to measure and evaluate observed changes” [30]. When reviewing the HRQOL reports of RCTs conducted in prostate and colorectal cancer, a wide variability has been noted in terms of the accuracy of HRQOL reporting. This large variability has also been noted in other HRQOL reports from different cancer disease sites [9-11]. Hence, the clinician’s task of interpreting the robustness of a given statement regarding HRQOL outcomes obtained in a trial can be difficult. The first part of the thesis clearly pointed out that it is not possible to rely on HRQOL reported outcomes in the literature with the same level of confidence. Furthermore, readers in general are commonly unfamiliar with specific HRQOL issues in cancer research and this can be a further barrier when trying to interpret a trial-based HRQOL report. Given this scenario, and the lack of a pragmatic easy-to-use checklist, the Minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials (Chapter 4) was devised to help not only investigators but readers in general. This checklist is primarily intended for reviewing and facilitating a critical appraisal and interpretation of HRQOL outcome reports and also for guiding investigators when writing the HRQOL report from a clinical trial. This checklist has been built up and tailored on the current evidence regarding HRQOL reporting. It is of pragmatic use, as it only contains 11 items that can be scored as ‘yes’ (giving a score of 1) or ‘no’ (giving a score of 0), the higher the score the higher the considered robustness of the outcomes. Furthermore, it is only based on the cancer literature and is exclusively focused on issues related to HRQOL reporting. The systematic adoption of this checklist is also expected to help raise the standard of HRQOL reporting in cancer clinical trials and to...
facilitate a more systematic evaluation of the clinical impact of HRQOL assessment in cancer research. Nevertheless, this checklist has not been devised as a comprehensive guideline for the optimal design of HRQOL assessment into clinical trial protocols as previous works have addressed this issue in a comprehensive way [20,24].

Using this checklist as a quality assessment instrument, and in an effort to address, at least in part, the issues raised by the aforementioned editorial [29], the thesis also investigated to what extent HRQOL outcomes (that have been found in RCTs over the last twenty years) are likely to support clinical decision-making. This investigation focused on prostate cancer. All the studies identified received a score according to the checklist criteria; they were ranked from the most to the least accurate reporting of HRQOL. From all the RCTs that have been conducted in prostate cancer and have used HRQOL either as a primary or secondary endpoint, only eight (out of the 24 evaluated) were most likely to support clinical decision-making (33%). Interestingly, all these eight studies were published in or after 1998. Yet, it is noteworthy that the study ranked as ‘best’ regarding scientific rigor was also the only one whose patient-reported outcome (pain) was used by the FDA for oncology drug approval (Mitoxantrone) [27].

Although the thesis investigated the likely impact of HRQOL studies conducted in prostate cancer, it would be useful to explore this issue in other cancer disease sites. For example, is the proportion of studies that can possibly well-inform and support clinical decision-making in colorectal, lung or breast cancer, different from the one in prostate cancer? Such an investigation could help shed light on the width of the gap between HRQOL research and clinical practice and identify critical aspects that need careful attention when designing and reporting future clinical trials in different cancer disease sites.

Some further considerations regarding criticism of the poor clinical impact of HRQOL assessment on clinical decision-making or treatment policies [29] merit attention. This thesis has only partially addressed the weakness of this evidence. Actually, this thesis suggests that the reason lies in the poor general level of reporting of HRQOL in RCTs and the weak methodological rigor in some of these studies. However, it is also possible that other factors have contributed to the poor impact of HRQOL measurement on clinical practice. Some studies, for example, were plagued by very poor HRQOL compliance that hampered clear conclusions regarding HRQOL results. There is evidence to suggest that clinicians’ reluctance and scepticism in assessing HRQOL in a RCT setting (rather than patients’ reluctance) can compromise the collection of HRQOL data, leading to unreliable findings [31]. This can lead one to wonder: how many studies were not even published because of this reason? Could they have had the potential to add useful evidence in terms of HRQOL outcomes? Unfortunately, there are no data and there probably never will be, to evaluate this issue further. Another possible factor could be that HRQOL should have been assessed in other more relevant settings. Yet, was the rationale for assessing HRQOL robust enough to justify such an assessment? Furthermore, it is also important to consider that guidelines dealing with good practice when incorporating HRQOL as an endpoint in a clinical trial protocol [24] or papers addressing the clinical significance of the outcomes, [3] were primarily published in or after 1996. On the other hand, the findings of the thesis (Chapters 2 and 3) clearly show that the large majority of RCTs, which are considered as the gold standard “by which health care professionals and others make decisions about treatment effectiveness” [32], have only been published over the last seven years. Furthermore, the clinical trial protocols of these studies were written even earlier, implying an even larger time lag between recommendation and implementation.
It is therefore possible to speculate that the relatively poor level of HRQOL reporting identified in some areas has merely stemmed from the general unfamiliarity of clinical researchers in oncology with HRQOL issues.

Given the need to bridge the gap between HRQOL research and clinical practice and given the fact that the current level of HRQOL reporting is less than ideal, the issue of raising the standard of reporting appears to be a vital task. To clearly make informed decisions about the overall treatment effectiveness, healthcare providers need to rely on a methodologically sound HRQOL assessment from a given study. The translation of HRQOL measurements into clinical practice, with the aim of improving patient care, has been highlighted as the next step in this field of research [29]. In this respect, accurate HRQOL reporting from cancer clinical trials appears to be the condition sine qua non for such a transition. Within this scenario, scientific journal policies could play an important role. Editorial boards as well as peer-reviewers should play a key role in influencing the quality of HRQOL reports by requiring, for example, some minimum standards for publishing HRQOL reports from clinical trials. With this in mind, the checklist presented in this thesis might be considered as useful, as the minimum criteria by which to evaluate a given HRQOL report.

What is the prognostic value of baseline HRQOL parameters? Do they predict survival both in loco-regional and metastatic disease?

Interest in the psychosocial aspects of cancer patients, as related to clinical outcomes, has a long history [33]. Given the extensive literature on this topic and because of the heterogeneity of concepts that have been studied, a preliminary distinction can be useful to discuss clinical findings. Within this line of research it is important to distinguish between studies, stemming mainly from behavioural research, that have used psychosocial theory-driven constructs, and those studies that have exclusively focused on HRQOL parameters. For example, the former studies have focused on social support, psychosocial distress, and mental adjustment, whereas the latter studies have examined the somewhat limited HRQOL aspects, such as pain, fatigue or emotional and physical functioning [34,35]. Studies that have investigated the link between psychosocial factors and clinical outcomes have often been plagued by methodological shortcomings, including relatively small cohorts and inadequate control of biomedical factors, which have hampered clear conclusions [36]. Whilst some studies that evaluated the relationships between psychosocial variables and survival have noted positive results [37,38], recent systematic reviews and meta-analysis suggest little consistent evidence that psychological coping styles or psychosocial interventions are related to survival in cancer patients [39,40]. Nevertheless, while the results of these studies remain controversial and still challenge researchers, they “have made the examination of the relationship of quality and quantity of life among cancer patients a legitimate scientific question” [41].

In parallel with this line of research, several studies have increasingly focused on exploring the predictive power of patients’ HRQOL parameters for length of survival. These studies have used methodologically sound HRQOL questionnaires, such as the EORTC QLQ-C30.
In this respect, collecting prospective longitudinal HRQOL data in a clinical trial setting is a useful way of examining the possible role of HRQOL parameters in predicting survival. Several studies have provided robust evidence that baseline HRQOL scores independently predict length of survival [42-45]. Furthermore, this evidence has also been reproduced in a wide range of different cancer populations, including breast [46], colorectal [35], lung [47], melanoma [48] and oesophageal [49] as well as in large cohorts of patients with varied malignancies [50]. In addition, some studies have shown that patients' self-reported HRQOL parameters not only independently predict survival, but also give a better survival estimate than important clinical data; in fact, the final model predicting survival included HRQOL variables but did not include clinical data such as performance status or tumor size [44,45,51].

Overall, the studies in this field have used different HRQOL questionnaires and while this has hindered clear outcome comparisons it has also provided complementary and robust evidence of the independent association between HRQOL and survival. It is worthy of note that the EORTC QLQ-C30 was the most commonly used questionnaire for this purpose [34,35,43-47,49] and this might be linked with the fact that it was also the most frequently used HRQL cancer measure [52]. Studies that have used the EORTC QLQ-C30 to evaluate baseline parameters, have found that different HRQOL variables independently predict survival, for example, pain in breast and lung cancer [46,53], physical functioning in oesophageal cancer [44] and fatigue in head and neck cancer patients [45].

It is worthy of note, that all the studies identified found, at least, one HRQOL parameter independently predicting survival in the multivariate analysis. However, the large majority of studies investigating the prognostic value of baseline HRQOL parameters for survival have been conducted on advanced metastatic cancer populations.

A relevant and pertinent question in this area of research, is to investigate whether HRQOL parameters can also predict survival in a non-metastatic disease population. In this thesis, the value of baseline HRQOL parameters in two different populations of breast cancer patients is explored: those with advanced metastatic disease (Chapter 6) and those with loco-regional disease (Chapter 7). The results of Chapter 6 confirm the independent predictive role of HRQOL parameters in metastatic breast cancer for survival and this is consistent with previous research [43,46,54]. However, no evidence of this association was found in a loco-regional breast cancer population (as shown in Chapter 7). This finding is also compatible with a study exploring HRQOL in a population with no distant metastasis, which did not find HRQOL predicting clinical outcomes [54]. Yet, it is also compatible with the negative result of a study (though not specifically focused on HRQOL parameters) which evaluated the prognostic value for survival of the initial level of psychological distress in stage II breast cancer patients [55]. The contradictory findings of the value of HRQOL parameters in predicting survival in metastatic and loco-regional disease seems to confirm Osoba’s previous hypothesis, that baseline HRQOL parameters “may not have predictive value in all patients with all cancers, particularly in those with early stage disease” [56].

Whilst there is now robust evidence of the independent predictive role of HRQOL parameters for survival in metastatic disease, the reason for this association is as yet unclear. Despite the large and growing number of studies in this area, very few, however, have examined the possible reasons for this correlation.

Some hypotheses have been proposed to explain the mechanisms underlying the association between HRQOL data and survival [42,54]. Patients’ HRQOL scores might
reflect an early perception of the severity of the disease in a more accurate way than conventional prognostic indices. In this case, patients who report worse HRQOL scores are the ones with a worse underlying disease. This hypothesis does not imply a true causative relationship between HRQOL parameters and survival. On the other hand, it is also possible that a better HRQOL score (which reflects a better physical and psychological state) could somehow have a positive effect on the disease process by, for example, slowing tumor progression. This causative explanation could be supported by some intervention studies (RCT settings) which have shown that psychosocial support (supportive/expressive and cognitive-behavioural group therapy) improved both psychological wellbeing (e.g. reducing anxiety and depression) and survival time [38,57].

Coates and colleagues [54] assumed that, if the mechanism underlying the association between HRQOL and survival is causative, one should expect to see HRQOL parameters being prognostic of clinical outcomes, not only in patients with metastatic disease, but also at an earlier stage of the disease. Given this assumption, and the fact that their study did not find a correlation between HRQOL parameters and disease-free survival in their non-metastatic breast cancer population, the authors argued in favour of the explanation that HRQOL scores merely reflect a more accurate perception of the severity of the underlying illness. In this respect, the fact that this thesis found evidence of the strong relationship between HRQOL and survival in metastatic disease, but not in earlier stages (neither overall survival nor disease-free survival) seems to exclude a true causative relationship between HRQOL and survival. Hence, the results described in Chapters 6 and 7 would support the hypothesis that patients’ awareness of the severity of their underlying illness is more accurate than medical prognostic indices. Thus, patients with worse underlying disease report worse HRQOL scores. In this respect, it would be possible to speculate that, for early stage disease, clinical examinations (such as performance status or tumor staging) are more likely to supersede patients’ self-reported HRQOL scores in predicting survival.

However, to definitely exclude any possible causative relationship between HRQOL and survival more research is required. Studies are needed to investigate the prognostic value of HRQOL in cancer populations with early disease stages. Furthermore, is it entirely correct to assume that if a better perception of HRQOL positively influences length of survival in metastatic disease this causative mechanism has also to be valid at an earlier stage? For example, would it not be possible to hypothesize some kind of buffering mechanism which could hamper a causative action before the disease starts to metastasize? Although the underlying neurobiological pathways are not entirely known, some studies have actually shown links between natural-killer (NK)-cell function, social support and cancer progression [41]. Hence, it is possible that with the progress of this research area, further insights will be obtained regarding the challenging questions: why do HRQOL parameters predict survival in cancer patients? Why is the current evidence different in metastatic and non-metastatic disease? Future prospective studies (possibly RCTs) should explore if specific interventions aimed at improving patient HRQOL, can also increase survival time. Studies should examine whether the manipulation of known HRQOL parameters (e.g. pain, physical wellbeing, appetite loss, fatigue) actually enhance survival, or any other relevant clinical outcome. In order to help answer the question if HRQOL parameters have the same prognostic value for survival in metastatic and non-metastatic disease, these studies should also investigate this issue in cancer patients with different disease stages and disease sites also.
Overall, the value of this area of study has also critical implications for clinical research. It can actually help better designing and analysing of future clinical trials. For example, if future studies should continue to confirm patients’ self-reported HRQOL data being more prognostic than traditional physician-reported performance status, HRQOL scores could be used to stratify patients in future clinical trials [56]. In any case, the added value of this line of research underscores, once again, the importance of collecting HRQOL data in cancer clinical trials.

**General Conclusion**

The number of RCTs incorporating HRQOL measurements has substantially increased in recent years. The inclusion of HRQOL endpoints in cancer research has helped in evaluating the overall treatment effectiveness from a patient’s perspective. On the one hand, this thesis has highlighted a number of multifaceted methodological challenges investigators face when assessing HRQOL, on the other, it has also shown the great value of collecting prospective HRQOL data during a cancer clinical trial.

As HRQOL evaluation in cancer research can still be regarded as a relatively new scientific discipline, it is not surprising that improvements are required in a few methodological areas such as data collection and interpretation of outcomes. It is expected that these improvements will be achieved, in part, when clear internationally agreed guidelines for the conduct and reporting of HRQOL trials will become available. Recently, some comprehensive guidelines have been developed to assist investigators and it is hoped that these will contribute to improving the conduct and interpretation of HROQL in cancer research. Furthermore, the checklist presented in this thesis is likely to help clinicians write HRQOL reports, as it addresses the essential issues; it is also likely to assist readers in general, when interpreting trial-based HRQOL reports.

A statistically significant learning curve, in terms of accuracy of HRQOL reporting since 1990, has been recently demonstrated in cancer research [58]. Only robust evidence-based HRQOL outcomes can properly inform clinical decision-making. Thus, if RCTs that include HRQOL evaluation are to fulfil their potential, i.e., allowing health-care providers to make informed decisions about the overall value and impact of a given treatment, investigators should continue to improve the design and the reporting of key HRQOL issues. The scientific rigor of HRQOL assessment in cancer research will influence the extent to which HRQOL outcomes will be accepted by different stakeholders, including the drug regulatory agencies.

The first step towards introducing HRQOL assessment in oncology has been devoted to the development of cancer and site-specific HRQOL questionnaires. The EORTC quality of life questionnaires and its related modular approach to the evaluation of HRQOL in different cancer disease sites, is unquestionably an excellent example of the successful achievement of measuring HRQOL in oncology. Whilst investigators should continue to provide robust evidence of HRQOL measurement as a useful tool in clinical research, future studies should also further explore the value of measuring HRQOL in routine clinical practice. In this respect, some recent studies stand as excellent examples of a promising area of research [59-61].
To conclude, it is important to highlight that only close collaboration between clinicians and HRQOL researchers can really guarantee the best results in this field of study. By helping clinicians familiarize themselves with HRQOL measurements in oncology, we will also help move HRQOL forward, from the research setting to routine clinical practice.

REFERENCES


