Understanding changes in quality of life in cancer patients: a cognitive interview approach
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CHAPTER 1

General introduction
1.1. Quality of life as outcome in treatment evaluation

The primary goals of cancer treatment are curing the disease, improving health, delaying health deterioration, or relieving symptoms. To demonstrate the effect of treatments beyond clinical efficacy and safety, patient-reported quality of life (QoL) is increasingly included as secondary, or even as primary, outcome in cancer clinical trials [1-4]. The assessment of QoL is of particular relevance when treatment is not expected to result in survival benefits, whereas it might affect patients’ QoL. Additionally, QoL outcomes may outweigh clinical outcomes, if therapeutic benefits are expected to be limited at the expense of major toxicity [5]. Moreover, in palliative care QoL may even become the only or primary outcome. Since assessments of change in QoL may form the basis of treatment decisions, it is important to know how patients arrive at such change assessments and how these should be interpreted.

1.2. Designs assessing change in QoL

The following three designs are commonly used in the context of treatment evaluation to measure change in patients’ QoL:

1.2.1. Pretest-posttest design

The prospective pretest-posttest design, also known as the baseline follow-up design, is most commonly used to assess change in QoL [e.g. 6-9]. This design entails the administration of a pretest and one or more posttest assessments. The mean difference in scores from pretest to posttest provides an indication of the magnitude and direction of change. This design implicitly assumes consistency in the content of patients’ cognitive processes underlying QoL assessment over time. For example, patients are assumed to refer to the same concept of QoL at consecutive assessments. Inconsistency in the cognitive processes underlying QoL assessment over time is referred to as response shift. Response shift is defined as a change in internal standards (i.e. recalibration), values (i.e. reprioritization) and/or concept of QoL (i.e. reconceptualization) as a result of health changes [10]. Numerous studies have indirectly demonstrated changes in the content of respondents’ cognitive processes underlying QoL assessments over time by revealing such response shift effects [e.g. 11-14]. Since response shift may render responses to QoL items over time incompatible, it poses a serious threat to the pretest-posttest design.

1.2.2. Thentest design

The retrospective pretest-posttest or thentest design is the most commonly used approach to detect and control for recalibration response shift in the prospective measurement of change in QoL [e.g. 15-18]. This design extends the pretest-posttest design with a retrospective pretest. Most times, after completing the conventional posttest assessment,
respondents are asked to complete the same questions again but with the instruction to report how they perceive themselves to have been prior to the treatment [19]. The first assumption inherent to this design is that by taking posttest and thentest in close proximity, the content of respondents’ underlying cognitive processes will be consistent between posttest and thentest. Consequently, comparison of posttest and thentest scores would eliminate treatment induced response shift effects, and provide an unconfounded assessment of the treatment effect. In addition, the mean change score from pretest to thentest would provide an indication of the magnitude and direction of recalibration response-shift effects [20]. The second assumption is that patients are able to accurately recall their pretest functioning when completing the thentest. However, the thentest has been criticized for its susceptibility to memory distortion of pretest functioning [19, 21].

1.2.3. Transition design
Transition questions are administered after the regular posttest assessment, and ask patients to rate the extent to which they have experienced change in their functioning since a referred point in the past, for example since pretest (e.g. Is your current quality of life better or worse since you started treatment?). The use of transition questions has become a popular anchor-based approach to determine the clinical significance of patient-reported change [22, 23]. The assumptions underlying this design are twofold. In arriving at a change evaluation, patients are assumed to (1) compare posttest and pretest functioning, and (2) accurately recall their pretest functioning. However, there is correlational evidence that patients do not make a change evaluation between their current and prior functioning, but rather base their responses to transition questions primarily on their current functioning [24, 25]. Second, like the thentest design, there is ample evidence that retrospective assessment is subject to recall bias [26-29].

1.3. Cognitive processes underlying quality of life assessment
Despite the abundance of data on QoL derived from clinical research, there is little knowledge on how patients actually arrive at their responses to QoL items, let alone at assessments of change therein. To increase such insight and consequently to better interpret (changes in) responses to QoL items, we need to examine the underlying cognitive processes [30].

1.3.1. Cognitive process models applicable to QoL assessment
Cognitive process models have been developed in diverse disciplines and research areas such as judgment theory, artificial intelligence, linguistics and survey research. Since we are interested in cancer patients’ cognitive processes underlying QoL assessment elicited by questionnaires, we will focus on models stemming from survey research. Several models have been proposed that comprehensively describe the response behaviour to question-
naire items [31-34]. The model developed by Tourangeau et al. [31] elaborately describes the cognitive processes involved and largely resembles earlier survey models. In addition, Rapkin & Schwartz developed a QoL appraisal model specifically addressing the cognitive processes used in answering a QoL questionnaire [35]. As illustrated in Table 1, both models show great resemblance as they share three cognitive processes and add one each. Combined, these models entail five cognitive processes underlying responses to individual QoL questionnaire items: (1) induction of a frame of reference, (2) recall of relevant information, (3) use of standards of comparison against which the retrieved information is judged, (4) use of an algorithm to prioritize and combine the retrieved information, and (5) reporting and response selection.

1.4. Aims of this study

The overall aim of this study was to increase our understanding of how cancer patients arrive at QoL (change) assessments, and how to interpret such (change) assessments. Specific aims were to qualitatively examine the assumptions underlying the three designs commonly used in the context of treatment evaluation, i.e. the pretest-posttest design, the thentest design and the transition design. To comprehensively examine these cognitive processes we adopted the combined models of Tourangeau et al. [31] and Rapkin & Schwartz [35] as a priori framework.

1.4.1. Review on patients’ self-nominated QoL domains

Several studies have addressed the first cognitive process of the models of Tourangeau et al. [31] and Rapkin & Schwartz [35], i.e. comprehension/frame of reference [e.g. 36, 37]. We aimed to provide a comprehensive overview of the extant studies, in which patients’ self-nominated QoL domains are examined. Therefore, the first objective of this thesis was:

1. to review which domains somatically ill persons nominate as constituting their QoL.

Two types of studies were relevant for this review: (1) studies using the Schedule for Evaluation of Individual Quality of Life (SEIQoL) [38, 39], and (2) studies using study-specific questions (e.g. How would you describe your quality of life). Specific objective of the review was:

1a. to examine whether these two methods of enquiry are related to the generation of different QoL domains.
### Table 1 - Cognitive process models of Tourangeau et al. [31] and Rapkin & Schwartz [35]

<table>
<thead>
<tr>
<th>Tourangeau et al.</th>
<th>Rapkin &amp; Schwartz</th>
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<tbody>
<tr>
<td><em>Survey answering model</em></td>
<td><em>QoL appraisal model</em></td>
</tr>
<tr>
<td><strong>Comprehension</strong></td>
<td><strong>Frame of reference</strong></td>
</tr>
<tr>
<td>- Paying attention to the question and accompanying instructions</td>
<td>- Assigning meanings to the questions</td>
</tr>
<tr>
<td>- Interpreting the question</td>
<td>- Identifying experiences that are found to be relevant to the given responses</td>
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<tr>
<td>- Making assessments concerning the information sought</td>
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<tr>
<td><strong>Retrieval</strong></td>
<td><strong>Sampling strategy</strong></td>
</tr>
<tr>
<td>Recalling relevant information</td>
<td>Retrieving relevant information</td>
</tr>
<tr>
<td><strong>Standards of comparison</strong></td>
<td><strong>Combinatory algorithm</strong></td>
</tr>
<tr>
<td>- Judging each sampled experience against subjective standards of comparison</td>
<td>- Prioritizing and combining all relevant experience to arrive at a QoL score</td>
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<tr>
<td><strong>Judgment</strong></td>
<td></td>
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<tr>
<td>- Judging the completeness or accuracy of the retrieved information</td>
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<tr>
<td>- Making inferences based on the process of retrieval</td>
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<tr>
<td>- Supplementing gaps in the retrieved information</td>
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<tr>
<td>- Combining the retrieved information into a single response</td>
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<td>- Making estimates that adjust for omissions in retrieval</td>
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<tr>
<td><strong>Reporting and response selection</strong></td>
<td></td>
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<tr>
<td>- Editing the initial response for consistency, acceptability or other criteria</td>
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<tr>
<td>- Mapping the judgment onto a response category</td>
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### 1.4.2. Do theoretical models capture the cognitive processes underlying QoL assessment?

The cognitive process models of Tourangeau et al. [31] and Rapkin & Schwartz [35] have not been specifically designed to serve as framework for qualitatively examining the cognitive processes underlying QoL (change) assessments. Therefore, the second objective of this thesis was:
2. to develop a qualitative analysis scheme capturing the cognitive processes underlying QoL assessment, based on the models of Tourangeau et al. [31] and Rapkin & Schwartz [35].

   Based on a pilot study, specific objectives were to examine whether:

   2a. patients’ responses can be categorized according to the distinct cognitive processes of the models;
   2b. an interview fragment can be categorized exclusively in one cognitive process;
   2c. the proposed models are exhaustive in capturing the cognitive processes underlying responses to QoL items or need to be extended.

1.4.3. Main study aims: examination of the assumptions underlying three designs used to measure change

Pretest-posttest design
To examine the assumption of:
3. consistency in the content of each distinct cognitive process underlying respondents’ QoL assessment between pretest and posttest.

Thentest design
To examine the assumptions of:
4a. consistency in the content of each distinct cognitive process underlying respondents’ QoL assessment between posttest and thentest;
4b. accurate recall of pretest functioning.

Transition design
To examine the assumptions of:
5a. comparison of posttest and pretest functioning in arriving at a change evaluation;
5b. accurate recall of pretest functioning.

If patients’ cognitive processes were not in line with the assumption(s) underlying the specific design, we aimed to examine how patients did reason when responding to the QoL (change) items.

1.5. Study design

1.5.1. Methods
This study’s main objectives were examined in two consecutively conducted studies. The pretest-posttest design was administered in both studies, extended with transition questions in the first study, and with the thentest in the second study. In accordance with the design used in treatment evaluation, we administered pretest assessments prior to,
and posttest and transition or thentest assessments at the end of a salient health-related intervention. Radiotherapeutic treatment is such an intervention that frequently induces changes in health status, within a relatively restricted period of time (e.g. days to weeks). Therefore, the study sample comprised cancer patients undergoing radiotherapy at the Department of Radiation Oncology at the Academic Medical Center (AMC) in Amsterdam. Pretest assessments took place on the same day the patient had a CT-simulator appointment or received first radiation treatment. The posttest and transition or thentest assessments were conducted on patients’ last day of radiotherapeutic treatment. Patients were purposefully selected based on factors conceptualized as affecting their treatment experience, i.e. gender, age, tumor site, and length of radiation treatment. Interview items were derived from the EORTC QLQ-C30 [40], a widely used QoL instrument in European clinical trials [41]. To limit patient burden, we selected seven items covering both global and specific content, including physical, psychological and social dimensions (details of the procedure and justification are provided in Chapter 3). The transition and thentest items were adapted versions of these EORTC QLQ-C30 items. We used the Three-Step Test Interview [42] combining cognitive think aloud interviewing and verbal probing techniques [43] to elicit the cognitive processes that patients used in answering the QoL (change) items. During these interviews, patients were instructed to read out loud each QoL item and to subsequently verbalise the thought processes used in providing their score. Immediately after the think-aloud response to each item, we probed to elicit more information about patients’ cognitive processes. All interviews were audio-recorded and transcribed verbatim.

1.5.2. Analysis
Qualitative analysis of all interviews was carried out by two researchers independently using the analysis scheme based on the cognitive process models of Tourangeau et al. [31] and Rapkin & Schwartz [35] (See Chapter 3). That is, all responses at each interview were analyzed according to the five distinct cognitive processes underlying QoL assessment. To examine the consistency assumption underlying the pretest-posttest design, the researchers independently determined whether the content of each cognitive process was similar at pretest and posttest, or rather changed over time. Similarly, to examine thentest's assumption of consistency in the content of the cognitive processes underlying QoL assessment between posttest and thentest, we compared the content of each cognitive process at posttest and thentest to determine whether it was similar or had changed. The second assumption of accurate recall was operationalized by examining whether the time frame employed and the description of pretest functioning provided in answering each thentest item were similar to those of the corresponding pretest item. To study the first assumption underlying the transition design, we examined whether patients’ responses to transition items were based on a comparison of posttest and pretest functioning. When responses were based on a comparison of current and prior functioning, we further examined transition’s design second assumption of accurate recall, which we operationalized in the same way as we had done for the thentest design.
1.6. Prior studies examining cognitive processes underlying QoL assessment

Few studies have addressed the cognitive processes underlying QoL assessment, and, if so, only partially and not systematically. The present study extends these previous investigations in four ways. First, a number of studies only addressed one or two cognitive processes underlying QoL assessment. In these studies, patients, elderly or healthy respondents were asked how they comprehended a global item regarding health or QoL [e.g. 44-47]. The studies that asked patients to define the concept QoL (i.e. the first cognitive process comprehension / frame of reference) are included in our review (see Chapter 2) [48]. Few other studies have (additionally) asked respondents whether they used subjective reference groups (i.e. the third cognitive process standards of comparison) [49-51]. In the present study, we have examined all five cognitive processes underlying QoL assessment by adopting the frameworks of Tourangeau et al. [31] and Rapkin & Schwartz [35].

Second, the studies to date have conducted a qualitative examination of patients’ cognitive processes underlying QoL assessment using only one design to measure change. A number of studies have examined change in the QoL domains respondents nominate in administering the SEIQoL in a pretest-posttest design [37, 52-56]. The studies by Westerman et al. [57, 58] employed a thentest design to explore response shift and its relation to adaptation among palliatively treated small-cell lung cancer patients. Wyrwich & Tardino [59] examined patients’ cognitive processes underlying health-related QoL transition questions. However, in the present study we have qualitatively examined the cognitive processes underlying QoL (change) assessments in all three designs.

Third, the extant studies do not, or only partially, address the assumptions underlying each design. Studies using a pretest-posttest design only addressed the assumption of consistency in respondents’ QoL cognitive processes over time for the first cognitive process [37, 52-56]. Westerman et al. [57, 58] did not address the assumptions underlying the thentest design, i.e. consistency in the content of the cognitive processes underlying patients’ QoL assessment between posttest and thentest, and accurate recall of pretest functioning. Wyrwich & Tardino [59] did address the first assumption underlying the transition design, by examining whether patients compare posttest and pretest functioning in arriving at a change evaluation. However, the second assumption inherent to this design of accurate recall of pretest functioning was not explored. In the present study, we have examined the assumptions inherent to the three designs.

Finally, most of the abovementioned studies have examined cognitive process(es) underlying the assessment of a global QoL or health item [37, 44-47, 49-50, 52-56] or a single QoL domain [57]. In this study, we have examined patients’ cognitive processes underlying the assessment of QoL items covering both global and specific content, including physical, psychological and social dimensions.
1.7. Outline of thesis

In Chapter 2 the structured literature review on somatically ill persons’ self-nominated QoL domains is presented. Additionally, this chapter provides guidelines for conducting and reporting qualitative research aimed at exploring domains respondents nominate as constituting their QoL. Chapter 3 describes the development of a qualitative analysis scheme capturing the cognitive processes underlying QoL assessment, which is based on the cognitive process models of Tourangeau et al. [31] and Rapkin & Schwartz [35]. Chapters 4 to 6 provide the results related to the examination of the assumptions underlying the three designs used to measure change. Chapter 4 describes the findings concerning the assumption inherent to the pretest-posttest design. In Chapter 5, the results related to the assumptions underlying the thentest design are presented. Chapter 6 describes the results of the study examining the assumptions underlying the transition design. In the general discussion in Chapter 7, the main findings of this study are discussed, followed by reflections on this study’s methodology. Additionally, we provide directions and implications for future research and implications for clinical practice.
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