Rehabilitation for cancer survivors
Cost-effectiveness & budget impact

Janne Charlotte Mewes
Rehabilitation for cancer survivors
Cost-effectiveness and budget impact

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REHABILITATION FOR CANCER SURVIVORS

COST-EFFECTIVENESS AND BUDGET IMPACT

DISSERTATION

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on the authority of the rector magnificus,
Prof. dr. H. Brinksma,
on account of the decision of the graduation committee,
to be publicly defended
on Friday 26 February 2016 at 14.45

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Introduction
Introduction

The number of people who are diagnosed with cancer is increasing. In the Netherlands, 57,000 people were diagnosed in 1990. In 2013, this was 102,000\(^1\), and the projected incidence for 2020 is 123,000\(^2\). During the last decades, the treatment methods for cancer improved and screening was intensified. Tumours are detected in an earlier stage in which the treatment more often is successful\(^3\). Therefore, more people have a survival of at least five years, which is seen as the critical period after which it can be said that someone is cured\(^4\). While in the Netherlands the overall 5-year survival rate was 47% in the period of 1989 to 1993, it rose to 62% in the period from 2008 to 2012\(^5\).

Caused by these developments, the number of people within the population who have survived cancer is growing. Who exactly is considered a cancer survivor depends on the definition that is used\(^6-9\). Broad definitions include anyone who has ever been diagnosed with cancer. Other definitions include family and friends who are affected indirectly by the disease as well\(^6\). Throughout this thesis, cancer survivors are defined as people diagnosed with cancer who have finished primary treatment with a curative intent. This excludes patients who are undergoing primary or palliative treatment. Statistics on the number of cancer survivors contain all people within the population who have ever had a cancer diagnosis and are still alive and thus do not reflect the exact definition that was used here. In the Netherlands, the number of cancer survivors according to this definition was 366,000 in the year 2000. It was expected to rise to 690,000 in 2015 and thus more than doubled\(^10\). The same development is observed in other industrialised countries\(^11, 12\). In the United Stated (US), the group of cancer survivors comprised 13.8m people in 2013\(^13\).

About 35 years ago, research into the phase of cancer survivorship commenced as it became clear that most survivors experience late and long-term symptoms\(^14\). It was first recognized what symptoms and problems may occur after treatment and later how prevalent they are. This led to further research on optimal care and rehabilitation after cancer\(^9, 15-18\). The symptoms that survivors experience are caused by the disease itself, as well as by the treatment\(^15\). These can be divided into general and cancer type- or treatment-specific symptoms. Those that are applicable to all survivors include fatigue, sleep disturbance, depressive symptoms, anxiety, cognitive limitations, pain, functional limitations, and sexual dysfunction\(^17\). Examples of cancer-type specific symptoms of breast cancer include numbness in the chest; tightness, pulling, or stretching in the axilla or chest; hot flashes and night sweats; lymphedema; premature menopause; sexual
problems; weight gain; and osteoporosis. For prostate cancer the most common are sexual, bladder, and bowel dysfunction, and osteoporosis; and for colorectal cancer bowel dysfunction. Depending on the subgroup of patients and the study, the percentage of cancer survivors who suffer from at least one symptom ranges up to 100 per cent \(15, 19, 20\) and people may suffer from 5 to 11 symptoms at a time. These symptoms often lead to problems in performing tasks in daily life, in the relationship with family and friends, and in resuming work. Depending on the social system of the respective country, problems in returning to work and paying privately for health care can lead to financial hardship and in many cases to private bankruptcy. Moreover, cancer survivors have an increased risk for getting a new form of cancer and for chronic diseases in general, such as cardiovascular disease. Considering the number of cancer survivors and its growth, this is a serious public health problem. It creates a huge symptom burden, prevents cancer survivors from returning to their daily life and workplace, and results in high societal costs. It is therefore essential that suitable rehabilitation is provided in order to alleviate these symptoms.

**Cancer rehabilitation**

According to the definition of the World Health Organization, rehabilitation for people with disabilities is “a process aimed at enabling [people with disabilities] to reach and maintain their optimal physical, sensory, intellectual, psychological and social functioning levels.” Rehabilitation of cancer survivors is specifically developed for impairments resulting from cancer. The most effective intervention for which the largest evidence base exists is physical exercise. It is effective for alleviating fatigue, improving physical fitness, reducing depression, and many other symptoms, and further increases health-related quality of life. In addition, it reduces the risk of cancer in general and may also lead to a lower risk for recurrences. As exercising is very challenging for most cancer survivors, an intervention specifically designed for cancer survivors is recommended. Cognitive behavioural therapy and psycho-education can be provided for alleviating, among others, fatigue, depression, and anxiety. Return-to-work interventions are designed to support cancer survivors in returning to the workplace, which often is a difficult process, and mostly consist of counselling with an occupational physician. Many other forms of interventions are evaluated in the literature as well, such as mindfulness-based stress reduction, music interventions, tai chi, or yoga. Health care for cancer survivors in general consists of survivorship, follow-up, and supportive care. Survivorship care is a term for all care that takes place after active treatment and should include follow-up care, health promotion, prevention of new and
secondary cancers, and management of late and long-term symptoms. However, it is unknown for how long follow-up of survivors should last and which care provider should be responsible.\textsuperscript{3} What also strongly is recommended is a survivorship care plan (SCP). This plan details the treatment that the patient received, the symptoms that may occur in the long-run, what patients can do themselves for prevention, and how the follow-up care should be structured. Follow-up care consists of regular consultations in order to detect recurrence of the disease. It is the current standard and is provided to almost all cancer survivors.\textsuperscript{36} Supportive care provides help for the physical, informational, emotional, psychological, social, spiritual, and practical needs that arise in the phases when people have cancer and beyond.\textsuperscript{37}

The major limitation in the evidence base on cancer rehabilitation is that the mechanisms of cancer rehabilitation interventions are not well understood. It therefore remains unknown which interventions are most effective for particular cancer survivor subgroups.\textsuperscript{38} Moreover, the generalisability of study results in many cases is limited as the patient samples often are not representative for the general group of cancer survivors since they mostly include women with breast cancer.\textsuperscript{39} In addition, hardly any evidence exists on the long-term outcomes of cancer rehabilitation.\textsuperscript{18, 40, 41} Shortcomings in the provision of cancer rehabilitation in practice are that it is not always clear which care provider is responsible and what type of rehabilitation should be provided.\textsuperscript{38} The interventions that have been implemented to date often treat single symptoms, such as lymphedema, while a comprehensive assessment of symptoms and patient needs leading to a tailored rehabilitation programme is missing.\textsuperscript{42}

During the last years, guidelines on the rehabilitation of cancer survivors were published in many countries.\textsuperscript{38} In the Netherlands, this was done by the Netherlands Comprehensive Cancer Organisation in 2011. Its guideline recommends that the rehabilitation need of all cancer survivors should be assessed and, if needed, be referred to a tailored rehabilitation programme. The general recommendation is that the importance of exercise is discussed with every patient and that all cancer survivors conduct at least moderate-intensity exercise. Further, cognitive behavioural therapy is recommended for survivors who are still fatigued one year after finishing curative treatment. Attention should be paid to the process of returning to work and to participating in society.\textsuperscript{10}

Cancer rehabilitation is implemented to varying degrees in most European countries and in North America. Many countries introduced initiatives and plans to further implement and qualitatively improve survivorship care.\textsuperscript{43} Reasons for why access to cancer rehabilitation is limited include that not all oncologists are yet aware of the
possibilities that exist and that the capacities for providing interventions are insufficient, which might partly be caused by the lack of reimbursement. In the Netherlands, cancer rehabilitation started with a programme called “Herstel en Balans” (Recovery and Stability) which was introduced almost twenty years ago, but will now cease to exist as general cancer rehabilitation is being offered more widely. This 12-week programme consists of physical exercise combined with psycho-education and is offered by most cancer centres. It has not been covered by basic health insurance due to its limited evidence of effectiveness and because exercising and fitness were considered someone’s individual responsibility. It needed to be paid out-of-pocket or by a premium health insurance plan. Rehabilitation in the Netherlands is reimbursed by health insurers when a multidisciplinary rehabilitation need is indicated. Thus, monodisciplinary interventions, interventions that have a preventive character, and “prehabilitation” that aims at improving physical functioning before surgery are not reimbursed. When hospitals still choose to offer these they have to cover the costs from the general hospital budget. In Germany, cancer rehabilitation typically is reimbursed. It is mostly offered as inpatient care and would need to be provided as outpatient treatment as well to increase flexibility. In other countries such as Italy, however, cancer rehabilitation is hardly implemented yet. In the US it is available, but highly fragmented and reimbursement is very much dependent on the individual insurance scheme.

Health care costs
Implementing cancer rehabilitation more widely would lead to additional costs to the health system. As in most countries health budgets are under pressure health insurances are hesitant to reimburse cancer rehabilitation.

The Netherlands had the highest EU-percentage of GDP-spending on health care in 2012 with 11.8%, and total spending increased from 41bn in 2000 to €85bn in 2013. The fast growth in the costs has been one of the major policy issues in the Netherlands during the last years. The US is the only country that spends a larger share of their GDP on health care than the Netherlands; about 20%. If current trends continue this would be half of the US economy in a couple of decades. Internationally, the development in cancer care spending is seen as problematic. The part of the health budget spent on cancer was 4.1% in Europe, 5.3% in the Netherlands in 2011, and 5% in the US in 2010. It is estimated that this will further increase in the coming years. This development is caused by the increasing number of cancer patients, increasing prices especially for cancer drugs, innovations coming to the market that are more expensive than existing care, an increased use of screening, overutilization, and
consumer demand\textsuperscript{57, 59}. As these developments are very concerning, any addition to the current care for cancer is critically evaluated.

In the Netherlands, interventions that are added to the benefit basket need to be necessary, effective, cost-effective, and affordable. As a weighing of the criteria takes place, these do not function as strict exclusion criteria. For analysing whether a health service is cost-effective, a cost-utility evaluation is the base-case approach, comparing the additional cost of an intervention to the incremental health benefits, being measured as quality-adjusted life years (QALYs). The outcome measure of the analysis is the incremental cost-effectiveness ratio (ICER) which expresses the incremental costs of the intervention for achieving one additional unit of effectiveness\textsuperscript{60}. The adoption decision depends on the amount someone is willing to pay for the additional effectiveness (called the willingness-to-pay threshold, or ceiling ratio). An intervention is considered cost-effective, when its ICER falls below that threshold\textsuperscript{61}. Still, cost-effective interventions can be so expensive that the available budget would not be sufficient to cover the costs, hence a budget impact analysis can be conducted that evaluates the affordability. This is done by comparing the total cost of illness in the current situation to that of the future situation when the new intervention is in use\textsuperscript{62}.

These cost-effectiveness analyses can be conducted from different perspectives, as, depending on the stakeholder, different effects and costs are considered relevant. Recommended for health economic evaluations is the societal perspective, in which all costs and effects that are caused by an intervention are included in the analysis\textsuperscript{60}. For budget impact analyses the perspective of the budget holder is recommended\textsuperscript{62}.

**Cost-effectiveness of cancer rehabilitation**

At the start of this research project, the evidence base on cost-effectiveness of cancer rehabilitation was very limited. One review was available that summarized the findings on the cost-effectiveness of five psychosocial interventions for anxiety and depression\textsuperscript{63}. It was found that the interventions were not very costly. The evidence on the cost-effectiveness of the intervention was incomplete, as only three studies provided ICERs and were inconclusive, as the comparators varied between studies. Those cost-effectiveness analyses that presented an ICER found that the interventions were more effective at higher costs and that these were within a reasonable range\textsuperscript{63}. Evidence that decision-makers and health care providers require for taking well-informed decisions was thus hardly available\textsuperscript{64}.

Several gaps can be identified in this evidence base. First, very little is known about the cost-effectiveness of rehabilitation for cancer survivors. In addition, many rehabilitation
interventions have not been evaluated on cost-effectiveness. Moreover, it cannot be concluded whether cancer rehabilitation in general might be cost-effective. As this is one of the criteria in the decision of which type of rehabilitation interventions should be reimbursed, more evidence is needed to take a well-considered decision. This is especially important since the share of health care costs spent on cancer is growing very fast and therefore decision-makers might be very hesitant to decide to reimburse an additional type of care for cancer survivors.

Second, evidence on the affordability of cancer rehabilitation is unavailable. The expectation is that it may be rather unaffordable, since the number of cancer survivors is huge and rising. Assuming average rehabilitation costs of €200 per patient and using the cancer incidence of 102,000 in 2013, this would result in a budget impact of €20.4m in the Netherlands. The projected incidence for 2020 is 123,000 which would lead to costs of €24m. For 2013, this would have represented 2.6% of the total health care spending of €94.2bn in the Netherlands. The considerations are thus legitimate. However, this calculation omits the possible financial benefits that might result from offering rehabilitation, such as may accrue from earlier return-to-work or higher productivity at work. Next to that, it is unknown what the average costs for rehabilitation are per cancer survivor, as a large variety of interventions exits.

Third, the standard methods in health economics are not sufficient for solving a specific decision problem in cancer rehabilitation. For many symptoms, such as fatigue, interventions consisting of several components, e.g. exercise and cognitive-behavioural therapy were developed. Often, the single or the multicomponent programme can be prescribed, but it is unknown if the multicomponent programme adds sufficient effectiveness to justify the additional resources that are required. However, when the effectiveness of the multicomponent programme is unknown, its cost-effectiveness cannot be compared to that of the single component with current methods, as for these data on the effectiveness of all interventions is required.

This thesis
The objective of this research is to increase the evidence base regarding the cost-effectiveness of cancer rehabilitation and the budget impact of implementing cancer rehabilitation interventions more widely. Moreover, it aims to advance the methodology on pragmatically assessing the potential cost-effectiveness of multicomponent interventions in cases where full data on costs and effects are unavailable. Each chapter contributes towards reaching these goals.
Chapter two contains a systematic literature review of the evidence base of the cost-effectiveness of cancer rehabilitation interventions and of the effectiveness of multicomponent cancer rehabilitation interventions. Chapter three evaluates the cost-effectiveness of cognitive behavioural therapy and physical exercise for breast cancer patients who suffer from treatment-induced menopausal symptoms. In chapter four, an approach was developed that allows estimating if a multicomponent intervention is more cost-effective than a single intervention in the absence of full evidence on its costs and effect. In chapter five, a budget impact analysis is presented of a multidisciplinary return-to-work intervention. This chapter also analyses in what way the allocation of the costs and benefits across the involved stakeholders that the intervention generates does incentivise to offer return-to-work interventions for cancer patients in a number of European countries. In chapter six, several implementation strategies for increasing adherence to (the guideline on) physical exercise were evaluated on their net benefit through a value of implementation analysis, as the adherence of professionals to the guideline advice and of patients to the prescribed intervention is low. In chapter seven the findings of this thesis are discussed and recommendations for policy and practice are given. Finally, this thesis’ summary can be found, as well as a summary in Dutch.

The research of this thesis was conducted as part of the “Alpe d’HuZes Cancer Rehabilitation Research Programme” (A-CaRe), which started in 2009. The aim of A-CaRe is to develop, implement, and evaluate cancer rehabilitation interventions. The first part of the project consists of clinical research into the effectiveness of exercise interventions in four clinical trials. The second part, A-CaRe 2 Move, is directed towards patient empowerment through ICT, a multidisciplinary return-to-work intervention, rehabilitation that can be conducted at home, and the implementation of cancer rehabilitation. The research presented in this thesis evaluates the cost-effectiveness and budget impact of (a part) of the A-CaRe 2 Move projects.
Introduction

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Effectiveness of multidimensional cancer survivor rehabilitation and cost-effectiveness of cancer rehabilitation in general: a systematic review

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Effectiveness of multidimensional cancer survivor rehabilitation and cost-effectiveness of cancer rehabilitation in general: a systematic review

Abstract

Introduction: Many cancer survivors suffer from a combination of disease- and treatment-related morbidities and complaints after primary treatment. There is a growing evidence base for the effectiveness of mono-dimensional rehabilitation interventions; in practice, however, patients often participate in multidimensional programs. This study systematically reviews evidence regarding effectiveness of multidimensional rehabilitation programs for cancer survivors and cost-effectiveness of cancer rehabilitation in general.

Methods: The published literature was systematically reviewed. Data were extracted using standardized forms and were summarized narratively.

Results: Sixteen effectiveness and six cost-effectiveness studies were included. Multidimensional rehabilitation programmes were found to be effective, but not more effective than mono-dimensional interventions, and not on all outcome measures. Effect sizes for quality of life were in the range of -0.12 (95% confidence interval [CI], -0.45–0.20) to 0.98 (95% CI, 0.69–1.29). Incremental cost-effectiveness ratios ranged from -€16,976, indicating cost savings, to €11,057 per quality-adjusted life year.

Conclusions: The evidence for multidimensional interventions and the economic impact of rehabilitation studies is scarce and dominated by breast cancer studies. Studies published so far report statistically significant benefits for multidimensional interventions over usual care, most notably for the outcomes fatigue and physical functioning. An additional benefit of multidimensional over mono-dimensional rehabilitation was not found, but this was also sparsely reported on. Available economic evaluations assessed very different rehabilitation interventions. Yet, despite low comparability, all showed favourable cost-effectiveness ratios. Future studies should focus their designs on the comparative effectiveness and cost-effectiveness of multidimensional programs.
Introduction

Progression in screening, early detection, and effective treatment of cancer has rapidly increased the percentage of cancer survivors in developed countries. In Europe, the 5-year survival rate for all cancers has reached ≥47% for men and 56% for women, and these are expected to rise in future years. In the U.S., 5-year survival rates of 68% for men and 67% for women were reported. Accordingly, the demand for rehabilitation after primary cancer treatment is increasing. In The Netherlands, for example, the number of people living with or having survived cancer is estimated to be ~692,500 (4%–5% of the population) by the year 2015, a large number of whom might benefit from cancer rehabilitation.

Because of the direct and long-term effects of cancer and its treatment, most survivors do not return to their previous state of well-being. Cancer survivors suffer from a range of problems, varying from fatigue, reduced physical fitness, and psychological problems to symptoms related to specific cancer types, such as lymphedema or difficulties with speaking and swallowing after head and neck surgery. Consequently, an important percentage of cancer survivors, ~36% according to a recent review, is not able to return to work. Furthermore, cancer survivors suffer from different symptoms and complaints. Cheng et al. reported an average of eight symptoms per patient. A combination of interventions, adjusted to the survivor’s individual needs, is likely required to restore health-related quality of life (HRQoL). Indeed, multidimensional rehabilitation is increasingly being recommended in national and international cancer rehabilitation guidelines.

During previous decades, the volume of research on the rehabilitation of cancer survivors has increased faster than research on rehabilitation in general. Most research conducted so far focused on physical exercise after cancer treatment, which has been shown to increase physical strength and HRQoL and to alleviate fatigue and other symptoms. Only a few studies suggest that cognitive and psychosocial rehabilitation interventions can reduce psychological symptoms. Furthermore, return-to-work interventions appeared successful in helping survivors resuming work. Besides alleviating particular post-treatment symptoms, rehabilitation likely mitigates cancer survivors’ elevated risk for chronic diseases, such as cardiovascular disease and osteoporosis, and the risk for a second primary cancer or recurrence. Performing physical activity has been shown to reduce the risk for cancer recurrence and chronic disease and is suggested in several guidelines and recommendations.
The evidence base for the long-term effects of rehabilitation is rather small because the follow-up duration is usually short\textsuperscript{22}. Although there is a growing body of literature, to what extent the effect of multidimensional rehabilitation is greater than the effect of single interventions remains unknown, because the various interventions are mostly tested in isolation. Considering the increasing number of cancer survivors, not only the treatment effects but also the costs involved to society and health care systems become an issue, as recently underlined in leading journals\textsuperscript{23, 24}. Data on the cost-effectiveness of rehabilitation will undoubtedly become more important to decision makers.

The first aim of this study was therefore to systematically review the research conducted on the effectiveness of multidimensional rehabilitation programs for cancer survivors. Because all rehabilitation services inevitably come at a cost, the second aim was to critically review published cost-effectiveness studies of cancer rehabilitation.

**Methods**

A systematic literature review was undertaken on (a) the effectiveness of multidimensional cancer survivor rehabilitation programs and (b) the cost-effectiveness of cancer rehabilitation. MEDLINE, PsycINFO, and the Cochrane Library were searched electronically using various combinations of keywords and medical subject headings (MeSH): neoplasms (MeSH), survivors, chronic cancer patients, rehabilitation, multicomponent, multidimensional, multifaceted, multi treatment, multimodal, complex, program, exercise, physical activity, physical exercise, physical therapy, return-to-work, reintegration, back to work, vocational rehabilitation, occupational rehabilitation, workplace, cognitive therapy, costs and cost analysis (MeSH), cost, and economic. Table 1 provides a detailed overview of the combinations of search terms used. Further, reference lists of included papers were hand searched.
**Table 1: Search terms used per database**

**Medline:**
Neoplasms [MeSH] AND survivors AND (Rehabilitation OR costs and cost analysis [MeSH] OR (exercise OR “physical activity” OR “physical exercise” OR “physical therapy”) OR (“return to work” OR reintegration OR “back to work” OR “vocational rehabilitation” OR “occupational rehabilitation” OR workplace))

**Cochrane Library:**
Neoplasms AND (rehabilitation OR survivors)

**PsycINFO:**
Neoplasms AND survivors AND rehabilitation,
Neoplasms AND survivors AND (cost OR economic),
Neoplasms AND survivors AND (exercise OR “physical activity” OR “physical exercise” OR “physical therapy”),
Neoplasms AND survivors AND (“return to work” OR reintegration OR “back to work” OR “(vocational) rehabilitation” OR “occupational rehabilitation” OR workplace),
Neoplasms AND (rehabilitation OR survivors)

**Selection criteria for all studies**

English language primary studies, systematic reviews, and meta-analyses were included, evaluating (a) the effectiveness of multidimensional cancer survivor rehabilitation programs and (b) the cost-effectiveness of cancer rehabilitation. Eligible study designs for primary studies were randomized controlled trials (RCTs) and quasi-experimental studies, including nonrandomized controlled studies and pretest-post-test studies. Non-systematic reviews and qualitative and observational studies were excluded. The methodological quality of studies was assessed but did not function as a selection criterion. A rehabilitation intervention was defined as an intervention directed at enhancing the International Classification of Functioning, Disability and Health (ICF) domains in cancer survivors, that is, body structure and function, activity, and participation. Studies evaluating medical devices were not included. Outcome measures included clinical endpoints and intermediate endpoints that could be linked to relevant endpoints. When two articles from the same study were found, only the most recent one that included follow-up and baseline data was included.
Selection criteria for effectiveness studies of multidimensional cancer survivor rehabilitation

Effectiveness studies of multidimensional rehabilitation published in January 1994 to June 2012 were considered. The participants included were adult cancer survivors with any kind of cancer. Various definitions of cancer survivorship are in use\textsuperscript{26}. Here, a “cancer survivor” is defined as a person diagnosed with any type of cancer who finished primary treatment either directly before the start of the study or earlier. The type of primary treatment did not function as a selection criterion. Hormone therapy could still be ongoing. The outcome of the therapy must have been positive to a degree that survival of one year was expected, which therefore also leads to the inclusion of chronic cancer patients. Palliative care patients, end-of-life patients, and adult survivors of paediatric cancer were excluded. Reviews, meta-analyses, and primary studies in which not all participants were cancer survivors were only considered when data were presented separately for cancer survivors.

Multidimensional rehabilitation was defined as a rehabilitation program that consisted of two or more rehabilitation interventions directed at the ICF dimensions. Interventions typically encompassed various types of exercise (also including exercise for specific tumour-type related complaints), cognitive-behavioural therapy (CBT), psychotherapy (also including psychotherapy, counselling, and self- and symptom management), and return-to-work interventions. Therefore, a rehabilitation program that included, for example, two different kinds of exercise (e.g., walking to relieve fatigue and weight lifting to increase muscle strength) was not considered multidimensional because both interventions target the dimension “physical functioning”.

Selection criteria for economic evaluations of cancer rehabilitation

Cost-effectiveness studies of cancer rehabilitation were those published in January 1995 to December 2011 that included adults diagnosed with any kind of cancer of any stage. In contrast to the inclusion criteria for multidimensional rehabilitation programs, cost-effectiveness studies could also include cancer patients who were still in treatment, chronic cancer patients who were not treated with curative intent, and cancer patients during or after treatment with a relatively short life expectancy. Adults experiencing late and long-term effects of paediatric cancer were excluded. Notably, economic evaluations assessing any cancer rehabilitation intervention, whether mono-dimensional or multidimensional, were included to obtain a sufficient evidence base for review.
Screening process
All identified titles and abstracts were screened by two authors (J.M. and L.S.) for relevance and, if relevant, full text articles were obtained and assessed against the selection criteria (J.M. and L.S.). Disagreements were resolved by discussion or referred to a third author (W.v.H.). Because titles and abstracts provide insufficient information to assess multidimensionality according to our definition, full text articles were obtained for all articles evaluating cancer rehabilitation effectiveness.

Data extraction
Data were extracted using a standardized form. For effectiveness studies, study country, type of intervention, intervention design, control group, participants, methods, outcome measures, measurement instruments, retention, baseline characteristics, and results were extracted. For economic evaluations, study country, type of intervention, design of intervention, comparator, outcome measures, measurement instruments, participants, methods, perspective, uncertainty analyses performed, effect results, cost results, economic results, results of uncertainty analyses, and results of modelling were extracted.

Data analysis
The effect size (ES) of selected outcome measures was calculated using Cohen’s $d^{27}$. Standard deviations were calculated according to Hedges$^{28}$. For controlled trials, the ES was expressed as the difference in the mean between the experimental and control groups at the last measurement point. For pretest-post-test studies, the ES was computed for the difference between the baseline and last measurements. In calculating 95% confidence interval (CI) for the ES, a normal distribution was assumed with standard errors calculated according to Hunter and Schmidt$^{29}$.

Methodological quality assessment
The methodological quality of papers was assessed using the Cochrane Collaboration’s risk of bias tool$^{30}$ for multidimensional effectiveness studies and the 10-point Drummond checklist$^{31}$ for economic evaluations.
Results

In total, 4,008 citations were identified from MEDLINE, PsycINFO, and the Cochrane Library. Of these, 187 were duplicates, leading to 3,821 unique articles. By reviewing titles and abstracts, 3,607 articles were excluded; full text papers were obtained for the remaining 214 articles. Of these, 195 articles were excluded. Three articles were identified through hand searching. Common exclusion reasons were that the intervention in question was not multidimensional and that the definition of survivor was unclear. A large number of studies that possibly fulfilled the inclusion criteria were excluded because the estimated life expectancy of the patients at the end of the primary treatment was not stated. Three articles were identified through hand searching, leading to a total of 22 articles included. Sixteen articles\textsuperscript{32-47} on the effectiveness of multidimensional cancer survivor rehabilitation were included, the data from which originated from 11 trials. The data from one of those trials were presented in two complementary articles\textsuperscript{46, 47} and the data from another trial were used in four articles\textsuperscript{42-45}. Six health economic evaluations\textsuperscript{48-53} were identified. No review was identified in which the included studies fulfilled the inclusion criteria. Figure 1 depicts the study's flow chart.
4008 articles identified from database searches
- Medline n=3200
- PsycINFO n=624
- Cochrane Library n=184

Excluding doubles n=187

3821 unique articles

Excluding articles on the basis of title and abstract n=3607

214 full text articles retrieved

Reasons for exclusion:
- Intervention is not multidimensional: n=114
- Participants receive treatment: n=31
- Survivor definition is unclear: n=17
- Only aggregated costs are measured: n=7
- Intervention is not rehabilitation: n=11
- Outcome measures are not relevant endpoints: n=4
- Review is unsystematic: n=4
- No quantitative data is provided: n=3
- Article is not in English: n=3
- First measurement data included in follow-up: n=1

Hand searched articles n=3

22 articles fulfill inclusion criteria

16 Effectiveness studies
6 Economic evaluations

Figure 1: Flow chart of study selection
Effectiveness of multidimensional interventions

Sixteen articles met the selection criteria for multidimensional cancer rehabilitation effectiveness studies32-47 (Table 2).

<table>
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<tr>
<th>Study, year, country</th>
<th>Intervention</th>
<th>Method, participants, n</th>
<th>Measurement</th>
<th>Outcome measures</th>
<th>Results</th>
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<tbody>
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<td>Berglund et al. (1994), Sweden</td>
<td>EXERC + INF + coping skills training / control group</td>
<td>RCT; cancer survivors; 199 in total, intervention group: 98, control group: 101</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T2), 6-months follow-up (T3), 12-months follow-up</td>
<td>Work status, sick leave, having received sufficient information, physical strength and activity, anxiety, depression, (problems with) QoL, activities at home and in the community, physical cancer symptoms, communication with staff, mental adjustment to cancer</td>
<td>Significant improvement in the intervention group at post-intervention on fighting spirit (subscale of mental adjustment questionnaire); at six-months follow-up on problems in communication with doctors; and throughout the whole follow-up period on having received sufficient information, physical strength, and physical training.</td>
</tr>
<tr>
<td>Fillion et al. (2008), Canada</td>
<td>PSY + EXERC / UC</td>
<td>RCT; breast cancer survivors; 87 in total PSY + EXERC: 44 UC: 43</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T2)</td>
<td>Fatigue, energy level, physical QoL, mental QoL, fitness, psychological distress</td>
<td>At T1 significant effect in the intervention group compared to the usual care group on physical QoL only. At T2 improvements on fatigue and energy level only.</td>
</tr>
<tr>
<td>Hanssens et al. (2011), Belgium</td>
<td>EXERC + PSY + counseling</td>
<td>Pre-test post-test cancer survivors; 36</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>QoL, fatigue, fear of movement, distress, anxiety, depression, physical condition</td>
<td>Significant improvements on QoL, physical condition, fatigue, and depression.</td>
</tr>
<tr>
<td>Hartmann et al. (2007), Germany</td>
<td>4w INPR + extra interventions (A) / 3w INPR + 2x 1w follow-up stays (B)</td>
<td>RCT; breast cancer survivors; 197 in total, intervention group: 98, control group: 99</td>
<td>Baseline (T0), after first 3-4w stay (T1), 12-months follow-up (T2)</td>
<td>QoL</td>
<td>No significant differences were found between A and B at T1. T1-T2: A improved on cognitive functioning, while it deteriorated in B, however, this was only significant for the subgroup of participants with impaired cognitive function at baseline. For other subscales no significant differences were found.</td>
</tr>
<tr>
<td>Heim et al. (2007), Germany</td>
<td>INPR + EXERC / INPR</td>
<td>RCT; breast cancer survivors; 63 in total, intervention group: 32, control group: 31</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T2)</td>
<td>QoL, anxiety, depression, fatigue, physical activity, motivation to perform exercise and sport</td>
<td>Both groups improved on muscle strength, global QoL, physical well-being, functionality, fatigue, aerobic capacity, subjective physical fitness, and health-related QoL from T0-T2. Only the intervention group improved further to T2 on subjective physical fitness, muscle strength, global QoL, physical well-being, functionality. Fatigue improved in both groups at T1 and T2, but was reduced significantly more in the intervention group.</td>
</tr>
<tr>
<td>Study</td>
<td>Design/Intervention</td>
<td>Participants</td>
<td>Outcome Measures</td>
<td>Results</td>
<td></td>
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<tr>
<td>----------------------------------------------------------------------</td>
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<td>-----------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Korstjens et al. (2008), The Netherlands</td>
<td>Longitudinal cohort study; cancer survivors; 658</td>
<td>Baseline (T0), halfway the intervention (T1), after intervention (T2)</td>
<td>QoL subscales global QoL, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue</td>
<td>At T1 significant improvements in all domains of QoL, except of cognitive functioning, in the intervention groups compared to baseline. At T2 significant improvements on all QoL-domains, except for role functioning, this only improved significantly for those not working at baseline.</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2010), South Korea</td>
<td>One-group pre-test post-test; gastric cancer survivors; 21</td>
<td>Baseline (T0), one week after intervention (T1)</td>
<td>Depression; QoL subscales emotional well-being, functional well-being, physical well-being, social well-being, general QoL</td>
<td>No significant improvements were found.</td>
<td></td>
</tr>
<tr>
<td>Rogers et al. (2009), US</td>
<td>RCT; breast cancer survivors; 41 in total, intervention group: 21, usual care group: 20</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>Objective physical activity, leisure time physical activity, motivational readiness for physical activity, fitness, muscle strength, body composition and anthropometrics, quality of life, sleep dysfunction</td>
<td>Significant improvements on activity, left handgrip, back/leg extensors, waist-to-hip ration, quality of life-subscale social well-being, and joint stiffness.</td>
<td></td>
</tr>
<tr>
<td>Sherman et al. (2010), Australia</td>
<td>Quasi-experimental trial; breast cancer survivors; 129 in total INF + EXERC: 87 WLC: 42</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>Functional ability score; self-reported energy levels, Trial Outcome Index; QoL subscales general QoL, physical-, social/family-, emotional-, functional-, and breast cancer-specific well-being; cancer-specific distress: intrusion and avoidance, perceived social support, satisfaction with social support, self-efficacy, familiarity with exercise</td>
<td>Significant effects at post intervention compared to baseline where found for the functional ability score, self-reported energy levels, Trial Outcome Index, functional well-being, satisfaction with social support, self-efficacy, and familiarity with exercise.</td>
<td></td>
</tr>
<tr>
<td>Van Weert et al. (2004), The Netherlands</td>
<td>One-group pre-test post-test; cancer survivors; 37</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>Physical capacity performance, muscle force, QoL, fatigue</td>
<td>Significant improvements on all physical outcome measures; the QoL-subscases physical functioning, role limitation, vitality, and change of health; fatigue-subscases physical fatigue and reduction of motivation.</td>
<td></td>
</tr>
<tr>
<td>Korstjens et al. (2008), The Netherlands</td>
<td>RCT; cancer survivors; 147 in total, CBT + EXERC: 76 CBT + EXERC: 71 WLC: 62</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T2), WLC not assessed at T2</td>
<td>QoL-subscases physical role limitations, emotional role limitations, physical functioning, social functioning, mental health, vitality, pain, general health perception, health change</td>
<td>At T1 significant improvements on physical role limitations, physical functioning, vitality, and health change in the intervention groups compared to the WLC. At T2 the WLC was not assessed, and no significant difference emerged on any of the outcome measures between CBT + EXERC compared to EXERC.</td>
<td></td>
</tr>
<tr>
<td>May et al. (2008), The Netherlands</td>
<td>RCT; cancer survivors; 147 in total, CBT + EXERC: 75 CBT + EXERC: 69</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>VO\textsubscript{peak}, W\textsubscript{peak}, exercise time, muscle strength left/right elbow flexors, muscle strength left/right elbow extensors, muscle strength left/right knee</td>
<td>On all outcome measures significant improvements were found at T1 in the intervention group compared to the control group.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention Details</td>
<td>Follow-up Time Points</td>
<td>Outcome Measures</td>
<td></td>
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<tr>
<td><strong>May et al. (2009), The Netherlands</strong></td>
<td>CBT + EXERC / EXERC / RCT; cancer survivors; 147 in total, CBT + EXERC: 76, EXERC: 71</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T2), 9-months follow-up (T3)</td>
<td>QoL, physical activity after rehabilitation</td>
<td>In both groups QoL and physical activity increased clinically significant. No difference between groups.</td>
<td></td>
</tr>
<tr>
<td><strong>Van Weert et al. (2010), The Netherlands</strong></td>
<td>CBT + EXERC + EXERC / EXERC / WLC RCT; cancer survivors; 147 in total, CBT + EXERC: 70, EXERC: 66, WLC: 60</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>General fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue</td>
<td>In the EXERC-group significant improvements were found in general and physical fatigue, and reduced motivation at T1 vs. WLC. In the CBT+EXERC-group a significant improvement was found on physical fatigue at T1 in comparison to WLC. Between EXERC and EXERC+CBT no differences were found.</td>
<td></td>
</tr>
<tr>
<td><strong>Van Weert et al. (2005), The Netherlands</strong></td>
<td>PSY, INF + EXERC / choice of these RCT (the results are presented as an aggregate of both groups); cancer survivors; 63</td>
<td>Baseline (T0), after intervention (T1), 3-months follow-up (T1)</td>
<td>QoL subscales (measured by RAND36) physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, pain, general health appraisal, change in health; QoL subscales (measured by RSCL) overall valuation of life, psychological distress, physical symptom distress, activity level.</td>
<td>At T1 significant improvements on all outcome measures, except for overall valuation of life, in the intervention groups compared to baseline. At T2 significant improvement on all outcome measures, except for pain and general health appraisal, in the intervention groups compared to baseline. 58% of the participants who could choose their program preferred the multidimensional rehabilitation program.</td>
<td></td>
</tr>
<tr>
<td><strong>Van Weert et al. (2006), The Netherlands</strong></td>
<td>PSY + INF + EXERC One-group pretest post-test; cancer survivors; 56</td>
<td>Baseline (T0), after intervention (T1)</td>
<td>General fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue</td>
<td>Significant improvements on all outcome measures.</td>
<td></td>
</tr>
</tbody>
</table>

/\=Compared to

PSY=Psycho-education, INF=Information, EXERC=Exercise, CBT=Cognitive-behavioral therapy, SHE=Self-help education, WLC=Waitlist control, w=Weeks, INPR=Inpatient rehabilitation, QoL=Quality of life, UC=Usual care, RCT=Randomised controlled trial

-----=Articles originate from the same study

Of these, the eight Dutch articles originate from four separate trials. The evaluated interventions all consisted of exercise combined with inpatient rehabilitation programs\(^{35, 36}\), CBT\(^{39, 42-45}\), psychological education\(^{33, 34, 37}\), psychological education and information\(^{41, 46, 47}\), self-help education\(^{38}\), information support\(^{40}\), and information support plus CBT\(^{32}\). Interventions lasted 4–15 weeks. The designs used were RCTs\(^{32-34, 36, 39, 41-46}\), pretest-posttest studies\(^{35, 38, 47}\), a quasi-experiment\(^{40}\), and a longitudinal study\(^{37}\). RCTs included
21–199 participants; the longitudinal study’s sample size was 658. Participants were survivors of any type of cancer\textsuperscript{32, 34, 37, 41–47}, breast cancer\textsuperscript{33, 35, 36, 39, 40}, and gastric cancer\textsuperscript{38}. Outcome measurements were performed directly at the end of the intervention\textsuperscript{34, 37, 39–41, 43, 45, 47} or after 1 week\textsuperscript{38}, 3 months\textsuperscript{33, 42, 46, 36}, 9 months\textsuperscript{44}, or 12 months\textsuperscript{32, 35}. Retention rates were in the range of 64%–100%.

Various outcome measures were reported (Table 2). All articles except one\textsuperscript{38} found significantly better outcomes in the intervention group(s) for all\textsuperscript{43, 47} or for some\textsuperscript{32-37, 39-42, 45, 46} of the outcome measures. Articles measuring subscales of fatigue (\(n=8\)) found statistically significant benefits, but not for all subscales\textsuperscript{41, 46} or for all measurements\textsuperscript{37}. For physical outcome measures, such as muscle strength, physical functioning, and energy levels, 12 of 13 articles reported significant benefits\textsuperscript{32, 34, 37-39, 41-47}. HRQoL and emotional, cognitive, psychological, and social outcome measures, however, varied strongly among studies, although none reported significant deteriorations. Additionally, improvements observed at the end of an intervention were not always sustained on follow-up. Articles comparing mono-dimensional with multidimensional interventions\textsuperscript{42-45} all originated from one trial and did not find a significant difference between the mono-dimensional and multidimensional intervention groups. Two articles compared a more comprehensive inpatient rehabilitation program with the standard program\textsuperscript{35, 36}. One\textsuperscript{35} did not find significant between-group differences and the other\textsuperscript{36} found no significant difference at the end of the intervention but greater improvements in physical outcome measures and fatigue on follow-up. HRQoL was the only outcome measure reported in most articles (\(n=13\))\textsuperscript{32-42, 44, 46}. When these could be calculated, ES values were in the range of -0.12 (95% CI, -0.45 to 0.20) to 0.98 (95% CI, 0.69 to 1.29) (Table 3). Statistically significant improvements at the last follow-up measurement were reported in three studies\textsuperscript{36, 38, 40}. 
### Table 3: Effect sizes of quality of life

<table>
<thead>
<tr>
<th>Article</th>
<th>T</th>
<th>Measurement instrument</th>
<th>Comparison</th>
<th>Outcome variable(s)</th>
<th>Effect size (Cohen’s d)</th>
<th>95%-confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillion et al. (2008)</td>
<td>Follow-up at three months</td>
<td>SF-12</td>
<td>Psycho-education combined with exercise compared to usual care</td>
<td>Physical quality of life</td>
<td>0.21</td>
<td>-0.03 to 0.83</td>
</tr>
<tr>
<td></td>
<td>(4 weeks past baseline)</td>
<td></td>
<td></td>
<td>Mental quality of life</td>
<td>0.40</td>
<td>-0.22 to 0.63</td>
</tr>
<tr>
<td>Korstjens et al. (2006)</td>
<td>Post-intervention</td>
<td>EORTEC QLQ-C30</td>
<td>One-group design; post-intervention compared to baseline</td>
<td>Global quality of life</td>
<td>0.51</td>
<td>0.40 to 0.62</td>
</tr>
<tr>
<td></td>
<td>(12 weeks past baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Korstjens et al. (2008)</td>
<td>Post-intervention</td>
<td>RAND 36</td>
<td>Intervention groups compared to waitlist control</td>
<td>General health perception</td>
<td>0.05</td>
<td>-0.22 to 0.32</td>
</tr>
<tr>
<td></td>
<td>(12 weeks past baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lee et al. (2010)</td>
<td>Post-intervention</td>
<td>FACT-G</td>
<td>One-group design; post-intervention compared to baseline</td>
<td>Global quality of life</td>
<td>-0.05</td>
<td>-0.67 to 0.57</td>
</tr>
<tr>
<td></td>
<td>(24 weeks past baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May et al. (2009)</td>
<td>Follow-up at nine months</td>
<td>EORTEC QLQ-C30</td>
<td>Exercise combined with cognitive-behavioral therapy compared to exercise</td>
<td>Global quality of life</td>
<td>-0.12</td>
<td>-0.45 to 0.20</td>
</tr>
<tr>
<td></td>
<td>(48 weeks past baseline)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sherman et al. (2010)</td>
<td>Post-intervention</td>
<td>FACT-B + 4</td>
<td>Exercise compared to Global quality of life</td>
<td>-0.43</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>(8 weeks past baseline)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Van Weert et al. (2005)</td>
<td>Follow-up at three months</td>
<td>RAND-36</td>
<td>Results of both intervention groups are presented as an aggregate; follow-up compared to baseline</td>
<td>General health appraisal</td>
<td>0.21</td>
<td>-0.14 to 0.56</td>
</tr>
<tr>
<td></td>
<td>(27 weeks past baseline)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

When comparing results from RCTs with those from nonrandomized studies, the findings did not differ. The only article that did not find an improvement for any of the outcome measures was a pretest-post-test study. The other nonrandomized studies, in general, found improvements for a greater proportion of the reported outcome measures than did the RCTs.

The methodological assessment (Table 4) showed that the risk for bias varied widely. The categories “selective reporting,” “other source of bias,” and “allocation concealment,” when applicable, were predominantly assessed as having a low risk for bias, whereas the category “incomplete outcome data” was, in many cases, assessed as having a high risk for bias. Regarding the categories “blinding of participants and
personnel” and “blinding of outcome assessment,” most articles were assessed as having an unclear risk for bias.

Table 4: Quality assessment of multidimensional effectiveness articles

<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other source of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berglund et al., 2004</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fillion et al., 2008</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hanssens et al., 2011</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hartmann et al., 2007</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Heim et al., 2007</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Korstjens et al., 2006</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Korstjens et al., 2008</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lee et al., 2010</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>May et al., 2008</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>May et al., 2009</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rogers et al., 2009</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sherman et al., 2010</td>
<td>N/a</td>
<td>N/a</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Van Weert et al., 2004</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Van Weert et al., 2005</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Van Weert et al., 2006</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>N/a</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Van Weert et al., 2010</td>
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<td>-</td>
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</tr>
</tbody>
</table>

-=High risk of bias, +=Low risk of bias, ?=Unclear risk of bias, n/a=not applicable

Economic evaluations

Six articles met the inclusion criteria for economic evaluations48-53 (Table 5). All economic evaluations were published in 2005–2011. Three articles were cost-effectiveness analyses (CEA), one was a combined CEA and cost-utility analysis, one was a cost-utility analysis, and one contained both a cost-minimization analysis (CMA) and a CEA. Four articles adopted a societal perspective48, 49, 51, 53, one used a health care system perspective50, and one used a hospital perspective52. Analyses were based on multicentre RCTs49-51, 53, a quasi-experimental design48, and modelling52. Intervention patients were compared with a control group of patients who received no intervention48, another intervention49, or standard care50-53. The included patients were
breast cancer patients\textsuperscript{48-51}, breast, colon, or cervical cancer patients\textsuperscript{53}, and head and neck cancer patients\textsuperscript{52}. The effectiveness outcomes measured in the articles were, in these combinations, the number of rehabilitated cases and quality-adjusted life years (QALYs)\textsuperscript{48}, distress and energy\textsuperscript{51}, mood and pain\textsuperscript{50}, fear of regression and QALYs\textsuperscript{53}, and QALYs\textsuperscript{49, 52}. Significant benefits over the control group were found for QALYs\textsuperscript{48, 52, 53}, energy\textsuperscript{51}, fear of regression\textsuperscript{53}, and mood and pain\textsuperscript{50}. The costs of the interventions were in the range of \texteuro{}19, for a videotape intervention\textsuperscript{41}, to \texteuro{}793, for a group-based exercise and psychosocial intervention\textsuperscript{48}. The incremental cost-effectiveness ratios (ICERs) when QALYs were measured and the intervention evaluated was effective were in the range of \texteuro{}16,976 per QALY (which implies cost savings), for adding CBT to standard inpatient rehabilitation\textsuperscript{53}, to \texteuro{}11,072 per QALY, for a group-based exercise and psychosocial intervention\textsuperscript{48}. For other outcome measures, incremental costs of \texteuro{}78,742, for adding CBT to standard inpatient rehabilitation\textsuperscript{53}, to \texteuro{}4,098, for supportive-expressive group therapy\textsuperscript{40}, were found for one unit of difference in effect. For outcomes for which no significant effect was established, usual care and doing nothing were the most cost-effective strategies. The CMA did not find a significant difference in costs\textsuperscript{50}.
Table 5: Summary of economic evaluations

<table>
<thead>
<tr>
<th>Study</th>
<th>Method, perspective, cost year</th>
<th>Intervention and comparator</th>
<th>Outcome, participants</th>
<th>Results</th>
<th>Sensitivity analyses and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al. (2005), Australia</td>
<td>CEA alongside trial, societal perspective, 2004</td>
<td>Home-based physiotherapy (DAART), n=36/ group-based exercise and psychosocial intervention (STRETCH), n=31; versus non-intervention group, n=208</td>
<td>Rehabilitated cases, QALYs; primary breast cancer patients</td>
<td>Non-intervention is more effective and less costly than the intervention groups. ICER for DAART is AUS$2,217 and for STRETCH AUS$ -31,367 compared to non-intervention. QALY: The intervention groups were more effective and more costly. ICER of DAART is AUS$ 1,344 and of STRETCH AUS$ 14,478</td>
<td>One-way. Most values did not influence the outcome. Leisure time valuation, health care expenditure and utility scores were most influential.</td>
</tr>
<tr>
<td>Haines (2010), Australia</td>
<td>CEA, societal perspective, 2006</td>
<td>Multimedia physical activity program consisting of home-based strength, balance, shoulder mobility and a cardiovascular endurance program, n=37; versus control group receiving an active intervention of flexibility and relaxation exercises, n=36</td>
<td>QALYs; breast cancer patients</td>
<td>The intervention group had greater effects at three-months but not at six months-follow-up. Total mean costs were AUS$3,864 for the physical activity program and AUS$3,594 for the control condition. Intervention was more expensive but not more effective. Willingness-to-pay would need to be AUS$484,884 or AUS$340,391 when health care cost-outliers are excluded.</td>
<td>One-way analysis excluding outlier costs. Without these the costs of the intervention group are lower than costs of the control group (AUS$3,290 vs. AUS$3,775 respectively).</td>
</tr>
<tr>
<td>Lemieux et al. (2006), Canada</td>
<td>CMA &amp; CEA alongside trial, health care system perspective, Fiscal period 2002/2003</td>
<td>Supportive-expressive group therapy, n=43; versus control group, n=82</td>
<td>CMA: health care utilization costs, CEA: mood, pain; metastatic breast cancer patients</td>
<td>Health care utilization costs were the same in both groups. The intervention was more effective and more costly. Incremental costs are CAN$5,550 and CAN$4,309 for an effect size of change in mood and pain respectively.</td>
<td>One-way. Not any of the analyses resulted in a difference of health care utilization costs in the two arms.</td>
</tr>
<tr>
<td>Mandelblatt et al. (2008), US</td>
<td>CEA alongside trial, societal perspective; not stated, patient-time costs are from 2002</td>
<td>Videotape intervention, n=128 / Videotape intervention + psycho-educational counseling, n=135; versus control group receiving printed information, n=389</td>
<td>Distress and energy, breast cancer patients in any stage after surgery</td>
<td>Counseling was less effective and more expensive than the videotape intervention. Distress: Videotape intervention costs $7,275 per unit of change in distress. Energy: Videotape intervention costs $2.22 per unit of change in energy.</td>
<td>One-way. Counseling intervention would need to be six times more effective on increasing energy and 20% more effective on lowering distress to be as cost-effective as the videotape arm.</td>
</tr>
<tr>
<td>Retél et al. (2011), The Netherlands</td>
<td>Cost-utility analysis based on modeling, health care perspective of the Netherlands Cancer Institute, 2008</td>
<td>Preventive (swallowing) exercise program, n=37; versus standard care, n=53</td>
<td>QALYs, head and neck cancer patients</td>
<td>Intervention is more effective and more costly, ICER of €3,197 per QALY.</td>
<td>One-way and two-way. Majority of analyses resulted in an ICER below €20,000 per QALY. For lower costs, the intervention is more effective and less costly than standard care.</td>
</tr>
<tr>
<td>Sabariego (2011), CEA, societal perspective, not standardized inpatient rehabilitation</td>
<td>Standard inpatient rehabilitation</td>
<td>Fear of progression</td>
<td>CBT is slightly more effective and less costly, with an ICER</td>
<td>N/a</td>
<td></td>
</tr>
</tbody>
</table>
Germany stated. Patient-time costs are from 2002 program plus cognitive-behavioral therapy (CBT), n=91; versus standard inpatient rehabilitation program plus non-directive and unspecific intervention (SET), n=83; and quality of life; breast, colon, and cervical cancer patients of minus €16,976 for an additional unit of effect in fear of progression. The ICER for quality of life was minus €78,742 suggesting CBT has similar effects and fewer costs than SET.

QAL=Quality-adjusted life year, CEA=Cost-effectiveness analysis, CMA=Cost-minimization analysis, ICER=Incremental cost-effectiveness ratio

1) This evaluation used the measurement at six-months. The original trial did not find any significant effect at the 12-months follow-up.

The methodological quality was moderate to good (Table 6). Positive aspects of the articles reviewed are that almost all economic evaluations gave a description of the interventions, non-intervention or, for ethical reasons, an intervention similar to doing nothing. Five articles\textsuperscript{48-51, 53} were CEAs alongside RCTs in the natural setting, reflecting what probably would happen in practice. A methodological limitation is that none of the economic evaluations were based on a systematic review of effectiveness data. Also, four articles assessed the cost-effectiveness of interventions that have not been shown or have only partly been shown to be effective\textsuperscript{48-51}. Finally, two articles did not include all relevant costs and effects\textsuperscript{50, 51} and three articles did not cover all relevant viewpoints\textsuperscript{51-53}. 


Table 6: Assessment of methodological quality of economic evaluations

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Well-defined question posed?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were both costs and effects examined?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study compare alternatives?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the viewpoint of the analysis stated?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the study placed in specific decision-making context?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Was a description of the alternatives given?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were any relevant alternatives omitted?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Was (should) doing-nothing (be) considered?</td>
<td>Yes</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Was the effectiveness established?</td>
<td>Partly</td>
<td>No</td>
<td>Partly</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Randomized controlled trial: Reflection of what happens in practice?</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes, n/a</td>
<td>Yes</td>
<td>Yes, n/a</td>
<td>Yes</td>
</tr>
<tr>
<td>Effectiveness data summarized through systematic review? Search strategy outlined?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Observational data or assumptions used: What are potential biases in the results?</td>
<td>n/a</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>4. Were all relevant and important costs and consequences identified for each alternative?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the range wide enough for the question?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Did it cover all relevant viewpoints?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Were capital and operating costs included?</td>
<td>n/a</td>
<td>N/a</td>
<td>Yes, n/a</td>
<td>Yes, n/a</td>
<td>Yes, n/a</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Were costs and consequences measured accurately in appropriate units?</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sources of utilization described and justified?</td>
<td>Yes, Yes</td>
<td>Yes</td>
<td>Yes, No</td>
<td>Yes</td>
<td>Yes, Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were any identified items omitted from measurement?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Special circumstances that made measurement difficult: Handled appropriately?</td>
<td>No</td>
<td>N/a</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>6. Costs and consequences valued credibly?</strong></td>
<td>Partly</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the sources of all values clearly identified?</td>
<td>No</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were market values used?</td>
<td>Yes</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Market value absent: Approximations used?</td>
<td>Unclear</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Valuation of consequences appropriate?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>7. Were costs and consequences adjusted for differential timing?</strong></td>
<td>n/a</td>
<td>N/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Were future costs and consequences discounted to their present value?</td>
<td>n/a</td>
<td>N/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Justification given for the discount rate used?</td>
<td>n/a</td>
<td>N/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>8. Was an incremental analysis of costs and consequences of alternatives performed?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td>Additional costs compared to additional effect?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>9. Was allowance made for uncertainty for the estimates of costs and consequences?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Appropriate statistical analyses of patient-level data?</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Justification for the ranges or distributions of values for the sensitivity analysis given?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N/a</td>
</tr>
<tr>
<td>Were conclusions sensitive to uncertainty?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>N/a</td>
</tr>
<tr>
<td><strong>10. Did the presentation and discussion of study results includes all relevant issues?</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the conclusion based on a cost-effect-ratio?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the results compared to previous studies?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Partly</td>
</tr>
<tr>
<td>Was the generalizability discussed?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were any other important factors</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Evidence on the effectiveness of multidimensional cancer survivor rehabilitation and the cost-effectiveness of cancer rehabilitation in general was systematically assessed in this review. The number of papers meeting the inclusion criteria, 16 effectiveness studies and 6 economic evaluations, shows that the evidence base for the effectiveness and economic impact of multidimensional cancer survivor rehabilitation and for cancer rehabilitation in general is scarce. Moreover, the majority of existing studies focused on exercise interventions plus a CBT or psychological educational intervention, whereas studies including other interventions, like return-to-work programs or patient empowerment, are lacking. A similar pattern was found for mono-dimensional interventions in the economic evaluations.

Regarding the type of participants, 5 of the 16 multidimensional studies exclusively included breast cancer patients, and of the articles that aimed to include survivors of any type of cancer, the majority of participants were breast cancer survivors. This pattern applies to the economic evaluations as well, of which the majority exclusively included breast cancer patients. Therefore, generalizability of the results to other tumour groups might be limited, and when using these findings for other cancer types this should be considered carefully. In conclusion, the evidence base for cancer rehabilitation is dominated by exercise intervention studies in breast cancer survivors, whereas published evidence for other aspects of cancer rehabilitation and other tumour populations is lagging behind.

Most studies evaluating the effectiveness of multidimensional rehabilitation (i.e., programs with exercise plus another intervention) reported statistically significant and clinically relevant benefits in at least one of the outcome measures reported. Although two studies found significant benefits in all outcome measures, most studies only reported significant benefits in some outcome measures, mostly fatigue and physical outcomes. The nonrandomized studies found significant improvements in a greater proportion of outcome measures than did RCTs, but in terms of conclusions the outcomes of randomized and nonrandomized studies

Discussion
were the same. When a multidimensional rehabilitation program was compared with the mono-dimensional interventions (i.e., exercise plus another intervention vs. exercise alone), no additional effect was reported\textsuperscript{42-45}. Adding another exercise intervention to a rehabilitation program that was already multidimensional resulted in further benefits for physical outcome measures and quality of life\textsuperscript{36}, whereas adding longer follow-up to inpatient rehabilitation did not result in greater effectiveness\textsuperscript{35}.

Statistically significant benefits associated with multidimensional rehabilitation were reported in all the studies that employed a one-group design (pretest-post-test studies and longitudinal cohort studies), except one\textsuperscript{38}, and in all quasi-experimental and experimental studies that compared multidimensional rehabilitation with usual care without dedicated rehabilitation or with waitlist controls\textsuperscript{32, 37, 38, 46}. The four articles, based on one trial that compared a multidimensional rehabilitation program with a mono-dimensional intervention\textsuperscript{42-45} did not observe the multidimensional intervention to be more (or less) effective than the exercise only control for outcomes that included physical activity, muscle strength, fatigue, and HRQoL. Although not evident from the quality score, methodological aspects may have contributed to this finding, for example, the open-access character of the program and operational differences among treatment sites. Furthermore, studies might have been underpowered to evaluate secondary outcomes such as HRQoL.

The economic evaluations all assessed very different interventions. Despite the low comparability of studies, all showed acceptable cost-effectiveness ratios for interventions that produced significant health gains. The included cost-utility studies reported ICERs well below the prevailing willingness-to-pay thresholds, or even cost savings, suggesting that cancer rehabilitation is potentially a cost-effective means of allocating scarce health care resources, if effective. When interpreting the results, it should be noted that trial participants could be cancer patients during treatment, chronic cancer patients, and cancer survivors. This could influence the results considerably, because a shorter life expectancy results in a lower potential to generate QALYs, and active disease causes higher treatment costs. Also, it is increasingly argued that higher ceiling ratios should be applied for patients with a high burden of disease, although this is currently not formalized nor a prevailing practice for any of the decision-making bodies.

Our results correspond to the findings of a previous review\textsuperscript{54} on economic evaluations of psychosocial interventions. Gordon et al.\textsuperscript{54} also reported acceptable ICERS, although the available studies showed great heterogeneity and were of suboptimal quality. Our review included four additional studies with acceptably low ICERS, which further adds to the evidence suggesting that cancer rehabilitation can be cost-effective. However, in
view of the large expected number of survivors, detailed information on cost-effectiveness from both the societal and health care perspectives is needed for making informed decisions. It might be relevant to use the experience from cardiac rehabilitation, for which multidimensional rehabilitation—though for a limited number of conditions—is recommended as standard practice and more evidence on the cost-effectiveness of multidisciplinary rehabilitation is available. For other diseases, such as low back pain, neglect, and traumatic brain injury, mixed results have been found for the greater effectiveness of multidimensional rehabilitation programs compared to single interventions.

Several methodological issues identified in this review give rise to recommendations for future studies. First, the underlying assumption of the need for multidimensional rehabilitation is that cancer survivors have one or more symptoms that, to be addressed appropriately, require multiple rehabilitation interventions. In addition, one would expect that the intervention or combination of interventions offered depends on the specific symptoms a patient experiences. However, in about half of the articles, it was not an explicit inclusion criterion for patients to have one or more specific symptoms. In the remaining articles, having several symptoms was specified as an inclusion criterion, but because the nature and severity of the symptoms at baseline were not described in a standardized way, it is unclear to what extent the interventions addressed the specific symptoms appropriately. Therefore, it is difficult to assess the ES that could reasonably have been expected for the chosen primary endpoints and whether or not the sample sizes were large enough to observe an incremental effect from multidimensional interventions over single interventions in a heterogeneous population.

Although many studies are available that report the prevalence of the symptoms from which cancer survivors suffer, a more detailed description of the prevalence of combinations of symptoms is lacking. Because trial participants might suffer from a great variety of symptoms, patient samples may actually be more heterogeneous than the predominantly clinical baseline measures show. In future studies on both multidimensional and single interventions, the match between the nature and severity of specific patient symptoms and the interventions offered should be described more explicitly.

Another potential methodological flaw in the current evidence base is the length of patient follow-up. In most articles, the follow-up duration was very short and the measurement was performed directly at the end of the intervention. Therefore, some effects that may typically occur over the longer run (e.g., changes in
emotional distress, depression) may not have been observed within these short follow-up times and could interfere, even if not chosen as the primary endpoint. Moreover, the incorporated studies included cancer survivors with an estimated life expectancy ~1 year. This can lead to the inclusion of chronic cancer patients with a life expectancy of 1-2 years or more and also cured cancer survivors in whom the disease will not return. Depending on life expectancy (and potentially other factors), these patients and survivors may have very different rehabilitation needs. However, from the included studies, it is not possible to distinguish firmly to which group the results apply: cancer survivors with a very good life expectancy outlook or chronic cancer patients. Future studies should provide more detailed descriptions of the treatment outcomes and the estimated life expectancy of the participants.

The quality assessment showed that future trials could be improved by using blinding in outcome assessments when possible. Regarding trial design, future studies should compare the multidimensional intervention with the single components it consists of and with usual care to detect any additional effect of multidimensional rehabilitation. An example of this design is a trial by Duijts et al.\textsuperscript{60}, in which CBT and relaxation combined with exercise was compared with CBT and relaxation, exercise, and a waitlist control for relieving symptoms of treatment-induced menopause. In addition, pragmatic trials, which are more suitable for providing information for clinical and policy decision making\textsuperscript{61}, could form a valuable addition to the evidence derived from RCTs. Research should also involve cancer types other than breast cancer. If all types of cancer are to be included in studies, greater effort should be made to obtain samples representative of the various subgroups and tumour types.

Regarding economic evaluations, it is recommended to use QALYs for enabling comparability among various rehabilitation programs and with other health services. Furthermore, the scarcity of economic evaluations should lead researchers to routinely include cost data in their studies.

Conclusion

Cancer rehabilitation guidelines are increasingly being implemented in many western countries and the evidence base is growing rapidly. Evidence for multidimensional interventions and the economic impact of rehabilitation interventions is still scarce, but studies published so far report statistically significant benefits for multidimensional interventions over usual care, particularly for fatigue and physical outcome measures.
No additional benefit of multidimensional rehabilitation over mono-dimensional intervention was found, but this was also sparsely reported on. These findings should be interpreted with caution because the existing literature base is dominated by exercise intervention studies in breast cancer survivors. Published evidence for combinations with other interventions in cancer rehabilitation, like return-to-work programs, and evidence for other cancer populations are lagging behind. The available economic evaluations assessed very different rehabilitation interventions. Yet, despite their low comparability, all showed acceptable cost-effectiveness ratios or cost savings for those interventions that produced significant health gains. Recommendations for future studies include better targeting of all available interventions to patients’ needs, longer trial follow-up, and the use of QALYs and cost data in all studies.
References


Systematic review
Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients

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Saskia F.A. Duijts
Hester S.A. Oldenburg
Marc van Beurden
Martijn M. Stuiver
Myra S. Hunter
Jacobien M. Kieffer
Wim H. van Harten
Neil K. Aaronson

Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients

Abstract

Introduction: Many breast cancer patients experience (severe) menopausal symptoms after an early onset of menopause caused by cancer treatment. The aim of this study was to assess the cost-effectiveness of cognitive behavioral therapy (CBT) and physical exercise (PE) compared to usual care.

Methods: We performed a cost-effectiveness analysis using a Markov model from a healthcare system perspective. Effectiveness data came from a recent randomized controlled trial that evaluated the efficacy of CBT and PE. Cost data were obtained from relevant Dutch sources. Outcome measures were incremental treatment costs (ITCs) per patient with a clinically relevant improvement on a measure of endocrine symptoms, the FACT-ES, and on a measure of hot flushes, the Hot Flush Rating Scale (HFRS); and costs per quality-adjusted life years (QALY) gained over a five-year time period.

Results: ITCs for achieving a clinically relevant decline in endocrine symptoms for one patient were €1,051 for CBT and €1,315 for PE, compared to the waiting list control group (WLC). The corresponding value for the HFRS was €1,067 for CBT, while PE alone was not more effective than the WLC. Incremental cost utility ratios were €22,502/QALY for CBT and €28,078/QALY for PE, suggesting each intervention is cost-effective compared to WLC.

Conclusion: CBT is likely the most cost-effective strategy for alleviating treatment-induced menopausal symptoms in breast cancer patients, followed by PE. The outcomes are sensitive to a reduction of the assumed duration of the treatment effect, from 5 to 3 and 1.5 years.

Implications for cancer survivors: Patients should be prescribed CBT, or, depending on individual need and preferences, PE.
Introduction

Many breast cancer survivors who undergo adjuvant chemotherapy experience a premature, treatment-induced onset of the menopause and associated symptoms, including hot flashes, night sweats, and vaginal dryness. The most common pharmacologic treatment for (severe) menopausal symptoms, hormone-replacement therapy, is contraindicated in breast cancer patients. Thus, effective non-pharmacologic treatments are needed to alleviate these symptoms.

A recent randomized controlled trial (RCT) comparing cognitive behavioral therapy (CBT), physical exercise (PE), and the combination of both (CBT+PE), demonstrated that PE leads to a significant decline in endocrine symptoms, urinary symptoms, and improvement in physical functioning over time, compared to usual care. CBT led to a significant decrease in the perceived burden of hot flushes and night sweats, and improved sexual activity. The combination of CBT and PE, however, did not lead to additional health benefits compared to CBT or PE only. Given the increase in the number of cancer survivors and the concomitant need for supportive care services, well-conducted health economic studies are needed to support efficient allocation of limited health care resources. The objective of this study was to estimate the short- and long-term incremental cost-effectiveness of CBT and PE, versus a waiting list control group (WLC) in the alleviation of chemotherapy-induced menopause in women with primary breast cancer. Because the combined CBT+PE treatment would always be more costly at no additional patient benefit, this treatment option was not considered in the analysis.

Methods

Overview

A cost-effectiveness analysis (CEA) from the Dutch healthcare system perspective was undertaken based on the RCT of Duijts et al., investigating the efficacy of CBT, PE, and CBT+PE in alleviating menopausal symptoms in breast cancer patients who experienced a premature, treatment-induced menopause. The data from this RCT were combined with additional (cost) data in a health economic model to compare the incremental costs for achieving a relevant decline in symptoms with CBT, PE or CBT+PE versus WLC over a time horizon of five years.
Trial description
The RCT participants were female breast cancer patients who were under 50 years of age, premenopausal at time of diagnosis, had undergone adjuvant chemotherapy and/or hormonal therapy, had experienced a treatment-induced menopause and reported at least a minimal level of menopausal symptoms. The CBT-intervention involved six weekly group sessions of 90 minutes each. The PE-intervention consisted of a 12-week home-based exercise program, individually tailored during an intake session with a physiotherapist. Each intervention arm was compared to a usual care, waiting list control group (WLC). Outcomes were measured at baseline, at twelve-weeks and at six months follow-up. We refer to Duijts et al. 2009 and 2012 for more details on the sample characteristics and interventions.

Primary outcomes of the RCT were endocrine symptoms, as measured by the endocrine subscale of the Functional Assessment of Cancer Therapy Questionnaire (FACT-ES), and perceived burden of hot flashes and night sweats, assessed with the 3-item subscale of the Hot Flush Rating Scale (HFRS). Health-related quality of life (HRQoL), as measured by the 36-Item Short Form Health Survey (SF-36), was a secondary outcome. For the HFRS, a change of at least two points on the ten-point scale is considered a relevant improvement. As a definition of clinically relevant difference for the FACT-ES has not been published, we used a distribution-based definition: an effect size of 0.5, which represents a half standard deviation difference based on the baseline score distribution.

The primary outcome of the economic evaluation was incremental treatment costs (ITC’s) for reducing one patient’s endocrine symptoms (FACT-ES) by a clinically relevant degree. The FACT-ES was chosen as the primary outcome because it assesses a broad range of endocrine symptoms relevant to women with breast cancer. The secondary outcome was the ITC’s for reducing one patient’s perceived burden of key menopausal symptoms (i.e., hot flushes and night sweats) by a clinically relevant degree. The tertiary outcome was the incremental cost per quality-adjusted life year (QALY) gained over a five year period.

Model
We programmed a Markov model (Excel, Microsoft, Redmond, WA) consisting of four health states; “menopausal symptoms,” “reduction in menopausal symptoms,” “recurrence,” and “death”. The criterion used for menopausal symptoms reflect the inclusion criteria used in the previous RCT; experiencing two or more menopausal
Cost-effectiveness analysis

symptoms “sometimes” or “often”. A recurrence could be local, regional, or a distant metastasis.
The accumulating costs and QALYs of a hypothetical cohort of 1000 patients with a starting age of 48 years, matched with the participants of the trial in terms of clinical characteristics, were analyzed over ten consecutive six-month cycles. The first cycle reflects the effectiveness and costs of the respective treatments as measured in the RCT. The outcomes were extrapolated up to a five-year time horizon. A longitudinal study on the duration of bothersome vasomotor symptoms showed symptoms to last 5.2 years on average. Other studies, summarized by Nachtigall et al. found that symptoms peak after 2-3 years, and then fade-out over the next 10-12 years. We therefore assumed that the time-period during which we can expect the interventions to have an impact on bothersome vasomotor symptoms as occurring in the natural course of the menopause, is five years. This assumption is varied in a sensitivity analysis to assess its impact on model outcomes (see sensitivity analyses).

The hypothetical cohort starts in the Markov health state “menopausal symptoms.” After the first cycle, and only at that point, patients could move from the health state “menopausal symptoms” to “reduction in menopausal symptoms”, as well as to “menopausal symptoms”. The probability of this transition is based on the proportion of patients who reported a clinically relevant improvement of at least half a standard deviation of the baseline score of the FACT-ES. From the health state “menopausal symptoms” and “improvement of menopausal symptoms,” patients could move to the health state “recurrence” in every subsequent cycle. Patients who did not move to “recurrence” stayed in their current health state. From each health state, patients could move to “death”.

Data input for the model

We calculated transition probabilities on the basis of the number of participants per trial-arm who had a clinically relevant improvement on the FACT-ES (N=100/235 across all groups). We calculated transition probabilities for local or regional recurrence and distant metastases on the basis of data from the Netherlands Cancer Registry (NCR) using the NCR cohort data matching the RCT sample characteristics for the period 2003-2006 (N=3,716). For background mortality, publicly available age- and gender-specific mortality data, excluding mortality due to breast cancer, were used to calculate transition probabilities. See Table 1 for the transition probabilities.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
<th>Values used in sensitivity analysis; distribution used in PSA</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transition probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT: &quot;menopausal symptoms&quot; to &quot;reduction in menopausal symptoms&quot;</td>
<td>Cycle 1: 0.484 From cycle 2 on: 0</td>
<td>+20%, -20%, effect lasts 1.5 years, effect lasts 3 years; Dirichlet</td>
<td>Patient-level data of Duijts et al., 2012</td>
</tr>
<tr>
<td>PE: &quot;menopausal symptoms&quot; to &quot;reduction in menopausal symptoms&quot;</td>
<td>Cycle 1: 0.453 From cycle 2 on: 0</td>
<td>+20%, -20%, effect lasts 1.5 years, effect lasts 3 years; Dirichlet</td>
<td>Patient-level data of Duijts et al., 2012</td>
</tr>
<tr>
<td>CBT+PE: &quot;menopausal symptoms&quot; to &quot;reduction in menopausal symptoms&quot;</td>
<td>Cycle 1: 0.482 From cycle 2 on: 0</td>
<td>+20%, -20%, effect lasts 1.5 years, effect lasts 3 years; Dirichlet</td>
<td>Patient-level data of Duijts et al., 2012</td>
</tr>
<tr>
<td>WLC: &quot;menopausal symptoms&quot; to &quot;reduction in menopausal symptoms&quot;</td>
<td>Cycle 1: 0.303 From cycle 2 on: 0</td>
<td>n/a, Dirichlet</td>
<td>Patient-level data of Duijts et al., 2012</td>
</tr>
<tr>
<td>From &quot;menopausal symptoms&quot; and &quot;reduction in menopausal symptoms&quot; to &quot;recurrence&quot;</td>
<td>0.003</td>
<td>n/a, fixed values</td>
<td>Netherlands Cancer Registry</td>
</tr>
<tr>
<td>“Recurrence” to “death”</td>
<td>0.427</td>
<td>n/a, fixed values</td>
<td>Netherlands Cancer Registry</td>
</tr>
<tr>
<td>Background mortality</td>
<td>Depending on age of cohort; 0.0009 at age 48 to 0.0013 at age 52</td>
<td>n/a, fixed values</td>
<td>Statistics Netherlands 2011</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal symptoms</td>
<td>Cycle 1: 0.7811 Cycle 2: 0.8126 From cycle 2 on gradually increasing to 0.8526 in the last cycle</td>
<td>+/-20%, Beta</td>
<td>Patient-level data of Duijts et al., 2012</td>
</tr>
</tbody>
</table>
## Cost-effectiveness analysis

<table>
<thead>
<tr>
<th>Reduction in menopausal symptoms</th>
<th>Cycle 2: 0.8277 From cycle 2 on gradually increasing to 0.8677 in the last cycle</th>
<th>-20%, 1.0; Beta</th>
<th>Patient-level data of Duijts et al., 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>0.7320</td>
<td>n/a, Beta</td>
<td>Lidgren et al., 2007</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>n/a, fixed values</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### Costs

- **Cognitive behavioral therapy, average intervention costs per participant**
  - €190.07
  - -20%; +20%, overhead of 25%
  - Program specification, Hakkaart-Van Roijen et al., 2008

- **Material**
  - **CD**
    - €2
  - **Booklet**
    - €3

- **Social worker’s salary**
  - Total salary costs:
    - €128.86
    - (Hourly rate: €34.65)

  - Costs per participant:
    - 1h individual intake session
      - €34.65
  - Costs for a group of eight:
    - 6 sessions of 1.5h
      - €311.85
    - 0.75h preparation for every session
      - €155.93
    - 1 follow-up session of 1.5h
      - €51.98
    - 0.75h for preparing follow-up session
      - €25.99
  - Staff training:
    - 24h training per 4 groups of eight
      - €207.90

  - **Total costs**
    - €133.86
  - **Total costs including 42% overhead**
    - €190.07

- **Physical exercise, average intervention costs per participant**
  - €196.98
  - -20%; +20%, overhead is 25%
  - Program specification, Hakkaart-Van Roijen et al., 2008

- **Material**
  - **Booklet**
    - €5
  - **Heart rate monitor (one for every 4 participant)**
    - €100/4

- **Physiotherapist’s salary**
  - Total salary costs
    - physiotherapist:
      - €99.50
      - (Hourly rate: €34.65)
<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h intake session</td>
<td>€34.65</td>
<td></td>
</tr>
<tr>
<td>0.5h preparation for intake session</td>
<td>€17.33</td>
<td></td>
</tr>
<tr>
<td>0.34h two calls</td>
<td>€11.79</td>
<td></td>
</tr>
<tr>
<td>0.75h final session</td>
<td>€25.99</td>
<td></td>
</tr>
<tr>
<td>0.25h preparation of final session</td>
<td>€8.66</td>
<td></td>
</tr>
</tbody>
</table>

**Costs for a group of eight:**

- **2h staff training per 8 groups** | €8.66/8

**Secretary’s salary**

- **Total salary costs**
  - secretary: €9.22
  - (Hourly rate: €27.96)

- **Total costs** | €138.72*
- **Total costs including 42% overhead** | €196.98*

**Cognitive behavioral therapy and physical exercise, average intervention costs per participant** | €387.05 | -20%; +20%, overhead is 25%, six and ten participants a group; fixed values

**Sum of costs of cognitive behavioral therapy and physical exercise**

**Disease state “menopausal symptoms”**

- **Health care use** | €310.39 in first cycle, gradually decreasing to €247.38 in last cycle
- **Medication** | €100 in first cycle, gradually decreasing to €65 in last cycle

**Disease state “perceived reduction in menopausal symptoms”**

- **Health care use** | €316.17 in first cycle, gradually decreasing to €220.17 in last cycle
- **Medication** | €100 in first cycle, gradually decreasing to €60 in last cycle

**Disease state “recurrence”**

- **Health care use** | €12,181 in first year in recurrence, €2,359 from Fixed values, Gamma
- **Retel et al., 2010** |
**Cost-effectiveness analysis**

<table>
<thead>
<tr>
<th></th>
<th>First year:</th>
<th>From second year on:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In- and outpatient costs</td>
<td></td>
</tr>
<tr>
<td>Drug costs</td>
<td>€12.181</td>
<td>€2.359</td>
</tr>
<tr>
<td>Drug costs</td>
<td>€10.263</td>
<td>€2.294</td>
</tr>
<tr>
<td>Drug costs</td>
<td>€1.918</td>
<td>€65</td>
</tr>
</tbody>
</table>

*) Numbers may not add up due to rounding

PSA=Probabilistic sensitivity analysis, CBT=Cognitive behavioral therapy, PE=Physical exercise, CBT+PE=Cognitive behavioral therapy combined with physical exercise, WLC=Waiting list control group

**Health-related quality of life**

The health-related quality of life (HRQoL) for the health states “menopausal symptoms” and “improvement in menopausal symptoms” were derived by converting the SF-36 data from the trial (N=233) to EQ-5D values, using the algorithm by Ara and Brazier\(^\text{21}\). The average HRQoL of the trial participants who had a clinically relevant improvement on the FACT-ES was assigned to the health state “reduction in menopausal symptoms”, and the average HRQoL of trial participants who did not have a relevant improvement on the FACT-ES to the health state “menopausal symptoms”. The HRQoL for “recurrence” was the weighted average of the HRQoL for local recurrence and metastasis\(^\text{22}\). See Table 1 for the utility values.

**Intervention costs**

The intervention costs consisted of health professional labor, staff training, administration, and material costs. Program managers provided detailed descriptions of the interventions, from which cost items and corresponding volumes were identified. Costs were calculated by multiplying cost prices or appropriate tariffs by volumes, following Dutch pharmaco-economic costing guidelines\(^\text{23}\). We assumed that staff training costs were incurred once for every four groups of eight participants that were offered CBT, and once for every eight groups of PE.

**Data input health care resource use**

The number of healthcare visits was obtained from the RCT\(^\text{4}\) and valued at an average cost of €210 for patients who improved and €216 for who did not improve. As
menopausal symptoms diminish over a time period of approximately five years\textsuperscript{17}, we assumed average health care costs to steadily decrease with the costs of two GP visits and one GP visit for those who did and did not improve, respectively. For pharmaceuticals (including analgesics, sleeping pills, anti-depressants, medication for hypertension, homeopathy, and others) we assumed an average cost of €100 in the first cycle, which then steadily decreased until reaching €60 in the last cycle in the group which improved, and €65 in the group that did not improve. We used published data to estimate the health care costs associated with the health state “recurrence”\textsuperscript{24}. The volumes of resources used and the associated unit costs are given in Table 1.

\textbf{Base case analysis}

We calculated the incremental treatment costs (ITCs) over a six-month time period for achieving a relevant difference on the FACT-ES and HFRS as follows:

\begin{equation*}
\text{Incremental treatment costs} = \text{NNT} \times \text{IC}
\end{equation*}

\text{NNT} = \text{Number needed to treat}
\text{IC} = \text{Intervention costs}

See Table 2 for the numeric values.
Table 2: Base case results

<table>
<thead>
<tr>
<th>Incremental treatment costs</th>
<th>CBT</th>
<th>PE</th>
<th>WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention costs</td>
<td>€190</td>
<td>€197</td>
<td>None</td>
</tr>
<tr>
<td>NNT to achieve a relevant improvement on HFRS</td>
<td>5.61</td>
<td>Lower than in WLC</td>
<td>n/a</td>
</tr>
<tr>
<td>NNT to achieve relevant improvement on ES</td>
<td>5.53</td>
<td>6.68</td>
<td>n/a</td>
</tr>
<tr>
<td>Incremental treatment costs to achieve relevant improvement on the HFRS</td>
<td>€1,067</td>
<td>Not more effective than WLC</td>
<td>n/a</td>
</tr>
<tr>
<td>Incremental treatment costs to achieve relevant improvement on the ES</td>
<td>€1,051</td>
<td>€1,315</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Model outcomes

<table>
<thead>
<tr>
<th></th>
<th>CBT</th>
<th>PE</th>
<th>WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs over a five-year period</td>
<td>€2,983</td>
<td>€2,983</td>
<td>€2,798</td>
</tr>
<tr>
<td>Incremental costs (including treatment and health care costs)</td>
<td>€184</td>
<td>€185</td>
<td>n/a</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>4.400</td>
<td>4.399</td>
<td>4.392</td>
</tr>
<tr>
<td>Incremental QALYs (compared to WLC)</td>
<td>0.0079</td>
<td>0.0067</td>
<td>n/a</td>
</tr>
<tr>
<td>ICER (Incremental costs/incremental QALYS)</td>
<td>€22,502</td>
<td>€28,078</td>
<td>n/a</td>
</tr>
</tbody>
</table>

NNT=Number needed to treat, QALY=Quality-adjusted life year, ICER=Incremental cost-effectiveness ratio, CBT=Cognitive behavioral therapy, PE=Physical exercise, WLC=Waiting list control group, n/a=Not applicable, HFRS=Hot Flush Rating Scale

The incremental cost utility ratio (ICUR), representing the additional costs required for the particular intervention to generate one additional QALY in comparison to WLC, was calculated as follows:

\[
\text{ICUR} = \frac{\text{Incremental costs of the intervention group} - \text{incremental costs of the WLC group}}{\text{Incremental QALYs of the intervention group} - \text{incremental QALYs of the WLC group}}
\]

To indicate whether an intervention can be considered cost-effective, the ICUR was compared to a range of societal “willingness-to-pay” values for one QALY, ranging from €20k to €80k in the Netherlands, with €30k per QALY commonly accepted as the prevailing ceiling ratio\textsuperscript{25}. In line with Dutch pharmaco-economic guidelines, future costs were discounted at 4% and effects at 1.5% annually\textsuperscript{23}. 
Sensitivity analyses
We performed one-way sensitivity analyses by varying input parameters across a range of plausible values (see Table 1). Probabilistic sensitivity analysis (PSA) was employed to estimate the joint decision uncertainty resulting from the uncertainty in the input parameters. To better reflect parameter uncertainty, parameter distributions in PSA were propagated through the model using 5,000 Monte Carlo simulations, instead of single point estimates. For the transition probabilities we used a Dirichlet, for costs a gamma, and for utilities a beta distribution. Distributions were fitted using the method of moments approach. The resulting 5,000 model outcomes were plotted on the cost-effectiveness plane. In addition, we generated cost-acceptability curves (CEAC’s), representing the probability of the interventions being cost-effective depending on the WTP for one additional QALY. Structural uncertainty in the model was addressed by varying the assumption regarding the duration of treatment effect from 5 years, to 3 and 1.5 years respectively, as informed by relevant literature on this topic.

Results
Base case analysis
Table 2 shows the results of all base case analyses. The costs of the interventions were €190 for CBT, and €197 for PE. The number needed to treat (NNT) to achieve a relevant difference on the FACT-ES was lower for CBT (5.53) than for PE (6.68). To achieve a relevant difference in one patient on the HFRS, the NNT was 5.61 for CBT, while PE was outperformed by the WLC. CBT required the lowest ITCs for one patient to achieve a relevant difference on the FACT-ES and the HFRS (€1,051 and €1,067, respectively). For the Markov model outcomes, total costs accumulated per patient over the five-year time period were higher in the PE and CBT groups compared to WLC. The total QALY-gain was similar across the intervention groups. ICURs indicate that CBT is likely the most cost-effective treatments, followed by PE.

Sensitivity analysis
The outcomes were most influenced by 1) the utility in the health states “menopausal symptoms” and “reduction in menopausal symptoms”, and 2) the duration of the treatment effect, with shorter effect duration resulting in lower cost-effectiveness. At a ceiling ratio of €30,000/QALY, the interventions would no longer be considered cost-effective when the duration of treatment effect is 3 or 1.5 years. The results were very
robust to the assumption that health care costs decrease and utilities increase during time. When these values were kept stable, the conclusions did not change. For the outcomes of this analysis see Figure 1.

![Cost-effectiveness analysis](image)

**Figure 1**: Outcomes of sensitivity analyses with values relevant for decision-making

CBT=Cognitive-behavioral therapy, PE=Physical exercise, QALYs=Quality-adjusted life years, ICER=Incremental cost-effectiveness ratio, part.=Participants

**Probabilistic sensitivity analysis**

The cost-effectiveness plane (see appendix 1) showed that most simulated model outcomes are situated in the northeast quadrant, followed by the northwest quadrant. This indicates that all interventions add costs, with the majority of the outcomes of CBT also adding effectiveness in comparison to WLC. The CEAC’s (see Figure 2) showed that PE has the highest probability of being cost-effective only up to a ceiling ratio of circa €26,000/QALY. Beyond that ceiling ratio, CBT has the highest probability of being cost-effective, with a probability of 49% of at a ceiling ratio of €30,000/QALY, up to 56% at €80,000/QALY.
Appendix 1: Cost-effectiveness plane

CBT= Cognitive-behavioral therapy, PE= Physical exercise, QALYs= quality-adjusted life years, ICER= incremental cost-effectiveness ratio
Discussion

The results of this study indicate that CBT is likely to be a most cost-effective strategy for alleviating treatment-induced menopausal symptoms in women with breast cancer, followed by PE which is also cost-effective compared to WLC. As both CBT and PE improve patients’ symptoms and are both effective and cost-effective, we believe that both can be recommended as non-pharmacological treatments for treatment-induced menopausal symptoms among women with breast cancer. The outcomes of this study were most sensitive to a reduction of the duration of the treatment effect from 5 to 3
and 1.5 years, which would in fact alter the adoption recommendation for both CBT and PE. This indicates that better empirical data on the duration of the intervention effects is necessary. These findings are in line with two systematic reviews, which found that effective cancer rehabilitation interventions are also cost-effective27, 28. In a recent UK trial (MENOS1)14, CBT was compared to usual care with higher compliance and effect sizes (d=1.19 and 1.07 at 9 weeks and 6 months post randomization respectively). This suggests that the current analyses might underestimate the cost-effectiveness of CBT14, as compliance in the RCT underlying this cost-effectiveness analysis was relatively low. In addition, the symptom burden required to be eligible to participate in the trial of Duijts and colleagues was minimal. Arguably, a sub-group of women with higher symptom burden might benefit more from the interventions, and also yield a better cost-effectiveness ratio.

For cancer survivors, supportive care and rehabilitation interventions are often offered using a “one size fits all” approach, where all patients are prescribed the same intervention, independent of their actual level of need or their preferences28. This study shows that CBT and PE are similarly effective in relieving symptoms and both have acceptable ICURs. We would therefore recommend that the choice of intervention be based on the patients’ lifestyle and preferences. For example, patients, who already meet exercise targets or, conversely, have an aversion to physical exercise, would probably benefit more from learning how to cope with their symptoms via the CBT program. Women who (believe that they already) have the behavioral skills and attitudes conducive to reducing symptoms, but nonetheless continue to be bothered by them, might benefit most from the physical exercise intervention. In addition, a more targeted approach may also improve patients’ compliance with the interventions, which was notably low in the trial4. While this may lead to better intervention outcomes which would benefit the patient and potentially his/her family, it might also affect the patient’s (un)paid productivity losses in two ways: 1) an increase in productivity losses due to more time spent at the intervention and 2) a potential decrease in productivity losses as (un)paid work would be disrupted less by menopausal symptoms. As productivity losses are typically the concerns of social insurance or governmental bodies, such other stakeholders may have an incentive and/or a responsibility in facilitating cancer survivors’ access to these interventions. Future analyses are thus strongly recommended to consider the (longer term) cost-effectiveness of these interventions from a societal perspective. More specifically, these should include the impact on productivity loss from (un-)paid work and the wider societal benefits in order to inform the multiple stakeholders to whom the costs and benefits of cancer rehabilitation apply.
References


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Cost-effectiveness analysis


A systematic approach for assessing, in the absence of full evidence, whether multicomponent interventions – “doing more” – can be more cost-effective than single component interventions

Janne C. Mewes
Lotte M.G. Steuten
Maarten J. IJzerman
Wim H. van Harten
A systematic approach for assessing, in the absence of full evidence, whether multicomponent interventions – “doing more” – can be more cost-effective than single component interventions

Abstract

Introduction: Multicomponent interventions (MCIs), consisting of at least two interventions, are common in rehabilitation and other healthcare fields. When the effectiveness of the MCI versus that of its single interventions is comparable or unknown, evidence of their expected incremental cost-effectiveness can be helpful in deciding which intervention to recommend. As such evidence often is unavailable this study proposes an approach to estimate what is more cost-effective; the MCI or the single intervention(s).

Methods: We reviewed the literature for potential methods. Of those identified, headroom analysis was selected as the most suitable basis for developing the approach, based on the criteria of being able to estimate the cost-effectiveness of the single interventions vs. the MCI a) within a limited time frame, b) in the absence of full data, and c) taking into account carry-over and interaction effects. We illustrated the approach with an MCI for cancer survivors.

Results: The approach starts with analysing the costs of the MCI. Given a specific willingness-to-pay-value, it is analysed how much effectiveness the MCI would need to generate to be considered cost-effective, and if this is likely to be attained. Finally, the cost-effectiveness of the single interventions relative to the potential of the MCI for being cost-effective can be compared.

Conclusions: A systematic approach using headroom analysis was developed for estimating whether an MCI is likely to be more cost effective than one (or more) of its single interventions.
Introduction

In many fields, such as rehabilitation or self-management, multicomponent interventions (MCIs) are common\(^1\). They may be recommended as part of guidelines, on the basis of evidence, or in situations where little or no evidence exists, based on the expectation that combining two or more interventions in an MCI is more effective than the single intervention\(^2\)\(^-\)\(^4\). Recommending an MCI on the basis of assumed incremental effectiveness over a single intervention is only reasonable when "doing more" indeed leads to better patient outcomes. However, it is not automatically the case that more interventions are better, nor that the combined effectiveness of more than one intervention follows an additive function. Reasons for this include interaction effects between interventions, which can cause an MCI consisting of two single interventions to have an effect that is greater or smaller than the sum of the two\(^5\)\(^-\)\(^{13}\).

As the financial pressure on health budgets compels consideration of cost-effectiveness data to inform reimbursement and implementation decisions, it is desirable to also take information on cost-effectiveness into account when recommending and using MCIs. For this purpose, the incremental cost-effectiveness of an MCI versus its single composite interventions ideally should be derived from clinical trials comparing the effects and costs of both the MCI and the single interventions against doing-nothing. However, as estimating the cost-effectiveness of all relevant interventions in clinical trials is expensive and time-consuming, the data on costs and effects of all interventions under comparison is in most cases incomplete and thus prohibits a full economic evaluation.

In order to still take cost-effectiveness considerations into account in the choice of an MCIs versus its single interventions, a pragmatic approach is needed that allows to estimate whether the MCI is more cost-effective than its single interventions in cases where empirical data on the effect and costs of the MCI are not (yet) or only partly available. This paper describes the development of such an approach and illustrates it using the example of the Dutch cancer rehabilitation guideline\(^1\).

Methods

The decision-problem is defined as follows; in absence of sufficient data to evaluate an MCI's cost-effectiveness, how can it be estimated whether that MCI is likely to be more
cost-effective than the single interventions it consists of? “Sufficient data” is data on key parameters required for analysing the MCI’s (cost)-effectiveness with quality that meets the standards of evidence-based medicine and health economic evaluations\textsuperscript{14-16}.

First, the literature was reviewed to identify methods for similar decision-problems that could contribute to developing an approach to solve the decision problem just defined. As it became clear during the development of the approach that the most important part would be to estimate the effectiveness of the MCI, a large part of the search strategy was directed to this issue. Scopus, including literature from fields other than health care, was searched up to March 2013. Key words used were multidimensional, multicomponent, complex, multimodal, multifaceted, multi-treatment, program*, system, evaluation, assessment, prediction, impact, “effect* estimates”, influencing factors, treatment impact, sequential design, combined design, carry-over effect, interaction effects, cost-effectiveness, costs, economic evaluation, and effectiveness. To qualify for inclusion, articles had to describe and/or apply a method that provided information for the development of the approach. Once included, the following information was retrieved descriptively from each of the articles: the methodological problem or the respective method addressed, the aim of the method, and a description of the method. If more than one paper on a respective method was identified, papers were included until saturation occurred. If papers from leading professional associations were identified that contained methodology guidelines, no more articles for the respective method were included. After data extraction, the identified methods, the number of included articles reporting that method and the type of articles per method found (methods description, methods development, application, or a mix of any of these), were summarized descriptively.

By analysing the Dutch cancer rehabilitation guideline\textsuperscript{1} the requirements that the approach needs to fulfil were identified:

(a) The guideline recommends an assessment of the patients’ needs and subsequently a tailored rehabilitation programme, consisting of exercise, cognitive behavioural therapy, psycho-education, return-to-work, etc., or a combination of two or more of these interventions\textsuperscript{1}. As a large amount of intervention-combinations needs to be compared, the approach should be applicable within a limited time frame, i.e. within up to 5-15 hours for performing the approach, excluding time for information retrieval and assessment, identical to the typical timeframe for mini-HTAs\textsuperscript{17}.

(b) For many of the recommended combinations of interventions in this guideline, none or limited data regarding the costs and/or effects were available\textsuperscript{1}. Thus, it
should be possible to carry out the approach when data on costs and effects of the MCI are limited.

(c) When single interventions are combined into an MCI, interaction and carry-over effects are likely to occur. In an interaction effect the independent variable’s effect on the dependent variable depends on the level of another independent variable. Carry-over effects occur when participation in one intervention influences the performance of the participant in and/or the additional effectiveness of another intervention. The final method should be able to take these effects into account.

Subsequently, all methods that were identified in the literature review were evaluated on fulfilling requirement one. Those who passed were evaluated on fulfilling requirement two, and those who passed this step on requirement three. Method(s) fulfilling all requirements were analysed on how to adapt them to fully suit the decision-problem. Finally, the developed approach was applied to an exemplar MCI from supportive care for cancer patients. It was illustrated how the approach can be used to estimate what is expected to be more cost-effective, the MCI or one of the composite interventions.

Results

Literature review
In the review, 30 papers were included from which six unique methods were extracted. These methods are: (1) assessing the influence of mediating factors, (2) statistical modelling of the (cost-)effectiveness of interventions (such as extrapolation and transfer of model results to other settings, logistic regression analysis, whole disease modelling, etc.), (3) retrospectively identifying success factors of interventions, (4) using decision-rules for estimating the effectiveness of multicomponent interventions based on its single components, (5) network meta-analyses/indirect treatment comparisons, and (6) headroom analysis/cost-effectiveness gap analysis. The methods are described in Table 1.
### Table 1: Methods identified in the literature review and their descriptions

<table>
<thead>
<tr>
<th>Method</th>
<th>Number and types of papers included</th>
<th>Aim of the method</th>
<th>Description of the method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessing the influence of mediating variables</td>
<td>4 papers included&lt;sup&gt;19-22&lt;/sup&gt;</td>
<td>To assess the impact of a mediating variable that influences the effect of an intervention on an outcome variable. Knowing about the mediating variable helps to find out about the mechanism through which the effectiveness of interventions is caused and about the potential effectiveness of a certain combination of interventions.</td>
<td>The association between the independent and the dependent variables are re-analysed on the influence of mediating variables.</td>
</tr>
<tr>
<td>Statistical modelling of the (cost-) effectiveness of interventions</td>
<td>10 papers included&lt;sup&gt;19, 22-31&lt;/sup&gt;</td>
<td>To assess the potential (cost-) effectiveness of an intervention in another setting or for another population through modelling.</td>
<td>Various methods were described, such as statistical techniques, e.g. logistic regression analysis, a causal modelling approach, whole disease modelling, and health economic modelling.</td>
</tr>
<tr>
<td>Retrospectively identifying success factors of an intervention</td>
<td>6 papers included &lt;sup&gt;20, 32-35&lt;/sup&gt;</td>
<td>To assess the contribution of the single interventions to the overall effectiveness of the multicomponent intervention.</td>
<td>Two methods were identified: (a) Decomposing interventions: the components of an MCI are analysed on the primary entity and dimensions they targeted, their delivery characteristics, and intensity. It is then analysed to what degree these contribute to the effectiveness, which enables to analyse which components probably caused the effect. (b) A</td>
</tr>
</tbody>
</table>
questionnaire was used to elicit expert opinion about which intervention components caused the effect.

<table>
<thead>
<tr>
<th>Method</th>
<th>Papers Included</th>
<th>Description</th>
<th>Preconditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using decision-rules or assumptions for estimating (cost-) effectiveness of combined interventions</td>
<td>4 papers included(^{22, 30, 36-38})</td>
<td>To estimate the effectiveness of an MCI, when only the effectiveness of the single interventions of which it consists is known.</td>
<td>Clear-cut decision-rules are used to analyse the effectiveness of combined interventions, such as using the sum (or a similar measure) of the effect of two single interventions for the effectiveness of the MCI.</td>
</tr>
<tr>
<td>Network meta-analysis and indirect treatment comparison</td>
<td>2 papers included(^{39, 40})</td>
<td>To assess the relative effectiveness of two treatments that were not compared head-to-head, but to a common comparator.</td>
<td>Statistical methods are used to establish the comparative effectiveness of two treatments that were not evaluated head-to-head. Preconditions are that the evidence was generated in randomised controlled trials and included homogenous participants across the trials.</td>
</tr>
<tr>
<td>Headroom analysis/cost-effectiveness gap analysis</td>
<td>3 papers included(^{41-43})</td>
<td>To assess the minimum required incremental effect or the maximum incremental costs of an intervention that is needed to achieve cost-effectiveness, in cases where either the incremental effect or the incremental costs are unknown.</td>
<td>When the willingness-to-pay for one unit of the effect is given, the equation for the ICER can be transformed. This allows assessing the minimum effectiveness an intervention is required to attain, given its costs and the willingness-to-pay, in order to be considered cost-effective.</td>
</tr>
</tbody>
</table>

MCI=Multicomponent intervention, ICER=Incremental cost-effectiveness ratio
Development of the stepwise approach

Choice of a method

Requirement a, being able to estimate the cost-effectiveness of an MCI versus its single interventions, was fulfilled by two methods; headroom analysis and using decision-rules. The remaining methods require statistical data analysis which is time-consuming, especially when conducted for several MCIs, and require advanced statistical expertise. Requirement b, being able to estimate cost-effectiveness in the absence of full data on incremental effects and costs, was fulfilled by both the methods that also fulfilled the first requirement. Requirement c, being able to take carry-over and interaction effects into account, was fulfilled by headroom analysis only, which therefore was used as a starting point for further development into an approach that enables to compare the cost-effectiveness of MCI to that of its composite interventions. Using decision-rules did not fulfil this requirement. The reason is that the same algorithm for determining the effect of combining interventions into an MCI is used for all interventions, irrespective of what kind of interventions are combined. For example, when the decision-rule is that the effect of the MCI is the sum of the effects of the single interventions, this is true for all interventions that are combined. Thus, this would apply irrespectively of whether an interaction or carry-over effect is assumed to occur that diminishes the effect or would lead to a synergy effect. Table 2 shows which methods fulfilled the requirements.
Table 2: Analysis of which methods fulfil the requirements

<table>
<thead>
<tr>
<th>Methods that were found in the literature review</th>
<th>Methods that fulfil requirement a): Being able to estimate the cost-effectiveness of the single interventions vs. the MCI within a reasonable time frame:</th>
<th>Method:</th>
<th>Explanation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Using decision-rules for estimating the effectiveness of combined interventions</td>
<td>Using decision-rules for estimating the effectiveness of combined interventions:</td>
<td>A decision-rule (such as the effectiveness of the MCI being the sum of that of the single interventions) is applied, which does not require time-consuming analyses or data collection.</td>
</tr>
<tr>
<td></td>
<td>• Statistically modelling (cost-) effectiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Retrospectively identifying success factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Assessing the influence of mediating factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Network meta-analysis and indirect treatment comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Headroom analysis / cost-effectiveness gap analysis</td>
<td>Headroom analysis / cost-effectiveness gap analysis:</td>
<td>Assessing the required incremental effect or cost for achieving cost-effectiveness does not take much time. Analysing whether the specific intervention is likely to reach the required incremental effect is done by expert opinion, which requires selecting and approaching experts, and experts gathering sufficient information for doing the estimation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Of the above, methods that fulfil requirement b): Being able to estimate (cost-) effectiveness in the absence of full data</th>
<th>Using decision-rules for estimating the effectiveness of combined interventions:</th>
<th>Method:</th>
<th>Explanation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Headroom analysis / cost-effectiveness gap analysis:</td>
<td>Can be used for estimating the effectiveness of the MCI when only that of the single interventions is known, thus the effectiveness of the MCI may be unknown.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Of the above, Methods that fulfil requirement c): Being able to take into account carry-over and interaction effects</th>
<th>Headroom analysis / cost-effectiveness gap analysis</th>
<th>Method:</th>
<th>Explanation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>When headroom analysis is adapted to MCIs, it can be accounted for carry-over and interaction effects in the analysis of whether the required minimum effect is attained.</td>
</tr>
</tbody>
</table>
The basis of headroom-analysis is the net-benefit framework, which is used to determine the incremental cost-effectiveness ratio (ICER) of an intervention:

$$\text{Incremental cost – effectiveness ratio (ICER)} = \frac{\Delta \text{Costs}}{\Delta \text{Effect}}$$  \hfill (1)

Headroom-analysis is used in cases in which either the incremental costs or the incremental effect of an intervention are unknown. The pivotal parameter in the headroom method is the maximum amount someone is willing to spend on one unit of additional effect, i.e. the willingness-to-pay (WTP). Then, depending on which of the other two parameters is known, i.e. either the minimum required incremental effect (MRIE) an intervention needs to attain, or the maximum costs it may have in order to be considered cost-effective can be calculated with the following equations:

$$\text{MRIE} \geq \frac{\Delta \text{Costs}}{\text{WTP}}$$  \hfill (2)

$$\text{Max} \Delta \text{C} \leq (\Delta \text{Effect} \times \text{WTP})$$  \hfill (3)

MRIE = Minimum required incremental effect
WTP = Willingness-to-pay
MaxΔC = Maximum incremental costs

The next step is to estimate to what extent the respective intervention is likely to attain the required effectiveness or to stay below a maximum cost. For being fully suitable to solve our decision-problem, headroom analysis should explicitly accommodate the estimation of whether the MCI can attain the minimum effect or stay below the maximum costs, and compare this to the cost-effectiveness of the single intervention. The “conventional” headroom analysis does not explicitly allow for this. Therefore, this was developed as part of this study and is described below.

**Development of the approach**

As costs of an intervention can be calculated relatively easily, i.e. in comparison to the effectiveness, this approach focuses on whether the MRIE would be attained. In order to accommodate MCIs in the headroom analysis-approach, the incremental effect and costs of a single intervention are replaced by those of the MCI in equation 2. The MCI is labelled “AB” and consists of the single interventions “A” and “B”.

$$\text{MRIE of AB} \geq \frac{\Delta \text{CostAB}}{\text{WTP}}$$  \hfill (4)

Afterwards, a qualitative estimation of how likely the respective intervention is to attain the minimum required effect (MRIE), given the incremental effects or costs and the WTP, needs to be performed. Then, it needs to be estimated if the MCI is likely to attain the MRIE, and how this compares to the cost-effectiveness of the single interventions. It is
not a precondition for the approach that the single interventions are cost-effective by themselves, as the MCI can be cost-effective when super-additive effects occur.

The step-wise approach
The approach consists of the following six steps:

1. Estimate intervention costs
When the costs of the MCI are not empirically investigated, these can be estimated using the cost calculation of the single interventions. It needs to be analysed which costs are (super-) additive when the composite interventions are merged into an MCI, and which costs are redundant or sub-additive. Further, detailed intervention descriptions can be used and, when required, the intervention developers may be willing to share more details and data upon request.

2. Choose a common outcome measure
Since the incremental effectiveness of the interventions under comparison is expressed in one outcome measure, of which the monetary value is determined through the WTP, the effectiveness of all interventions needs to be expressed in that same outcome measure. Most suitable for economic evaluations are generic outcome measures, such as quality-adjusted life years (QALYs).

3. Determine the WTP
The WTP for the selected outcome measure, i.e. the maximum amount society is willing to pay for an additional unit of effect, needs to be determined.

4. Analyse the minimum required incremental effect (MRIE)
The MRIE of the MCI needs to be assessed by completing equation 4, using the WTP and the cost of the MCI as determined in step 1.

5. Qualitatively assess how likely the MCI is to attain the MRIE
The potential for the MCI to attain the required MRIE needs to be assessed. For this the following information and any other information that is considered relevant to assess the potential effect of the MCI should be gathered from experts or identified in the literature (as far as available):

- The effectiveness of the single interventions, as this indicates the potential effect size.
• The interaction and carry-over effects that are assumed to occur in an MCI, and whether these diminish, enlarge, or do not influence the MCI’s effectiveness.
• The intensity of the intervention (e.g. in physical exercise interventions this could be walking vs. running). More intense interventions may lead to larger effect sizes. Too high intensity might lead to exhaustion and diminish the effect of the MCI.
• The effect-causing mechanisms of the single interventions and whether these differ. When this is the case, it can be assumed that the effect is larger than that of one intervention.
• The effect of similar (combinations of) interventions or of the respective intervention in another patient group can give an impression of the reachable effect.
• The symptom burden at baseline. A higher burden may lead to a greater potential for achieving high effect.
• The natural course of the symptoms. If, e.g., the symptoms fade out by themselves, the potential for a high effect of the MCI is smaller than when symptoms would increase without any treatment.
• The duration of the treatment effect. As QALYs are a function of utility and the duration in which the utility is higher than in the comparison group, this has a high influence on the QALY-gain.

Based on these aspects, a qualitative estimation could be conducted of how likely the MCI is to attain the MRIE; for example on a 4-point Likert-scale defined as ‘very likely’, ‘likely’, ‘unlikely’, ‘or very unlikely’.

6. Compare the cost-effectiveness of the single interventions to the potential of the MCI for being cost-effective
   The potential for the MCI to be cost-effective depends on the cost-effectiveness of the single interventions. If the MCI is likely or very likely to be cost-effective, but the single interventions are not, the MCI should be adopted. In turn, when one or both single interventions are cost-effective, but the MCI is unlikely or very unlikely to be cost-effective, the most cost-effective single intervention is recommended. In Table 3 it is shown in which cases the MCI or the single interventions should be adopted.
**Table 3: Overview of which intervention is identified as most cost-effective**

<table>
<thead>
<tr>
<th>The MCI is estimated to be likely or very likely cost-effective</th>
<th>The single interventions are cost-effective</th>
<th>The single interventions are not cost-effective</th>
<th>One of the single interventions is cost-effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undecided*</td>
<td>The MCI</td>
<td>Undecided*</td>
<td>The MCI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The MCI is estimated to be unlikely or very unlikely cost-effective</th>
<th>The most cost-effective single intervention</th>
<th>Undecided*</th>
<th>The cost-effective single intervention</th>
</tr>
</thead>
</table>

MCI=Multicomponent intervention, ICER=Incremental cost-effectiveness ratio, WTP=Willingness-to-pay

*) In case of “undecided” the choice can be based on patient preferences or on the budget impact. Another possibility is to repeat the approach with a willingness-to-pay that resembles the ICER of the (most) cost-effective single intervention. In that way, it can be analysed if the MCI still is considered cost-effective when the WTP is as high as the ICER of the single intervention.

**Application of the stepwise approach**

An example from supportive cancer care is used as an illustration, which consists of interventions for alleviating treatment-induced menopausal symptoms in breast cancer patients. The MCI consists of two single interventions, cognitive behavioural therapy (CBT) and physical exercise (PE), which are both also prescribed as stand-alone interventions. CBT has a cost of € 190 and adds 0.0079 QALYs compared to usual care, PE costs €197 and adds 0.0067 QALYs. The ICER for CBT is €22,500/QALY and €28,100/QALY for PE (differences from directly dividing these values are due to rounding).

1. Estimate intervention costs

For the MCI, the costs of CBT and PE are additive, i.e. the sum of those for PE and for CBT; €387. They are not sub-additive, as the time for planning appointments and the required resources for providing the interventions remain the same.

2. Choose a common outcome measure

QALYs are chosen as the common outcome measure for all interventions involved in the comparison, as these are recommended for health economic analyses.
3. Determine the WTP
Willingness-to-pay is assumed at € 30.000 per QALY.

4. Analyse the minimum required incremental effect (MRIE)
The MRIE for the MCI consisting of both PE and CBT is 0.0129:
\[
\text{Min}\Delta\text{Effect}_A + \text{Min}\Delta\text{Effect}_B \geq \left( (\Delta\text{Costs}_A + \Delta\text{Costs}_B) \div \text{WTP} \right)
\]
\[
\text{Min}\Delta\text{Effect}_A + \text{Min}\Delta\text{Effect}_B \geq (€387 \div 30,000) = 0.0129
\]

5. Estimate if the MCI and the composite interventions are likely to attain the MRIE
The following information was considered:
- In order to attain the MRIE, an effect of almost the sum of that of CBT and PE is required.
- When combining CBT and PE it is likely that an interaction effect occurs. For participating in the MCI, patients need to travel to the hospital at least twice a week, which might be exhausting and could reduce the effect of the interventions as patient might be more tired.
- CBT and PE have different effect-causing mechanisms. While CBT aims to influence the perception of the symptoms, PE is assumed to actually reduce the severity and frequency of symptoms. Therefore, the MCI is expected to be more effective than CBT or PE alone.
- The baseline quality-of-life was 0.78, indicating a relatively low symptom burden.
- Menopausal symptoms fade out during a period of approximately five years, leading to an average maximum effect duration of five years.
- The evidence on the effectiveness of exercise for reducing vasomotor symptoms is inconclusive. A meta-analysis found an effect size of 0.3 of exercise on health-related quality of life (HRQoL) in breast cancer patients.
- The effect of the MCI cannot last longer than the 5 years for which the symptoms normally are experienced. Moreover, the potential effect size becomes smaller throughout the years, as the symptoms diminish naturally.

It was estimated that the MCI is unlikely to reach the MRIE of 0.0129. The MRIE is almost the sum of the effects of PE and CBT, as no sub-additive effects for the costs occur. The main reason for the conclusion is that the symptom burden of the patients was relatively low. As the symptoms fade out by themselves and the single interventions PE and CBT do not result in effect sizes of that magnitude, the potential for reaching the high MRIE is small. CBT+PE is assumed to have a larger effect than one of them alone, as they
have different effect-causing mechanisms. However, the intensity of following both interventions is assumed to be tiresome for some participants, which would further diminish the combined effect, so that it is unlikely to reach the sum of PE and CBT.

6. Compare the potential for cost-effectiveness of the MCI to that of the composite interventions

The single interventions CBT and PE are cost-effective. The MCI may add further effectiveness; however, it is estimated that the MRE of 0.0129 QALYs is unlikely to be attained. Thus, when aiming to choose a cost-effective intervention, one of the single interventions should be preferred.

Discussion

We developed and illustrated an approach that enables to estimate which intervention is likely to be more cost-effective, an MCI or its composite interventions, when empirical data on costs and effects of the MCI are incomplete. It is intended to be pragmatic and feasible to perform within a short time frame and without advanced health economic expertise, as this would limit its use by decision-makers. The approach builds on headroom analysis, which was extended in order to accommodate MCI s. Given the costs of the MCI and the willingness-to-pay, the MRIE of the interventions in order to attain cost-effectiveness can be assessed. Subsequently, a qualitative yet systematic assessment of how likely the MCI is to achieve the MRIE can be made. Depending on whether the single interventions are cost-effective, it can be assessed whether the MCI is likely to be more cost-effective.

The literature review showed that methodology concerning this specific decision-problem is rather scarce. Reasons for this gap are that guideline developers traditionally have been more concerned with effectiveness than cost-effectiveness, that including economic evidence into guidelines makes the process of developing them even lengthier and more resource intensive, and that clear criteria of when an intervention is considered cost-effective are lacking. A framework to overcome this was developed by Gandjour and Lauterbach for assessing the break-even point of guidelines. Our approach adds the option to estimate the potential for cost-effectiveness of an MCI in the absence of full data and in a pragmatic way that can be conducted by decision makers.
The approach presented here is developed for national decision making, but with little adaptation it can also support local decision makers. Hospitals or health care providers can use it to decide how to implement a comprehensive guideline advice by replacing the WTP by their budget or the reimbursement, in order to analyse how to achieve the best use of the available resources. This would form a beneficial addition to the current mini-HTAs, which are used e.g. for making decisions on local budgets\textsuperscript{17}. Another variant of the approach is to not analyse the MRIE and then decide if the intervention potentially can attain this, but to first estimate the range of the effect that the intervention is thought to attain, and to then determine the range of ICERs that this corresponds to. Subsequently, the intervention with the most favourable ICER range can be chosen.

As the key missing information in the puzzle of the cost-effectiveness is the effect of the MCI, research should focus on how to assess the additivity of the health benefits of interventions when they are combined into an MCI, as this so far is seen as a "black box". One direction that could be taken is to use the various approaches that sensitivity analysis offers, which also take the already existing information and clinical expertise into account\textsuperscript{55}. Another direction is the approach by Basu et al. in which prediction models are used that analyse the utility of a joint health state, i.e. a patient experiencing several symptoms, from the utility of single health states, i.e. from patients having only one symptom\textsuperscript{56}.

Moreover, to evaluate the benefit of the developed approach in practice, future research is needed. Comparisons should be made of the results of this approach versus those of an economic evaluation alongside an RCT, in order to gain more insight into the validity of the results of headroom analysis for multicomponent interventions.

**Conclusion**

We developed a systematic approach to estimate, in the absence of suitable data on costs and effects, if an MCI can be more cost-effective than its composite, single interventions. The purpose of this method is to support the decision of which interventions to recommend in guidelines based on cost-effectiveness considerations, in the absence of full (and timely) data. We illustrated the use of this method in the field of cancer survivorship. Further research is needed in which headroom analysis for MCIs is applied to multicomponent guidelines, to test the method’s practical use and impact.
References


Return-to-work intervention for cancer survivors: Budget impact and allocation of costs and returns in the Netherlands and six major EU-countries

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Monique H.W. Frings-Dresen
Maarten J. IJzerman
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Return-to-work intervention for cancer survivors: Budget impact and allocation of costs and returns in the Netherlands and six major EU-countries

Abstract

Introduction: Return-to-work (RTW)-interventions support cancer survivors in resuming work, but come at additional healthcare costs. The objective of this study was to assess the budget impact of a RTW-intervention, consisting of counselling sessions with an occupational physician and an exercise-programme. The secondary objective was to explore how the costs of RTW-interventions and its financial revenues are allocated among the involved stakeholders in several EU-countries.

Methods: The budget impact (BI) of a RTW-intervention versus usual care was analysed yearly for 2015-2020 from a Dutch societal- and from the perspective of a large cancer centre. The allocation of the expected costs and financial benefits for each of the stakeholders involved was compared between the Netherlands, Belgium, England, France, Germany, Italy, and Sweden.

Results: The average intervention costs in this case were €1,519/patient. The BI for the Netherlands was €-14.7m in 2015, rising to €-71.1m in 2020, thus the intervention is cost-saving as the productivity benefits outweigh the intervention costs. For cancer centres the BI amounts to €293k in 2015, increasing to €1.1m in 2020. Across European countries, we observed differences regarding the extent to which stakeholders either invest or receive a share of the benefits from offering a RTW-intervention.

Conclusion: The RTW-intervention is cost-saving from a societal perspective. Yet, the total intervention costs are considerable and, in many European countries, mainly covered by care providers that are not sufficiently reimbursed.
Background

Many cancer survivors experience difficulties in returning to work. Approximately 40% have not resumed work 24 months post treatment\(^1\). Furthermore, cancer survivors have an increased risk for unemployment compared to the general population\(^2,3\). Supporting patients in returning to the workplace may improve health and quality of life, and avoid high societal costs associated with unemployment and long-term inability to work\(^4-6\). When successful, RTW-interventions can increase productivity through reducing sick leave and might save costs to society. However, RTW is not or only partly reimbursed by health insurers in most European countries, including the Netherlands. The main reason is that the interventions are expected to be expensive and unaffordable. However, when they are effective, return-to-work interventions can produce financial benefits, although their size is unknown. To date, no budget impact analysis of these interventions or of any other cancer rehabilitation intervention has been published. Evidence on the budget impact would quantify to what extent return-to-work interventions are beneficial from a financial point of view or if these intervention would add costs to the system. Therefore, the primary aim of this study was to evaluate the expected budget impact (BI) of RTW-interventions for cancer survivors. In a budget impact analysis, the expected financial impact of an intervention on the budget of a health system is analysed\(^7\).

Return-to-work interventions typically consist of counselling by an occupational physician directed on return-to-work possibilities. We considered an intervention that combines counselling with physical exercise, as a Cochrane review showed that multidisciplinary RTW-interventions are most effective. Moreover, physical exercise is strongly recommended for cancer patients in several organisations’ guidelines\(^8-12\). The analysis was conducted from the Dutch societal perspective and from the perspective of a cancer centre over the time period 2015 to 2020. The latter perspective serves to estimate the BI for cancer centres that plan to introduce RTW and want to investigate its year-by-year financial impact. The secondary objective was to identify the allocation of costs and financial returns of providing RTW for cancer survivors for several European countries. This provides insights in financial incentives for and against RTW-implementation.
Methods

Budget impact analysis
The budget impact of a multidisciplinary RTW-intervention was assessed following the International Society for Pharmaco-economics and Outcome Research-guidelines over a time horizon of 5 years. We compared the situation in which the intervention gradually is implemented to current practice, where only 5% of the eligible patients can follow the intervention. We considered a Dutch societal perspective and that of a cancer centre serving a population of 1m inhabitants, which equals the catchment area of large European cancer centres\textsuperscript{7,13}. All input parameters are presented in Table 1.
Table 1: Input parameters for the budget impact analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for the Netherlands</th>
<th>Value for a hypothetical cancer centre</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer incidence in the Netherlands:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>110,215</td>
<td>6,533</td>
<td>Signaleringcommissie</td>
</tr>
<tr>
<td>2016</td>
<td>112,776</td>
<td>6,675</td>
<td>Kanker of the Dutch</td>
</tr>
<tr>
<td>2017</td>
<td>115,337</td>
<td>6,816</td>
<td>Cancer Society, 2011</td>
</tr>
<tr>
<td>2018</td>
<td>117,899</td>
<td>6,805</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>120,460</td>
<td>7,097</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>123,021</td>
<td>6,237</td>
<td></td>
</tr>
<tr>
<td>Percentage of eligible patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with 5-year survival</td>
<td>62%</td>
<td></td>
<td>Dutch Cancer Registry</td>
</tr>
<tr>
<td>% aged 25-64</td>
<td>40%</td>
<td></td>
<td>Dutch Cancer Registry</td>
</tr>
<tr>
<td>% with treatment outcome that allows RTW</td>
<td>80%</td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>% who want to resume work</td>
<td>85%</td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>% who wish to follow intervention</td>
<td>70%</td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>% eligible for intervention</td>
<td>12%</td>
<td>Product of the above</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>(=0.32<em>0.80</em>0.85*0.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capacity in current practice:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015-2020, yearly</td>
<td>5%</td>
<td>5%</td>
<td>Assumptions</td>
</tr>
<tr>
<td>Capacity in new situation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>20%</td>
<td>30%</td>
<td>Assumptions</td>
</tr>
<tr>
<td>2016</td>
<td>30%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>40%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>50%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>60%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>70%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Percentage of patients for whom the intervention is reimbursed in current situation:</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of patients for whom the intervention is reimbursed in new situation:</td>
<td>10%</td>
<td>Assumption</td>
<td></td>
</tr>
<tr>
<td>Intervention costs</td>
<td>€ 1,517</td>
<td></td>
<td>Assessment of the costs based on intervention description and information provided from the staff who delivered the intervention.</td>
</tr>
<tr>
<td>Additional weekly working hours in the new situation</td>
<td>5.8h</td>
<td>Thijs et al., 2011</td>
<td></td>
</tr>
</tbody>
</table>

Approval of an ethics committee and the participants’ consent were not required for this research, as the data were derived from the literature and from health professionals.
Dutch law does not require medical or ethical reviews for interviews with health care professionals. Confidentiality was ensured by not disclosing the names or hospitals of the interviewees and only referring to them by country. The study on which the cost calculation is based had received approval from the respective ethics committee.12

**Intervention description and uptake of the intervention**

The RTW-intervention, including counselling and exercise, is prescribed at the start of cancer treatment to all cancer patients who potentially can and wish to resume work. The counselling includes two one-hour sessions with an occupational physician specialised in oncology. The exercise component consists of 24 group sessions of moderate to high-intensity physiotherapy in groups of five. The duration of the exercise programme is 12 weeks, starting at the onset of chemotherapy. Some hospitals also provide a sports medical capacity-assessment before and after the programme. A more detailed description of the intervention was published previously.12, 14

**Eligible Population**

Patients with any type of cancer are eligible when they are; a) of working age, i.e. between 25 and 64 years, b) treated with curative intent,15, 16 c) expected to have a treatment outcome that allows returning to work, d) wishing to return to work, and e) willing to follow the intervention. For each criterion, the percentage of all cancer patients to whom this applies was analysed and is given in Table 1. The percentage of patients who are eligible was calculated by multiplying 100% with the percentages of all criteria. This resulted in an eligibility percentage of 12% of all cancer patients that are diagnosed yearly (see Table 1).

**Capacity**

As there currently is insufficient capacity for providing the intervention, not all patients eligible for a multidisciplinary return-to-work intervention can follow it. Reasons for the limited capacity are that the implementation in general is still in the starting phase and that many health professionals are not fully aware of the possibilities that cancer rehabilitation offers. In order to offer the intervention to all eligible patients and provide the intervention on a larger scale, hospitals would, e.g., first need to employ more physical therapists and occupational physicians, and create the appropriate organisational structures for providing the intervention on a larger scale.

As a result of the above, currently only a small (i.e. 5%) subgroup of survivors is prioritized to receive multidisciplinary rehabilitation treatment. Thus, of the 12% of the
cancer patients who are eligible, 5% can follow the intervention. This capacity is assumed to remain at that 5% level throughout the analysis’ time horizon for current practice. This is compared to the situation in which hospitals start to implement the intervention and gradually increase the capacity to enrol patients, starting with 30% of eligible patients in 2015 to 70% in 2020. Thus, in 2015, 30% of the 12% eligible survivors follow the intervention. Finally it is expected that in 2017 most of the eligible survivors (70%) can participate in multidisciplinary return-to-work interventions.

The capacity in a single cancer centre that is used for the analysis from the perspective of a hypothetical cancer centre rises much faster, from 30% in 2015 to 90% in 2020. It is assumed that once a cancer centre decides to offer the intervention it would take measures to relatively quickly provide it to all eligible patients. However, they would also be faced by shortages of staff, especially for occupational physicians. The percentage from the Dutch societal perspective remains lower at 70%, because it is assumed that not every hospital will offer the intervention. Thus, some hospitals will not offer return-to-work interventions at all, whereas some offer it to 90% of the eligible patients, leading to an overall percentage of 70%.

Costs of the intervention and impact on other costs
Intervention costs include staff costs, administration, materials, and 42% overhead, according to the Dutch manual for cost research\(^\text{17}\). Volumes of resource use were obtained from the intervention protocol and health professionals participating in a feasibility study of the intervention\(^\text{12, 14}\). Unit costs were determined following Dutch guidelines for pharma-economic research\(^\text{17}\). Staff training costs of €335 were considered as part of the overhead. Hospitals receive reimbursement for providing RTW-interventions to patients formally indicated for multidisciplinary rehabilitation. This is circa 10% of the eligible population. In current practice, all patients who receive the RTW-interventions are indicated for multidisciplinary rehabilitation and thus receive reimbursement.

An impact on other costs occurs through changes in the patients’ productivity. The effect of RTW on resuming work was taken from a Dutch trial. In the intervention group the participants followed an 18-weeks exercise programme, consisting of a high intensity resistance and endurance training. This was compared to standard medical care that was received by an age-matched control group. Patients with any type of cancer of 18-65 years of age were included who were treated with curative intend and were in paid employment at the time of diagnosis. 110 patients were included in the analysis, 72 in the intervention group and 38 in the control group. The adherence of the participants
was very high with 96% and thus slightly higher than for the multidisciplinary return-to-work intervention where it was 86%. A significant difference in the time to resume work was not found. However, the intervention was found to increase productivity significantly by 5.8 hours/week for one year. Thus, the participants in the intervention group were able to work more in the long-term. This 5.8 hours/week that are worked more than in current practice was used for the productivity benefit in this analysis and was valued at €30.02/hour, according to the Dutch manual for cost research.

**Analysis**

For analysing the budget impact, a spreadsheet model (Figure 1) was created in Microsoft Excel (Redmond, WA). The budget impact equals the total cost of the RTW-intervention minus the productivity gains that accrue from RTW, in the new situation vs. current practice. In the model, the number of patients following the intervention was identified by multiplying cancer incidence with the percentage of eligible patients and the capacity of hospitals to provide the intervention. The number of patients was then multiplied with the intervention costs, which resulted in the total costs of the RTW-intervention. For the Dutch societal perspective, the productivity gains equal the number of patients who follow the intervention multiplied with the additional yearly working time generated and with the hourly productivity costs. For the cancer centre’s perspective, the benefit consists of receiving reimbursement from the health insurer for delivering RTW to the 10% of the patients indicated for multidisciplinary rehabilitation.
Figure 1: Structure of the budget impact model

**Sensitivity analysis**
The influence on the budget impact of the effectiveness of the intervention was analysed, in order to test the robustness of the model outcomes. For this purpose, the effect in a range of 0 to 5.8 additional weekly working hours, which corresponds to 0 to 302 hours a year, was used to display its effect on the budget impact graphically. This also allowed analyzing where the budget impact changes from being cost-saving to adding costs, i.e. where the line of the budget impact crosses the x-axis from being cost-saving to adding costs.

**Analysis of the incentive structure to implement RTW in the Netherlands and in several EU-countries**
The allocation of costs and financial returns across stakeholders involved in RTW was analysed, to identify potential (dis)incentives for implementing RTW-interventions. For this purpose, an email survey was conducted among comprehensive cancer centres that are members of the Organisation of European Cancer Institutes (n=40) from the Netherlands, Belgium, England, France, Germany, Italy, and Sweden. At least one
respondent from each country was required. In the survey each cancer centre-representative with professional knowledge about the healthcare and welfare system in their respective country, was asked to tick in a list of stakeholders which of these (1) bear the costs of sick leave of cancer patients, (2) are responsible for the reintegration of cancer patients into the workplace, (3) bear the costs for offering an RTW-intervention, and (4) benefit financially from cancer patients following a RTW intervention. The list of stakeholders included health insurers, hospitals, patients, employers, pension insurance schemes, and the state. The nature of the financial benefits depends on the stakeholder and includes, e.g., for a hospital reimbursement by the patients’ health insurers, for health insurers a reduction in the patients’ future health care needs, for patients the ability to continue working and receive an income, or for employers the prevention of sick leave and subsequent production losses.

For the analysis, the results of the survey were assessed in 2*2 tables showing how many and which stakeholders both pay and gain from RTW, how many only pay or only gain, and how many do not pay or gain.

Results

Budget impact analysis

Base case results

The number of patients following the intervention under current (Dutch) practice on national level was estimated to be 651 in 2015 and increase to 726 patients in 2020. This increase only reflects the rising cancer incidence, while the percentage of patients who are eligible for the interventions remains stable in this model. In the new situation in which RTW-interventions are rolled out more widely, 2,602 patients would participate in the intervention in 2015. As cancer incidence and the capacity both rose, it is estimated that 10,166 patients would follow the intervention in 2020.

The same reasoning as described above was applied to estimate the number of patients receiving a RTW-intervention in a large cancer centre. In current practice this number would rise from 39 to 43 in the 5-year period in our model, due to the growth in cancer incidence. After implementing RTW, the number could increase from 231 in 2015 to 769 in 2020, as the capacity for treating the eligible patients is assumed to grow.

The average costs of the RTW-intervention are estimated at €1,517 per patient, of which €567 (37%) are for consultations with the occupational physician, €879 (59%) for the exercise part, and €46 for administration and printed materials.
The total health care costs when implementing RTW for the Netherlands are €4.0m to €15.4m from 2015 to 2020. The benefits in terms of productivity gains are €23.6m to €92.0m in 2015 to 2020. The BI for the Netherlands is €-14.7m in 2015, rising to €-71.1m in 2020, meaning that from a societal perspective RTW for cancer survivors in the Netherlands would be cost-saving. The productivity gains are large and outweigh the intervention costs by far. In fact, with rising incidence and a growing proportion of patients following RTW, cost savings further increase year-by-year. However, the intervention is rather expensive to its providers and the initial health care costs are considerable.

For a large cancer centre, the costs for the intervention compared to current practice, from 2015 to 2020 increase from €351k to €1.2m. The financial benefit in terms of reimbursement from 2015 to 2020 is only €58.6k to €116.8k. The BI for a cancer centre is €292.8k in 2015 and rises to €1.1m in 2020. Thus, for a cancer centre providing this service, the high intervention costs cause RTW to be an expensive intervention to offer, as they get only reimbursed for 10% of the patient population. Table 2 shows the base case results.
Table 2: Results of the budget impact analysis

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</thead>
<tbody>
<tr>
<td></td>
<td>DUTCH SOCIETAL PERSPECTIVE</td>
<td></td>
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</tr>
<tr>
<td>Current practice:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>651</td>
<td>666</td>
<td>681</td>
<td>696</td>
<td>711</td>
<td>726</td>
</tr>
<tr>
<td>Health care costs [in €]</td>
<td>987,901</td>
<td>1,010,858</td>
<td>1,033,815</td>
<td>1,056,772</td>
<td>1,079,729</td>
<td>1,102,686</td>
</tr>
<tr>
<td>Productivity benefits [in €]</td>
<td>5,889,947</td>
<td>6,026,819</td>
<td>6,163,690</td>
<td>6,300,562</td>
<td>6,437,434</td>
<td>6,574,306</td>
</tr>
<tr>
<td>New situation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Number of patients</td>
<td>2,602</td>
<td>3,994</td>
<td>5,446</td>
<td>6,959</td>
<td>8,532</td>
<td>10,166</td>
</tr>
<tr>
<td>Health care costs [in €]</td>
<td>3,951,605</td>
<td>6,065,149</td>
<td>8,270,522</td>
<td>10,567,724</td>
<td>12,956,753</td>
<td>15,437,611</td>
</tr>
<tr>
<td>Budget impact [€]</td>
<td>14,706,137</td>
<td>25,079,802</td>
<td>35,909,126</td>
<td>47,194,109</td>
<td>58,934,752</td>
<td>71,131,054</td>
</tr>
<tr>
<td></td>
<td>PERSPECTIVE OF A REFERENCE CANCER CENTRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current practice:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>39</td>
<td>39</td>
<td>40</td>
<td>40</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>Health care costs [in €]</td>
<td>58,560</td>
<td>59,828</td>
<td>61,093</td>
<td>60,999 €</td>
<td>63,611 €</td>
<td>64,864 €</td>
</tr>
<tr>
<td>Benefits (reimbursement) [in €]</td>
<td>58,560</td>
<td>59,828</td>
<td>61,093</td>
<td>60,999 €</td>
<td>63,611 €</td>
<td>64,864 €</td>
</tr>
<tr>
<td>New situation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>231</td>
<td>473</td>
<td>724</td>
<td>723</td>
<td>754</td>
<td>769</td>
</tr>
<tr>
<td>Health care costs [in €]</td>
<td>351,358</td>
<td>717,939</td>
<td>1,099,674</td>
<td>1,097,987</td>
<td>1,144,994</td>
<td>1,167,550</td>
</tr>
<tr>
<td>Benefit (reimbursement) [in €]</td>
<td>58,560*</td>
<td>71,794</td>
<td>109,967</td>
<td>109,799</td>
<td>114,499</td>
<td>116,755</td>
</tr>
<tr>
<td>Budget impact [€]</td>
<td>292,798</td>
<td>646,145</td>
<td>989,706</td>
<td>988,188</td>
<td>1,030,495</td>
<td>1,050,795</td>
</tr>
</tbody>
</table>

*) According to the model, this would be €35,136, assuming that hospitals receive reimbursement for 10% of the patients. As this is lower than the benefit in the current situation, it is expected that as long as in the new situation there still are patients with a multidisciplinary rehabilitation need (for whom the costs are reimbursed by
insurance), these would be treated preferentially to patients for whom the costs are not reimbursed.

**Sensitivity analysis**

Figure 3 shows that even when the benefit of the RTW-intervention was much smaller than expected based on current data it would still be cost-saving. The health care costs equal the productivity benefits, i.e. the BI is zero, when the RTW-intervention enables patients to return to work 50.6 hours earlier in 2020 compared to usual care. This value corresponds to an increased weekly working time of approximately 1h/week, which is more than five times lower than the value used in the base case analysis (5.8h/week).

**Figure 3:** The impact of earlier RTW on the budget impact in 2020. From 2020 on a steady state is assumed.
Analysis of the incentive structure for implementing RTW

The Netherlands

Health care providers that offer RTW-interventions carry their costs themselves, apart from the health insurances’ reimbursement for about 10% of patients with a multidisciplinary rehabilitation need. The financial returns from earlier RTW are received by employers, the patients, and pension funds. Thus, a misalignment exists between the stakeholders that pay for RTW and those that receive the financial benefits in terms of increased productivity or in preventing invalidity pension. As this situation discourages to offer RTW on a large scale, its substantial cost-savings to society are forgone. A cancer centre or hospital would need to highly value the intangible benefits, such as being a provider of high-quality care, attractiveness for patients, or being a leading cancer centre, in order to make up for the costs. See Table 3 for the results of this analysis.
### Table 3: Distribution of RTW intervention costs and financial returns across the stakeholders for the Netherlands

<table>
<thead>
<tr>
<th>Responsibilities in RTW</th>
<th>Health insurance</th>
<th>Hospitals/Healthcare providers</th>
<th>Employers</th>
<th>Patients/Employees</th>
<th>The state</th>
<th>Pension insurance scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General responsi-bility for reimbursing necessary health care</td>
<td>Sick pay for first 2 years, reintegration of sick employees into the workplace</td>
<td>Sick pay after 2 years of inability to work</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carrying the costs of RTW interventions</th>
<th>Reimbursement for patients with multidisciplinary rehabilitation need</th>
<th>Interven-tion costs</th>
</tr>
</thead>
</table>

| Receiving the financial returns of RTW | Lower future health care costs, however, high budget impact | Fewer productivity losses, no replacement for employee needed | Ability to generate an income | Less early-retirement-pension payments |

| Incentive for financing RTW for cancer patients * | Lower future health care costs in the long-run, considerable budget impact | Carrying the costs, but hardly receiving financial returns. | Status quo is financially beneficial for employers. | Incentive for an acceptable out-of-pocket payment | Not receiving any financial returns | Status quo is financially beneficial. |

*) The distribution of costs and financial benefits in which the costs as well as the financial returns are incurred by the same stakeholder incentivizes the financing and implementation of RTW. For stakeholders who receive financial benefits, but do not need to carry the costs, the current financing arrangement is very attractive. Thus, they do not have an interest in changing the financial structure. However, if they would need to take over (a part of) the financing, this would be acceptable. For stakeholders who need to carry the costs, but do not receive financial returns, an incentive to finance RTW does not exist, as they it will only cost them.
EU-countries
Eleven of the 40 questionnaires (28%) that were sent to cancer centres were returned (Belgium=1, England=2, France=1, Germany=2, Italy=3, Sweden=1, The Netherlands=1). Respondents included researchers, scientific directors, medical directors, a director of the psychosocial service, an HR-manager, and a social worker. In four of the six EU-countries included in this analysis, similar misalignments of costs and financial benefits as in the Netherlands were observed, as shown in Figure 4. The most beneficial situation for implementation of RTW-interventions is found in Germany and France. In Germany, the employers, health insurance, and pension insurance have financial incentives to support RTW, by being both responsible for financing RTW and receiving its financial benefits. In France this applies to employers and health insurers. In Belgium, the National Health Service in England, and the Netherlands patients/employees and one other stakeholder pay for and gain from RTW, while in Italy and Sweden the patients are the only stakeholders mentioned in both categories.
Budget impact analysis of return-to-work interventions

<table>
<thead>
<tr>
<th>Belgium</th>
<th>England</th>
<th>France</th>
</tr>
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<tbody>
<tr>
<td>Stakeholders, who:</td>
<td>Stakeholders, who:</td>
<td>Stakeholders, who:</td>
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<td>(Co-)</td>
<td>(Co-)</td>
<td>(Co-)</td>
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<tr>
<td>Pay</td>
<td>Pay</td>
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<tr>
<td>Do not</td>
<td>Do not</td>
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<tr>
<td>pay</td>
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</tr>
<tr>
<td>Benefit financially</td>
<td>Benefit financially</td>
<td>Benefit financially</td>
</tr>
<tr>
<td>HI, P, PI, S, E</td>
<td>P, E, HI, PI, S</td>
<td>HI, P, E, PI, S</td>
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<tr>
<td>Do not</td>
<td>Do not</td>
<td>Do not</td>
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<tr>
<td>benefit financially</td>
<td>benefit financially</td>
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<tr>
<td>HO</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Germany</th>
<th>Italy</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stakeholders, who:</td>
<td>Stakeholders, who:</td>
<td>Stakeholders, who:</td>
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<tr>
<td>(Co-)</td>
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<td>Pay</td>
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<td>Benefit financially</td>
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</tr>
<tr>
<td>E, HI, PI</td>
<td>P, PI, S</td>
<td>P, HI, S, E</td>
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<tr>
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<table>
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<tr>
<th>The Netherlands</th>
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<tr>
<td>Stakeholders, who:</td>
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<td>(Co-)</td>
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<tr>
<td>Pay</td>
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<tr>
<td>Benefit financially</td>
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<tr>
<td>Do not</td>
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<tr>
<td>benefit financially</td>
</tr>
</tbody>
</table>

Figure 4: Incentive in EU-countries for financing RTW for cancer patients.

HI=Health insurance, HO=Hospital or health care provider, E=Employer, S=State, PI=Pension insurance scheme, P=Patient / employee
The stakeholders placed in the framed square have a financial incentive for financing RTW interventions. The more stakeholders are placed in the framed square, the greater the incentives for implementing RTW are. If this is the patient / the employee, this is less
beneficial than when this is another stakeholder, as it is not feasible that the patients carry the costs for the intervention alone.

**Discussion**

From the Dutch societal perspective, the BI of the RTW-intervention for cancer survivors is negative, i.e. the RTW-intervention yields more financial benefits than it costs. The BI for cancer centres is high, as these mainly shoulder the costs of providing the intervention. The way in which costs and financial benefits in the Netherlands are allocated, leads to a disincentive to offer RTW-interventions for cancer survivors. Of the six countries included in the European comparison, only Germany and France provide a payment structure that rewards the provision of RTW by health care providers. In order to reduce the misalignment of costs and financial benefits in and outside the healthcare system and facilitate larger scale patient access, the payment and reimbursement structures need adjustment. For many countries, a more sustainable way of financing RTW may include shifting a larger share of the costs to employers or pension schemes, which primarily benefit financially from RTW-interventions. Alternatively within the current financing system, the intervention could be prescribed more selectively to patients at highest risk of not returning to work. In addition, the counselling by the occupational physician could possibly be prescribed as a monodimensional intervention, when this matches with the individual patient’s need. As the costs for the counselling make up 37% of the intervention costs, this would decrease the health care costs considerably for all stakeholders involved.

This study has some limitations; first, the potential overall health benefits of exercise programs, beyond returning to work, that may lead to lower future health care resource use are not included in the analysis. Thus, the cost savings of RTW-interventions are probably underestimated. Welfare benefits that are influenced by RTW, such as sick pay, and invalidity and retirement pension, have not been included due to a lack of data. This might also lead to an underestimation of the potential cost savings and precludes a quantification of the financial benefits of RTW to the state. Finally, while a healthcare system perspective is recommended for BI analysis, we deviated from this recommendation to show the relation between the intervention costs and the productivity gains that extend beyond the health care system.

Regarding transferability of the costs of the Netherlands to other countries, it can be noted that the intervention costs mainly consist of labor costs and thus depend on the
income level in the respective country. The number of patients who follow the intervention is a product of cancer incidence, the percentage of eligible patients, and capacity for treating patients. These would need to be adjusted to the respective country as well.

Moreover, the limitations of the data that was used for the productivity benefits which were derived from the study by Thijs et al.\(^{18}\) need to be mentioned. First, given the evidence for the effectiveness of exercise it was considered unethical to randomize patients. Thus, instead, an age-matched control group recruited in another hospital was used. Still, the baseline characteristics of both groups were comparable. Second, most of the participants, around 70\%, were breast cancer patients and around 80\% were female. This is an issue in cancer survivorship research in general\(^{20}\) but yields questions about the generalizability of the outcome. As breast cancer patients often are relatively young and have good treatment outcomes, they participate in intervention research more often than other groups. However, the criteria for being eligible for the intervention included treatment with curative intent and a treatment outcome that is sufficient for being able to return to work. Thus, this also is a selected group of cancer survivors, of which many might be breast cancer survivors, as these patients would fulfil these criteria more often than e.g. lung cancer patients. Therefore, and given the robustness of our findings against alternative effectiveness inputs (i.e. 5 times smaller), we consider it safe to conclude that the intervention is cost-saving for the general group of cancer survivors who are eligible for multidisciplinary return-to-work interventions.

In order to increase patient access to RTW-interventions, a consensus among stakeholders on how to arrange the financing of RTW-interventions needs to be found when the value of RTW-interventions is sufficiently demonstrated. For this purpose, more research is needed that assesses the effectiveness of RTW, and on the subgroups of patients who would benefit the most. Moreover, the value of the intangible benefits for the stakeholders and the intervention’s indirect benefits would need to be investigated to support this process.

**Conclusions**

This study analysed the BI of a multidisciplinary RTW-intervention for cancer survivors and explored the allocation of the costs and financial benefits of RTW across the stakeholders involved in six EU-countries. From the Dutch societal perspective, the productivity gains of the RTW-intervention outweigh the intervention costs by far.
However, the total healthcare costs are considerable and shouldered almost exclusively by health care providers. Therefore, the BI of RTW for cancer centres is very high and the current financing system does not provide the appropriate incentives for implementing RTW on a larger scale. A similar misalignment of financial incentives exists in other EU-countries, with only Germany and France providing an incentive for stakeholders to pay for RTW. To ensure patient access to RTW-programs, future investigations into the real-world effectiveness and societal impact of RTW-programs for cancer survivors are needed, as well as a consensus on how to fix the current financial misalignment.
References


Value of implementation analysis of strategies to increase the adherence of health professionals and patients to (the guidelines for) physical exercise for cancer survivors

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Submitted
Value of implementation analysis of strategies to increase the adherence of health professionals and patients to (the guidelines for) physical exercise for cancer survivors

Abstract

Background: In order to increase the adherence of health professionals and cancer survivors to guideline-recommended physical exercise, effective implementation strategies (ISTs) are required. As these have costs, it needs to be examined if these provide value for money and which has the highest value.

Methods: The net-benefit framework of health economic evaluations is used to conduct a value-of-information analysis of nine ISTs. Seven are directed on health professionals and two on cancer survivors. The analysis consists of four steps; (1) analysing the expected value of perfect implementation (EVPIM), which represents the maximum cost an implementation strategy may have in order to be cost-effective, (2) assessing the estimated costs of the various ISTs, (3) comparing the ISTs’ costs to the EVPIM to decide which of these are considered cost-effective, and (4) assessing the total net benefit of the ISTs, to identify which strategy has the greatest value.

Results: The EVPIM for physical exercise in the Netherlands is €293m. The total costs for the ISTs range from €34k for printed educational materials for professionals to €120.0m for financial incentives for patients, and thus all are well below the EVPIM. The total net benefit of the ISTs that are directed on professionals ranges from €5.7m for printed educational materials to €30.9m for reminder systems. Of the strategies that are directed on patients, only the motivational programme had a positive net benefit of €100.4m.

Conclusion: All but one IST have a positive total net benefit. The largest improvements in adherence were created by a motivational programme for patients, followed by a reminder system for professionals. Most ISTs that are directed at professionals lead to very small increases in adherence and thus only contribute partially to achieving the highest possible total net benefit. This suggests that it is most valuable to invest in increasing the adherence of patients by one of the most effective ISTs and to conduct further research into making the ISTs that are directed at professionals more effective.
Introduction

The evidence base on the effectiveness of physical exercise for cancer survivors (PE) is growing. It has been shown that exercise interventions are an effective way to alleviate late and long-term effects of cancer treatment, such as fatigue and health-related quality of life (hrqol)\textsuperscript{1-5}. Subsequently, PE is recommended for cancer survivors by professional organisations in various countries\textsuperscript{1-5}. However, the fact that a clinical guideline is developed and published does not mean that the adherence of professionals and patients to the recommendations is sufficient\textsuperscript{6-9}. In the Netherlands, a guideline on cancer rehabilitation was published in 2011 and recommends that all cancer survivors who have completed active curative treatment and are physically able should exercise, ideally by following an exercise intervention of at least moderate intensity\textsuperscript{2}. Still, only very few of the eligible cancer survivors are referred to PE. One of the reasons might be that the guideline is relatively new and not all professionals are yet aware of the possibilities. Of the survivors who are prescribed PE, only slightly more than half take part in at least three quarters of the sessions\textsuperscript{7, 10, 11}. Thus, efforts should be undertaken to increase the adherence of professionals to the guideline and of cancer survivors to the prescribed interventions, next to the general implementation of the guideline.

As costs are attached to implementation strategies (ISTs), it is worth to evaluate them on their cost-effectiveness before choosing which one to use. Although it is already relatively common to evaluate interventions on their cost-effectiveness, less so this is the case for efforts to enhance the implementation of clinical guidelines\textsuperscript{8}. However, as the ISTs, just like the intervention itself, require financial resources that could also be spent elsewhere, it should be evaluated if it is worthwhile to perform them\textsuperscript{9, 12, 13}. Therefore, the aim of this study is to analyse the total net benefit (TNB) of various ISTs for increasing adherence of health professionals to the exercise-recommendations of the rehabilitation guideline and of cancer survivors to their prescribed intervention, and to identify which IST is the most beneficial.

Methods

The analysis is based on the value-of-implementation framework of Fenwick et al.\textsuperscript{6} and Hoomans et al.\textsuperscript{8, 14} and consisted of the following steps:

(1) Analysing the expected value of perfect implementation (EVPIM).
(2) Assessing the costs of the ISTs under comparison.
(3) Comparing the ISTs’ costs to the EVPIM, in order to decide which of these forms a cost-effective way of spending implementation resources.
(4) Evaluating the ISTs that are cost-effective on their TNB, to identify which IST has the greatest value.

The methodology is described in detail elsewhere.\textsuperscript{6, 8, 13, 14}

**Intervention and patient description**

In this study, a standard exercise intervention used in cancer rehabilitation is evaluated. A typical average intervention duration is 12 weeks,\textsuperscript{15} with two weekly sessions of 90 minutes delivered by a physiotherapist to groups of six patients. The physiotherapist also conducts a 20-minute intake session and in-between consultation. The patients are adult cancer survivors, diagnosed with any type of cancer, who have completed active treatment. They experience at least one late or long-term symptom through cancer or cancer treatment that can be alleviated through exercising, such as fatigue, low quality of life, reduced physical fitness, or reduced physical functioning. The mean age is 58.\textsuperscript{16-19}

**1 Analysis of the expected value of perfect implementation (EVPIM)**

1.1 Analysis

The EVPIM is analysed using the net-benefit framework of health economic evaluation. The net benefit is deducted from the decision-rule for analysing whether an intervention is considered cost-effective based on the incremental cost-effectiveness ratio (ICER). The ICER expresses the additional cost of an intervention for gaining one additional unit of effectiveness, in comparison to usual care:\textsuperscript{20}

\begin{equation}
ICER = \frac{\Delta C}{\Delta E},
\end{equation}

with \( \Delta C \) being the incremental costs and \( \Delta E \) being the incremental effectiveness of the intervention.

An intervention is considered cost-effective when its ICER is lower than the willingness-to-pay, which is the maximum amount society is willing to spend for one additional quality-adjusted life year (QALY):

\begin{equation}
\Delta C + \Delta E < WTP
\end{equation}

Another way for deciding if an intervention is cost-effective given the willingness-to-pay is to analyse the intervention’s net benefit (NB). The net benefit expresses the value of the additional health benefit in monetary terms. To do so, the incremental effect is multiplied with the willingness-to-pay and the incremental costs are deducted. An
intervention is cost-effective at the chosen willingness-to-pay when the NB is at least zero\(^2\).

\[
NB = WTP \times \Delta E - \Delta C
\]

(3) \(NB \geq 0\)

The NB in health economic evaluation thus is similar to a NB in business administration, where it represents a monetary profit after all costs have been deducted from the revenue. However, as health does not have a market price or a price tag attached, in health economics the willingness-to-pay is used to determine what a QALY is worth.

Based on the NB, the EVPIM can be analysed. It represents the difference between the NB of the exercise intervention being implemented perfectly with 100% adherence and with adherence on the current level\(^6\). The total net benefit of the guideline in perfect use represents the NB of the clinical guideline extended over the yearly patient population for the time period in which it is used\(^3\):

\[
Net \ benefit \ of \ the \ clinical \ guideline \\
NB_{cg} = \Delta E_{cg} \times \lambda - \Delta C_{cg}
\]

(5)

\[
Total \ net \ benefit \ of \ the \ guideline \ in \ perfect \ use \\
TNB_{cg,\text{perfect}} = NB_{cg} \times d_{cg} \times spp
\]

(6)

\[
Total \ adherence \\
Adr = adr_{hp} \times adr_{pt}
\]

(7)

\[
Total \ net \ benefit \ of \ the \ guideline \ in \ current \ use \\
TNB_{cg,\text{current}} = TNB_{cg,\text{perfect}} \times adr
\]

(8)

\[
Expected \ value \ of \ perfect \ implementation \\
EVPIM_{cg,\text{current}} = TNB_{cg,\text{perfect}} - TNB_{cg,\text{current}}
\]

(9)

With:
\[
\Delta E_{cg} = \text{Incremental effectiveness of the clinical guideline} \\
\lambda = \text{Willingness-to-pay} \\
\Delta C_{cg} = \text{Incremental costs of the clinical guideline} \\
NB_{cg} = \text{Net benefit of the clinical guideline} \\
TNB_{cg,\text{perfect}} = \text{Total net benefit of the clinical guideline in perfect use} \\
d_{cg} = \text{Duration of guideline usage}
\]
Chapter 6

\[ s_{pp} = \text{Size of the patient population served} \]
\[ \text{adr} = \text{Total adherence} \]
\[ \text{adr}_{hp} = \text{Adherence by health professionals} \]
\[ \text{adr}_{pt} = \text{Adherence by patients} \]
\[ \text{TNB}_{cg,\text{current}} = \text{Total net benefit of the clinical guideline in current use} \]
\[ \text{EVPIM}_{cg,\text{current}} = \text{Expected value of perfect implementation} \]

If the EVPIM has a positive value it is cost-effective to use this amount to invest in implementation strategies that aim at improving the current level of implementation\textsuperscript{14}.

1.2 Data

The incremental effectiveness of PE for cancer survivors is based on the meta-analyses of Fong et al.\textsuperscript{22} and Mishra et al.\textsuperscript{15} These meta-analyses have included 34 and 33 randomized controlled trials, respectively, and found that physical exercise had a significant impact on health-related quality of life. From these, the studies in which the SF-36 questionnaire was used were identified\textsuperscript{16-19, 23, 24}, from which the corresponding EQ-5D-value can be deducted. This is done by first computing the mental and physical component scales (if not already stated in the paper) for the baseline and last follow-up measurement in the intervention and control groups, using the SF-36 manual and the Dutch reference scores\textsuperscript{25}. The algorithm by Ara and Brazier was used to derive the corresponding EQ-5D utility values\textsuperscript{26}. Then, the difference in EQ-5D score from baseline to the follow-up measurement is analysed per study for the intervention and control group. Afterwards, the difference in improvement between the intervention and control group is calculated per study. From these values, the weighed mean difference in the EQ-5D-value from baseline to follow-up is generated. To analyse the QALY-gain, this difference is multiplied by 5 years, as studies on the effect duration of PE with a long follow-up period found the effectiveness to last this long\textsuperscript{27-29}.

The intervention costs consist of costs for the physiotherapist for preparing and conducting all sessions and consultations, as well as of administrative costs. The intervention costs are assessed based on the intervention description and on previous research into the required time for the tasks\textsuperscript{30}. Health care costs include consultations and medication, and are based on previous research\textsuperscript{30}. The WTP is set at €30,000 for one additional QALY\textsuperscript{31} and the guideline’s duration is 5 years. The size of the patient population is assessed using the projections for 2015-2020 of cancer incidence in the Netherlands of the Dutch Cancer Society\textsuperscript{32}. It is assumed that 42% of all cancer survivors are eligible for PE. This percentage is based on the number of cancer patients who are
aged 20 and older (99%\textsuperscript{33}), an estimated percentage of patients that is able to follow an exercise intervention of 60%, and on 70% of these patients being willing to participate in the intervention.

The adherence of patients who have completed at least 75% of the prescribed exercise programme is 53%\textsuperscript{10}. The adherence of professionals to the guideline is assumed to be 5%. After the full implementation of the guideline, the adherence of health professionals is expected to rise to 85%. All data are given in Table 1.
Table 1: Data used in the analysis and results that are valid for all implementation strategies (up to equation 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variable name</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental effectiveness of the clinical guideline (additional quality-adjusted life years over the 5-year time horizon)</td>
<td>$\Delta E_{cg}$</td>
<td>0.0774 QALYs</td>
<td>Analysis based on Fong et al.\textsuperscript{22} and Mishra et al.\textsuperscript{15}</td>
</tr>
<tr>
<td>Willingness-to-pay</td>
<td>$\lambda$</td>
<td>€ 30,000</td>
<td>Assumption</td>
</tr>
<tr>
<td>Incremental costs of the clinical guideline (average per patient)</td>
<td>$\Delta C_{cg}$</td>
<td>€ 167</td>
<td>Calculated as described in the methods section</td>
</tr>
<tr>
<td>Net benefit of the clinical guideline</td>
<td>$NB_{cg}$</td>
<td>€ 2,155</td>
<td>Result of the analysis</td>
</tr>
<tr>
<td>Size of the patient population served</td>
<td>$s_{pp}$</td>
<td>49,767 patients</td>
<td>Calculated as described in the methods section</td>
</tr>
<tr>
<td>Duration of guideline usage</td>
<td>$d_{cg}$</td>
<td>5 years</td>
<td>Assumption</td>
</tr>
<tr>
<td>Total net benefit of perfect use of the clinical guideline</td>
<td>$TNB_{cg,\text{perfect}}$</td>
<td>€ 536,273,407</td>
<td>Result of the analysis</td>
</tr>
<tr>
<td>Adherence by professionals</td>
<td>$adr_{hp}$</td>
<td>85%</td>
<td>Assumption</td>
</tr>
<tr>
<td>Adherence by patients</td>
<td>$adr_{pt}$</td>
<td>53%</td>
<td>Adams et al., 2015\textsuperscript{10}</td>
</tr>
<tr>
<td>Adherence</td>
<td>$Adr$</td>
<td>45%</td>
<td>Result of the analysis</td>
</tr>
<tr>
<td>Total net benefit of current (or future) use of clinical guidance</td>
<td>$TNB_{cg,\text{current}}$</td>
<td>€ 243,414,499</td>
<td>Result of the analysis</td>
</tr>
<tr>
<td>Expected value of perfect implementation</td>
<td>$EVPIM_{cg,\text{current}}$</td>
<td>€ 292,858,907</td>
<td>Result of the analysis</td>
</tr>
<tr>
<td>Number of health professionals targeted per year</td>
<td>$N_{hp}$</td>
<td>650 professionals</td>
<td>Dutch Oncology Association\textsuperscript{34}</td>
</tr>
<tr>
<td>Number of patients targeted per year</td>
<td>$N_{pt}$</td>
<td>49,767 patients</td>
<td>Calculated as described in the methods section</td>
</tr>
</tbody>
</table>
2 Cost-assessment of the ISTs

2.1 The ISTs

The following strategies for further increasing adherence after the general implementation of the guideline are evaluated:

Directed at health professionals:

- a) Continuing education meetings and workshops (CME)
- b) Educational outreach visits (EOV)
- c) Printed educational materials (PEM)
- d) Local opinion leaders (LOPL)
- e) Audit and feedback (AF)
- f) Reminder systems (RS)
- g) A multifaceted strategy (MF) consisting of CME and AF

The multifaceted interventions for changing professional practice often are assumed to be more effective than single interventions\(^{35}\), although more recent reviews did not find evidence for this being the case\(^{36, 37}\). We included a multifaceted strategy in order to demonstrate the impact of combining two ISTs on the total net benefit.

Directed at patients:

- h) Motivational programme (MP)
- i) Financial incentives (FI)

See Table 2.

Table 2: Description and effectiveness of the implementation strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description of the strategy</th>
<th>Effectiveness (source, type of evidence, influence on adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directed at health professionals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Continuing education meetings and workshops</td>
<td>The most common form is an educational meeting, which includes various forms of courses and workshops. These meetings vary in their length, intensity, the number of participants, and its degree of interaction(^{36}). Used for the cost calculation: Two workshops of four hours length are provided to health professionals in their location by two staff. The average group size is ten participants.</td>
<td>Forsetlund et al., 2009(^{36}) Cochrance review, 6% RD (IQR 2.9% to 15.3%) (for dichotomous outcomes), 19 studies included, 21 comparisons</td>
</tr>
<tr>
<td>B. Educational outreach visits</td>
<td>Health professionals are visited in their own premises by a trained person. Aim of the visit is to inform health professionals with the objective of improving their behaviour(^{38}).</td>
<td>O’Brien et al., 2007(^{38}) Cochrance review,</td>
</tr>
<tr>
<td>Section</td>
<td>Description</td>
<td>Used for the cost calculation:</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>C. Printed educational materials</td>
<td>Printed educational materials are information provided in paper format, including articles published in journals, guidelines, and monographs. These can be sent by post or mail, be delivered in person, or made available in public, e.g. on the internet.</td>
<td>Three information mailings about the guideline are developed by a clinical researcher and sent in three mass mailings.</td>
</tr>
<tr>
<td>D. Local opinion leader</td>
<td>A local opinion leader is a person who is able to positively influence the behaviour of others. The local opinion leader is able to do so through being perceived as a credible person with authority, being very interconnected, and having a very influential position within a network.&lt;sup&gt;40&lt;/sup&gt;</td>
<td>The local opinion leaders conduct three tutorials of one hour length in groups of three at the premises of the health professionals.</td>
</tr>
<tr>
<td>E. Audit and feedback</td>
<td>It is measured how well health professionals adhere to a clinical guideline. Subsequently, they receive feedback on their level of compliance and it is assumed that they adapt their behaviour.&lt;sup&gt;41&lt;/sup&gt;</td>
<td>The audit and feedback is conducted individually with every oncologist. The intervention is delivered by a senior colleague. The audit sessions last 1.5 hours. Feedback is provided verbally in a one-hour session and an action plan is provided.</td>
</tr>
<tr>
<td>F. Reminder systems</td>
<td>Reminders systems are measures to support the memory of health professionals. The reminders can be delivered via computer software, in printed form, or by telephone.</td>
<td>The reminders are generated automatically through a computer system, but provided paper-based.</td>
</tr>
<tr>
<td>G. Multifaceted</td>
<td>This strategy consists of continuing medical education and audit and feedback combined.</td>
<td>Assumptions</td>
</tr>
</tbody>
</table>
Value-of-implementation analysis

### Strategy

#### Directed at patients

**H. Motivational programme**

- The motivation programme consists of 5 steps: (1) extensive counselling and information provision, (2) reinforcement techniques that pronounce the patients’ efforts, (3) setting up a “treatment contract” between the therapist and the patient, (4) asking patients to place the treatment contract in a prominent place in their home, (5) patients filling in an exercise diary.

**Friedrich et al., 1999**

- Randomized controlled trial with chronic low back pain patients, N=93, 81.8% versus 51% of the sessions were attended in the motivation + exercise group versus exercise only group.

**Used for the cost-calculation:**

- Three individual counselling sessions with a physiotherapist are provided. The treatment contract and exercise diary are discussed during these sessions. The reinforcement techniques are used during the exercise sessions and do not result in additional costs.

**I. Financial incentives**

- Financial incentives (cash or another reward that has a monetary value) are given to patients based on specified exercise behaviour.

**Mitchell et al., 2013**

- Meta-analysis with healthy adults, N=554

**Used for the cost-calculation:**

- Patients receive €30/week when they attend all scheduled exercise sessions in a given week.

RD = risk difference, IQR = interquartile range

### 2.2 Analysis

The costs of the ISTs are calculated as follows:

(10) \[ TC_{IST} = C_{dev} + (C_{per\_pat} \times N_p \times D_{a\_impl}) + (C_{per\_hp} \times N_{hp} \times D_{a\_impl}) \]

With:

- \( TC_{IST} \) = Total cost of implementation strategy
- \( C_{dev} \) = Costs of developing an implementation strategy
- \( C_{per\_pat} \) = Per patient costs of executing the implementation strategy targeted at patients
- \( N_p \) = Number of patients targeted per year
- \( D_{a\_impl} \) = Duration of active implementation
- \( C_{per\_hp} \) = Per patient costs of executing the implementation strategy targeted at health professionals
- \( N_{hp} \) = Number of health professionals targeted per year
2.3 Data
For the general implementation of the clinical guideline, a national project was required by the organisation that developed the guideline, which would costs €3.78m. The ISTs’ development costs include the costs for the researchers who are assigned with this task. For every IST it is analysed which actions are required to develop and execute the strategy. It is then assessed how much time is required by which type of staff for training and for executing the strategy, and which material, services, and/or travel and meeting costs are needed. Subsequently, the costs are assessed according to the Dutch manual for cost research.

3 Analysing if the ISTs are cost-effective
The total costs of the ISTs, as analysed in step 2, are compared to the EVPIM, which was analysed in step 1. If the total costs are lower than the EVPIM, the IST is considered cost-effective.

4 Analysis of the total net benefit of the ISTs
4.1 Analysis
The TNB of perfect use of the guideline is the value of the amount of health that is realised in the hypothetical situation that professionals and patients are 100% adherent. However, in the current situation the adherence is only 45%. The health gain produced by the guideline when the adherence is 45% expressed in monetary terms is the TNB of current guideline use. The potential TNB that can be realised by increasing adherence from 45% to 100% is expressed as the EVPIM. When an IST is effective in further increasing adherence up from 45%, it realises a part of the EVPIM; this part is the TNB of the IST. It is analysed using the following equations, which are adapted from Hoomans et al.

For ISTs directed at professionals:
(11) \[ \text{TNB}_{\text{IST}} = \text{TNB}_{\text{cg, perfect}} \times (\Delta \text{adr}_{\text{IST}} \times \text{adr}_{\text{pt}}) - \text{TC}_{\text{is}} \]

For ISTs directed at patients:
(12) \[ \text{TNB}_{\text{IST}} = \text{TNB}_{\text{cg, perfect}} \times (\Delta \text{adr}_{\text{IST}} \times \text{adr}_{\text{hp}}) - \text{TC}_{\text{is}} \]

With:
\( \text{TNB}_{\text{IST}} = \text{Total net benefit of the implementation strategy} \)
\( \text{TNB}_{\text{cg, perfect}} = \text{Total net benefit of the clinical guidance in perfect implementation} \)
Value-of-implementation analysis

\[ \Delta \text{adr}_{\text{IST}} = \text{Change in adherence caused by the IST} \]
\[ \text{Adr}_{\text{pt}} = \text{Adherence by patients} \]
\[ \text{Adr}_{\text{hp}} = \text{Adherence by health professionals} \]
\[ \text{TC}_{\text{IST}} = \text{Total cost of an implementation strategy} \]

With the TNB of the ISTs, the total net benefit of the clinical guideline plus the implementation strategy can be analysed.

\[
(13) \quad \text{TNB}_{\text{cg, current} + \text{IST}} = \text{TNB}_{\text{cg, current}} + \text{TNB}_{\text{IST}}
\]

With:
\[ \text{TNB}_{\text{cg, current} + \text{IST}} = \text{Total net benefit of the clinical guideline plus the implementation strategy} \]

4.2 Data

The change in adherence for the ISTs is taken from the literature, specifically from Cochrane reviews, a randomized controlled trial, and a meta-analysis\textsuperscript{36-44}. These included different kinds of health professionals and interventions, as data specifically for exercise and cancer survivors was not available. See Table 2.

5 Sensitivity analyses

In order to test the robustness of the results, sensitivity analyses are conducted. The effect on the results of changing the willingness-to-pay to €20,000/QALY and €50,000/QALY is analysed, as well as that of the ISTs’ costs and effect being halved or being 1.5 times as high.

Results

1 EVPIM

The pooled difference of the health-related quality of life as measured by the EQ-5D among the studies included in the meta-analyses was 0.015 (rounded) over 12 months. Over a time horizon of five years, this accrued to an expected incremental effectiveness of PE compared to usual care of 0.077 QALYs. The average intervention costs of PE were €221 per patient. The difference in health care costs between PE and usual care was €54. The total costs over the 5-year period were €2,327 for PE and €2,160 for usual
care, leading to incremental costs of €167 for PE. The total net benefit of the guideline was €2,155 per patient over the 5-year time horizon. This value represents the health gain caused by the guideline when one QALY is considered worth €30,000, taking into account the costs that were made for the exercise intervention.

The average annual patient population eligible for PE from 2015 to 2020 was 49,767. This led to a total net benefit of the clinical guideline in perfect use of €536m over the 5-year period. This is the value that would be achieved when every year, for five years, all 49,767 eligible patients have a health gain of 0.077 QALYs through participating in PE, when one QALY is worth €30,000 to society, taking into account the average incremental costs of €167 per patient.

The adherence of health professionals and patients combined to the clinical guidance in current use was 45%, as patients can only be compliant when they were prescribed the exercise intervention in the first place. The total net benefit of the clinical guidance on PE in current use was €243 million. This equals the monetary value of the QALY-gain that is achieved when not 100%, but only 45% adherence is achieved, with one QALY being worth €30,000 to society. The EVPIM over the 5-year period of guideline usage was €293m. This is the monetary value of the health benefit that could be achieved by increasing the adherence from 45% to 100%. See Table 1 for the results.

2 Costs of the implementation strategies

The development costs for the ISTs varied from €13k for printed educational material to €1.8m for the reminder system. The costs per professional for executing the ISTs ranged from €18 for printed educational material to €2,108 for the multifaceted strategy and from €160 for the motivational programme to €481 for financial incentives per patient. The total costs for the ISTs ranged from €34k for printed educational material to €120m for financial incentives. See Table 3 for the results.
Table 3: Input parameters and results for the implementation strategies

<table>
<thead>
<tr>
<th>Strategies directed at health professionals</th>
<th>Development cost of an implementation strategy</th>
<th>Costs for executing an implementation strategy per health professional/patient per year</th>
<th>Total costs of an implementation strategy</th>
<th>Change in adherence</th>
<th>Total net benefit of implementation strategy</th>
<th>Total net benefit of clinical guidance plus implementation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing educational meeting (CME)</td>
<td>33,654 €</td>
<td>1,033 €</td>
<td>705,302 €</td>
<td>0.06</td>
<td>16,476,898 €</td>
<td>259,891,397 €</td>
</tr>
<tr>
<td>Educational outreach visits (EOV)</td>
<td>13,376 €</td>
<td>916 €</td>
<td>609,096 €</td>
<td>0.05</td>
<td>13,709,404 €</td>
<td>257,123,903 €</td>
</tr>
<tr>
<td>Printed educational materials (PEM)</td>
<td>699,180 €</td>
<td>18 €</td>
<td>34,388 €</td>
<td>0.02</td>
<td>5,693,012 €</td>
<td>249,107,512 €</td>
</tr>
<tr>
<td>Local opinion leaders (LOPL)</td>
<td>806,532 €</td>
<td>1,238 €</td>
<td>934,996 €</td>
<td>0.09</td>
<td>24,838,304 €</td>
<td>268,252,803 €</td>
</tr>
<tr>
<td>Audit and feedback (AF)</td>
<td>733,686 €</td>
<td>1,075 €</td>
<td>756,236 €</td>
<td>0.03</td>
<td>7,834,864 €</td>
<td>251,249,363 €</td>
</tr>
<tr>
<td>Reminders systems (RS)</td>
<td>1,812,176 €</td>
<td>77 €</td>
<td>1,185,842 €</td>
<td>0.11</td>
<td>30,887,598 €</td>
<td>274,302,097 €</td>
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<tr>
<td>Multifaceted strategy (MF)</td>
<td>767,340 €</td>
<td>2,108 €</td>
<td>1,461,538 €</td>
<td>0.08</td>
<td>21,448,062 €</td>
<td>264,862,562 €</td>
</tr>
<tr>
<td>Strategies directed at patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motivational programme (MP)</td>
<td>34,506 €</td>
<td>160 €</td>
<td>39,962,821 €</td>
<td>0.31</td>
<td>100,433,556 €</td>
<td>343,848,056 €</td>
</tr>
<tr>
<td>Financial incentives (FI)</td>
<td>11,502 €</td>
<td>481 €</td>
<td>119,778,428 €</td>
<td>0.12</td>
<td>-67,129,786 €</td>
<td>176,284,713 €</td>
</tr>
</tbody>
</table>

3 Cost-effectiveness of the ISTs

The costs of all ISTs were well below the EVPIM of €293m. Thus, it would be worth investing in these strategies in order to realize at least part of the potential net benefit of the ISTs.
4 Total net benefit of the ISTs
The ISTs that are directed at professional added another 2% for printed educational material up to 11% for reminder systems to the current adherence. Of the ISTs that are directed at professionals, reminder systems had the highest TNB of €30.9m and printed educational material had the lowest with €5.7m. The ISTs directed at patients increased their current adherence by 31% through the motivational programme and by 12% through financial incentives. Of these, only the motivational programme had a positive TNB, which was of €100.4m. Financial incentives had a negative TNB of €-67.1m.
A positive TNB indicates that the monetary value attached by society to the health gain that is created by the IST is higher than the costs of the IST. However, it cannot be spoken of a cost-saving here, as a health gain cannot be sold, does not appear on someone’s balance sheets, and does not lead to actual cost-savings. It rather means that the costs of the strategy are higher than the monetary value that society places on the health gain that it produced.
The TNB of the clinical guideline plus the implementation strategy was positive for all ISTs and ranges from €249.1m for printed educational material to €343.8m for the motivational programme. All results are displayed in Table 3.

5 Sensitivity analyses
When the willingness-to-pay was reduced to €20,000/QALY, all ISTs that had a positive net benefit maintained this. With a willingness-to-pay of €50,000/QALY, the net benefits increased. When the total costs of the ISTs were halved, the net benefit was only influenced marginally, as the costs were very small in comparison to the net benefit. Thus, when costs were 1.5 times as high this only had a marginal effect on the results as well. Reducing the effectiveness of the ISTs by one half resulted in net benefits that were approximately half of what they were before, but all that were positive in the base case analysis maintained this. Subsequently, when the effect was 1.5 times larger, the net benefits increased even more. See Table 4.
Table 4: The total net benefit of the ISTs as a result of the sensitivity analysis [in €]

<table>
<thead>
<tr>
<th>Strategies directed at professionals</th>
<th>WTP: €20,000/QALY</th>
<th>WTP: €50,000/QALY</th>
<th>Total costs are halved</th>
<th>Total costs 1.5 times higher</th>
<th>Effect is halved</th>
<th>Effect is 1.5 times higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>CME</td>
<td>10,304,584</td>
<td>28,821,526</td>
<td>16,829,549</td>
<td>16,124,247</td>
<td>7,885,798</td>
<td>25,067,998</td>
</tr>
<tr>
<td>EOV</td>
<td>8,565,809</td>
<td>23,996,594</td>
<td>14,013,952</td>
<td>13,404,856</td>
<td>6,550,154</td>
<td>20,868,654</td>
</tr>
<tr>
<td>PEM</td>
<td>3,635,574</td>
<td>9,807,888</td>
<td>5,710,206</td>
<td>5,675,818</td>
<td>2,829,312</td>
<td>8,556,712</td>
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<tr>
<td>LOPL</td>
<td>15,579,833</td>
<td>43,355,245</td>
<td>25,305,802</td>
<td>24,370,806</td>
<td>11,951,654</td>
<td>37,724,954</td>
</tr>
<tr>
<td>AF</td>
<td>4,748,707</td>
<td>14,007,178</td>
<td>8,212,982</td>
<td>7,456,746</td>
<td>3,539,314</td>
<td>12,130,414</td>
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<tr>
<td>RS</td>
<td>19,365,945</td>
<td>53,930,903</td>
<td>31,480,519</td>
<td>30,294,677</td>
<td>14,850,878</td>
<td>46,924,318</td>
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<tr>
<td>MF</td>
<td>13,218,311</td>
<td>37,907,566</td>
<td>22,178,831</td>
<td>20,717,293</td>
<td>9,993,262</td>
<td>32,902,862</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategies directed at patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP</td>
</tr>
<tr>
<td>FI</td>
</tr>
</tbody>
</table>

WTP=Willingness-to-pay

Discussion

This study analysed the total net benefit of ISTs for increasing the adherence of health professionals to the cancer rehabilitation guideline on exercise and of cancer survivors to their prescribed exercise interventions. The EVPIM, i.e. the value that would be created by increasing adherence to the clinical guideline on exercise of professionals and to the prescribed exercise interventions by cancer survivors from the current 45% to 100% was very high, i.e. €293m over the 5-year period of guideline use. The total costs of the implementation strategies all were way below the EVPIM, and had costs between €34k for printed educational material and €120m for financial incentives. The net benefits ranged from €-67.1 for financial incentives to €100.4m for the motivational programme, with financial incentives being the only strategy that had a negative net benefit.

The results showed that all but one of the implementation strategies led to high TNBs and can thus all be recommended. Based on the net benefit, the motivational
programme for patients should be chosen. Although it has the highest costs, its effect is manifold higher than that of the remaining strategies. Of the strategies directed at professionals, reminder systems had the highest net benefit, but also very high costs. Thus, high up-front development costs are worth it when these lead to higher effectiveness in the long-run. However, high initial costs can be an issue when these cannot be covered. Therefore, although the motivational programme has by far the highest TNB it might not be the most feasible IST, due to the high costs. The same is true for reminder systems. Therefore, when resources are limited, the most feasible IST is local opinion leaders, which ranks third in the TNB, but has more acceptable costs. When time and money are scarce, even the cheapest strategy, printed educational materials, is preferable to not doing anything, as it resulted in a positive net benefit. The most critical is to conduct any of the strategies with a positive TNB at all in order to create a health benefit that otherwise would be forgone.

For strategies that are directed on increasing the adherence among patients, only two ISTs could be included. Several other studies and two reviews were identified that measured the effect of an adherence intervention in exercise. However, of these the data was not fully suitable: The interventions were not found to be effective, the study did not include a control group, did not measure adherence, had methodological shortcomings (not randomized, self-reported adherence, inadequate presentation of the results), or compared the effect of exercise plus the adherence intervention to doing-nothing, so that it was not possible to isolate the effect of the adherence intervention.

This study has a number of limitations that require mentioning them. First, the meta-analyses we used for deducting the effectiveness of physical exercise interventions for cancer survivors included studies of all types of cancer. However, most studies included only breast cancer survivors. This limits the generalizability of the results and is a general problem in the research on physical exercise for cancer survivors. Second, the data for the effectiveness of the intervention, as well as that of the implementation strategies, were derived from systematic reviews and meta-analysis that summarized the effect using a broad range of studies. The data thus does not represent the effectiveness of a very specific intervention or IST used, but that of the broader group this intervention or IST belongs to. Third, the literature used for the effectiveness of the ISTs shows that the effectiveness of ISTs is influenced by variables such as the intensity of the intervention, the credibility of the organisation who delivers the intervention, etc. Thus, depending on the specific intervention that is used, the effects on changing adherence differ. Finally, the literature data that was used for the effect of the ISTs on adherence is not based
specifically on cancer patients. It therefore needs mentioning that this study provides indications of what is possible with the evaluated ISTs, rather than exact results. However, the results were very clear in that the TNBs can be huge. Moreover, the sensitivity analysis showed that the outcomes of our analysis were robust to changes in the input parameters.

Although all but one IST led to a positive TNB, they only realized a small part of the EVPIM of €293m. Thus, there is a high potential for creating higher net benefits and more health by using more effective ISTs. Therefore, future research should concentrate on developing ISTs that more significantly improve adherence. In order to attain results that are more specific for exercise interventions for cancer survivors, more research should be conducted that analyses the effectiveness of implementation strategies for promoting adherence to cancer survivorship guidelines.

Conclusion

All but one of the evaluated implementation strategies had positive total net benefits for increasing the adherence of health professionals and patients. The greatest net benefits were achieved by a motivational programme for patients and a reminder system for health professionals. However, these also had the highest costs. The most feasible strategy is local opinion leaders, which had moderate costs and ranked third for the total net benefit. Most of the strategies directed at professionals only had a marginal contribution to achieving the highest possible value of implementation. Thus, in order to realize higher net benefits, further research into the effectiveness of the various implementation strategies for increasing compliance is needed.
References


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Value-of-implementation analysis
Discussion
Discussion

To date, many eligible cancer survivors do not have access to cancer rehabilitation interventions. One explanation of this insufficient response to unmet needs is the lacking reimbursement for the largest group of cancer survivors by health insurance. Therefore, the aim of this thesis was to expand the evidence base on the cost-effectiveness and budget impact of cancer rehabilitation interventions and to advance the methodology for evaluating multicomponent interventions on their cost-effectiveness. The following section presents the main findings of this thesis after which the implications for policy and practice, the methodological considerations, and the suggestions for future research are discussed.

Main findings

In chapter two, the literature on the cost-effectiveness of rehabilitation for cancer survivors and on the effectiveness of multidimensional cancer rehabilitation was systematically reviewed. The results showed that the evidence base on the cost-effectiveness of cancer rehabilitation for patients and survivors was rather small. When the interventions were found to be effective, they were also considered cost-effective or even cost-saving. The identified multidimensional rehabilitation interventions were effective, however, those studies that evaluated the effect of the multidimensional intervention compared to the single intervention found no additional benefit for the multidimensional interventions.

In chapter three, two interventions for alleviating treatment-induced menopausal symptoms in breast cancer patients, cognitive behavioural therapy and physical exercise, were evaluated on their cost-effectiveness. The interventions were compared to usual care and evaluated over a time horizon of five years. The ICER was €22,500 per QALY for cognitive behavioural therapy and €28,000 per QALY for physical exercise. Thus, both interventions were considered cost-effective at a prevailing threshold of €30,000 per QALY. The choice of the intervention can therefore be based on the individual preferences of the survivor.

Multicomponent interventions (MCI) are common in cancer rehabilitation, but a method to estimate their cost-effectiveness in comparison to the single components, when head-to-head studies do not exist, is lacking. Therefore, such an approach was
developed in chapter four. The approach explicitly is a pragmatic approach for use when a decision needs to be taken while full evidence is not (yet) available. It consists of six steps of which the first four lead to identifying the minimum effect that the MCI needs to attain in order to be considered cost-effective, given its costs and the willingness-to-pay for an additional unit of effectiveness. In step five, a qualitative but systematic assessment is made of how likely the MCI is to attain this effect size. Finally, the expected cost-effectiveness of the MCI can be compared to that of the single interventions. It can then be concluded which one should be adopted.

Chapter five presented the budget impact analysis of a multidisciplinary return-to-work intervention consisting of counselling sessions with an occupational physician and a supervised exercise programme. From the Dutch societal perspective, the intervention was cost-saving, as the productivity gains were much higher than the costs of the intervention. From the perspective of a hypothetical large cancer centre the budget impact was very high as most costs for the interventions are not reimbursed by health insurance. It was also analysed how the costs and financial rewards of providing return-to-work interventions were distributed among the involved stakeholders in several EU-countries. In most of them, the stakeholders paying for return-to-work interventions did not receive the financial benefits, which dis-incentivized their reimbursement.

In chapter six, an expected value of perfect implementation-analysis of strategies to further increase the adherence of professionals and patients to (the guideline on) physical exercise was conducted. Examples of such implementation strategies include audit and feedback, local opinion leaders, financial incentives provided to patients, or printed educational material. The expected value of perfect implementation, i.e. the health gains that are forgone by not increasing the adherence expressed in monetary terms, was €293m. All but one of the nine strategies had a positive net benefit and could therefore be recommended. The motivational programme for patients had the highest net benefit, followed by electronic reminders systems for professionals. The latter also had the largest development costs. Because currently only a small part of the full potential of exercise interventions is realised due to low adherence rates, further implementation and research efforts should concentrate on developing strategies that are more effective in increasing adherence.
Implications for policy & practice

Cost-effectiveness of cancer rehabilitation
The systematic review on the cost-effectiveness of cancer rehabilitation in chapter two found that effective interventions typically are cost-effective. Two interventions that were not evaluated on cost-effectiveness previously, cognitive behavioural therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients, were analysed in this thesis with the result that these also provide value for money. The same was found for eight of the nine implementation strategies that aim at increasing the adherence of patients and professionals to exercise interventions. From these results it can be concluded that cancer rehabilitation generally, when the interventions are effective and do not have unusually high costs, is cost-effective. Thus, the criterion of being cost-effective can be considered fulfilled and is an argument for providing access to cancer rehabilitation for all cancer survivors who have a need for it and to include it into the package of reimbursed care.

Implement comprehensive rehabilitation as stepped care
In this thesis, the separate rehabilitation interventions for cancer survivors were found to be cost-effective. However, what is required in order to provide suitable rehabilitation is not a fragmented implementation of separate interventions, but a thorough assessment of the individual patient’s need and a tailored rehabilitation programme that is available for all cancer survivors, irrespective of the location in which they are treated. As cancer survivors mostly suffer from several symptoms, many would benefit from a multicomponent programme. These may consist of various combinations of interventions, yet not all of these combinations have been evaluated on their cost-effectiveness. This especially seems important because it was found in chapter two that multicomponent interventions not always have an added benefit compared to a single intervention. However, evaluating all possible combinations of interventions on their cost-effectiveness neither is efficient nor necessary, as an incredible and unrealistic amount of research would need to be conducted in order to establish the required evidence. Moreover, this information would be of very limited benefit for decision-makers. The decision that needs to be taken is whether cancer rehabilitation should be provided as reimbursed care to survivors. This requires that individual treatment plans would generally be acknowledged. Therefore, it is advised that cancer rehabilitation is implemented and reimbursed, but multicomponent interventions should be provided to cancer survivors as stepped care.
This way, first, only one intervention is provided, which is targeted at the individual’s primary need and proven (cost-)effective. Afterwards, it is assessed whether the need for the second additional intervention is still existent and if so an additional intervention may be prescribed, and so on. By doing so, it is ensured that interventions are only used when patients have an indicated need, in which case it is likely that the intervention is effective and cost-effective for that patient. In cases where e.g. a hospital wishes to offer a certain intervention standardly as a multicomponent programme of which the cost-effectiveness is unknown, the approach developed in chapter four should be used. It can then be analysed if the intervention has the potential to be at least as cost-effective as the single intervention.

**Affordability**

For cancer rehabilitation, affordability might be an issue, due to the high number of survivors, which will continue to grow in the years to come. In chapter five, the budget impact of a multidisciplinary return-to-work intervention was analysed. It was found that the financial benefits in terms of productivity gains from survivors who are enabled to resume work earlier are so high, that the intervention has a negative budget impact, i.e. is cost-saving, from the societal point of view. As yet this is the only formally conducted budget impact analysis in cancer rehabilitation; no evidence exists on other interventions. However, it can be expected that other interventions are cost-saving as well: In chapter five, a more expensive intervention with average patient costs of €1,500 was evaluated. Other interventions evaluated in this thesis, such as physical exercise and cognitive behavioural therapy, have much lower average patient costs of less than €200. Thus, when these achieve the very small effect of enabling patients to resume work 6.7 hours earlier (i.e. €200 divided by productivity costs of €30 an hour), they already are cost-saving from a societal perspective. Next to productivity benefits, savings in terms of reduced future health care costs would be realised. For example, a physical exercise intervention improves health in general and reduces the risk for a cancer recurrence or a second cancer in addition to its primary effect of alleviating the symptoms for which it was prescribed. Considering the amount of costs that could be prevented (for example, one inpatient day in the hospital of €460 or in intensive care of €2,200, a visit to the GP of €30 or to the physiotherapist of €40, or an EC visit of €150), it is very likely that other rehabilitation interventions are cost-saving as well.

The problematic part of the affordability of cancer rehabilitation thus does not lie in the size of the budget impact on societal level, as the interventions might result in large cost-savings, but in the distribution of the costs and financial benefits, as was shown in
chapter five. Although cancer rehabilitation is assumed to be cost-saving from the societal perspective, this is not the case from the perspective of the stakeholders who pay for these interventions, such as hospitals. Therefore, the distribution of costs and financial benefits of the interventions should be adapted in order to make the financing of cancer rehabilitation more viable.

**Reimbursing cancer rehabilitation**

Based on the paragraphs above, it is recommended to implement guideline-recommended cancer rehabilitation, as it is cost-effective and is expected to be cost-saving from a societal perspective. In the long-run, implementing guideline-based cancer rehabilitation would lead to savings for the health insurances through better health of the survivors. From these savings, the costs for rehabilitation measures could be covered. However, the additional expenses occurring in the short-run need to be financed. Two possibilities exist; increasing the money that is coming in by raising the insurance premiums, or decreasing the money that is going out elsewhere. The latter option should be chosen as in the field of cancer care, possibilities for costs savings exist that would not lead to a lower quality of care. One example is introducing value based pricing, a payment mechanism in which drugs receive reimbursement based on their added benefit. Here, the benefit is defined much broader than in cost-effectiveness analysis. The drug is then priced accordingly. In addition, oncology is a field where overtreatment can be observed, especially for care at the end of life.

In cancer, it can be seen very clearly that the focus of where the money goes is misaligned. What is happening at the moment is that first, many resources are spent on detecting if people have cancer and subsequently on cancer treatment and cancer drugs that often are not cost-effective. In the following, cancer survivors have finished treatment and could go back to their previous lives. However, many of them experience symptoms that prevent that they can pick up their daily life again and resume work, although cost-effective interventions are available. Thus, after a huge amount has been spent on detecting and curing cancer, insufficient reimbursement limits access of survivors to effective and cost-effective care for their late and long-term symptoms, because these are considered too expensive. This calls for a major rethinking of where the available resources are spent on.
Methodological considerations

Throughout the chapters of this thesis, it was not always possible to take the heterogeneity among cancer survivors into account. Cancer survivors differ considerably in terms of cancer type, treatment received, treatment outcome, the phase of survivorship they are in, their age, their preferences for certain (forms) of interventions, etc.\textsuperscript{17} It is thus important that this heterogeneity is taken into account. This is especially relevant for the cost-effectiveness, as the more an intervention matches the patient’s needs, the more effective and therefore the more cost-effective it would be. Rather than finding “one-size-fits-all-approaches”, solutions for the specific subgroups need to be found.

In the systematic review in chapter two it was found that the trials evaluating the multidimensional interventions often include all types of cancer survivors, as long as they were suffering from at least any two symptoms of a list. Moreover, most studies had included a majority of breast cancer patients. The explanation probably is that breast cancer has a high incidence and that the patients are in a relatively good condition compared to other cancer types, which enables them more often to be physically able to take part in interventions\textsuperscript{18}. Therefore, the results of chapter two tell us which intervention on average has an effect in a broad patient group. But it does neither tell us if there were differences regarding the (cost-) effectiveness of the interventions depending on the subgroup, nor whether the patients’ needs were met.

For the models that were built in chapter five and six, data from the literature was used. This was the case in chapter five, for the effectiveness of the intervention. This again originates from a study which included a large majority of female and breast cancer patients\textsuperscript{19}. In chapter six, several studies from two meta-analyses were used for analysing the QALY-gain of exercise interventions. All but one of these included only breast cancer patients\textsuperscript{20, 21}. Therefore, it was not possible to draw conclusions specifically for certain subgroups of patients.

Suggestions for future research

Evaluate cancer rehabilitation as a whole

This thesis has provided evidence on the value for money of cancer rehabilitation, on the basis of which it is considered safe to conclude that it is cost-effective in most cases.
This is especially the case when the interventions are effective, when patients have a need for the specific intervention, and when the interventions are inexpensive, e.g. when they are provided as a group intervention. If the current evidence still would be considered insufficient for assuming that cancer rehabilitation in general is cost-effective, an economic evaluation of implementing the guideline as a whole, rather than of specific interventions, should be conducted. This would require a large research project in which the cost-effectiveness of the current situation in which only very few cancer survivors receive rehabilitation is compared to that in which all cancer patients are treated according to the guideline. This would be much more valuable than evaluating the separate interventions, as the decision that needs to be taken is whether to reimburse cancer rehabilitation in general. The intention of the Dutch guideline is that for every patient the rehabilitation need is assessed. If the patient requires rehabilitation, a tailored programme is prescribed. This, however, is only possible when all kinds of interventions are available. Otherwise, the ability of the physician to prescribe the most suitable programme for the patient, taking into account the patient’s preferences, would be limited. Moreover, the differences in the costs and cost-effectiveness of the various interventions in cancer rehabilitation are so small that it is inefficient to conduct thorough research projects and take reimbursement decisions for every single one of them.

Explore the possibilities of e-health interventions

A new form in which cancer rehabilitation can be provided is e-health. It could make cancer rehabilitation accessible for patients who live far away from treatment facilities or have limited transportation means. Also, many cancer survivors would prefer to not visit the hospital again for rehabilitation. Within the A-Care2-Move project, of which this research is part of, three IT-interventions were developed; (1) an interactive internet portal that aims to empower cancer survivors by improving their skills to cope with the disease, by providing knowledge on lifestyle changes that can positively influence the patient’s health status, and by increasing their motivation, (2) a telemonitoring device that supports patient in spreading their energy for activities throughout the day, and (3) a web-based exercise programme which patients can follow from home. Providing interventions as e-health might also reduce costs. However, previous research has shown that it is unclear if cost-savings are realised or if e-health adds costs by forming an addition to current health services rather than a replacement. It therefore needs to be carefully analysed which e-health solutions in cancer rehabilitation can improve the provided care and are at least as cost-effective as the standard
interventions. In the interpretation of the results of a cost-effectiveness analysis of the telemonitoring device and the web-based exercise programme it should be taken into account that for patients who are not mobile or live far away from a hospital that offers such an intervention, these might be the only possibilities to follow rehabilitation interventions.

**Implementation of cancer rehabilitation**

The analysis of the net benefit of implementation strategies for exercise interventions in chapter six showed that their effect on improving the adherence of health professionals was very small, between two and eleven per cent, which leaves a large potential for improvement. Thus, even when investing in these implementation strategies, only a small part of the potential health gains would be realized. It is therefore crucial to investigate and develop more effective implementation strategies. During the last years, many articles were published that analysed the association between patient characteristics and exercise adherence\(^{27, 28}\). From these, interventions should be developed and evaluated on their effectiveness, in order to identify more effective implementation strategies. These also have the potential to further increase the cost-effectiveness of exercise interventions, as these are most beneficial for those patients not contemplating exercise as yet, and when the cancer survivors participate in as many sessions as possible.

**Conclusion**

This thesis has set out to analyse the cost-effectiveness and budget impact of cancer rehabilitation interventions and strategies to implement these. From the results it can be concluded that cancer rehabilitation is very likely to be cost-effective from a societal perspective. As multicomponent interventions are not expected to always be cost-effective, these should be implemented as stepped care or be evaluated on their estimated cost-effectiveness using the approach that was developed in this thesis. Based on this thesis’ results, cancer rehabilitation can also be considered affordable, and most interventions are expected to even be cost-saving. Therefore, it is highly recommended to include cancer rehabilitation into the package of reimbursed care. However, the cost-savings that would be realised in the long-run still would need to be financed in the short-run.
References


Discussion
Summary
Summary

Introduction
As the incidence of cancer is rising and more patients survive their disease, the number of people within the population who have a history of cancer is rising. The expected number for the Netherlands was 690,000 for 2015 and is supposed to have doubled since the year 2000. Unfortunately, most cancer survivors experience bothersome late and long-term symptoms, such as fatigue, low physical functioning, low quality of life, depression, anxiety, cognitive limitations, and pain. These prevent many of them from returning to their previous daily lives and often from returning to work. In order to alleviate the symptoms, survivors can follow a rehabilitation programme. However, these are not implemented widely. A major obstacle in the further implementation of cancer rehabilitation is the limited reimbursement by health insurance.

As the pressure on the health care budget is high, health services that are added to the Dutch health insurance scheme are assessed on their cost-effectiveness and affordability, next to the criteria of being necessary and effective. At the start of this research, the evidence base on the cost-effectiveness of cancer rehabilitation was very small. Therefore, the aim of this thesis was to increase the evidence base on the cost-effectiveness and budget impact of cancer rehabilitation.

Chapter 2: Systematic literature review
In order to analyse what is already known and what the gaps in the evidence-base are, a systematic literature review was conducted on two topics; the effectiveness of multidimensional rehabilitation interventions for cancer survivors, consisting of at least two interventions, and the cost-effectiveness of rehabilitation interventions for cancer survivors and patients. On the effectiveness of multidimensional interventions, 16 articles could be included. Except for one study, significant improvements were found in the intervention groups, mostly for the outcomes fatigue, physical functioning, muscle strength, and energy levels. Interestingly, the articles that compared the effect of a multidimensional programme to one of the included single interventions did not find an additional effect for the multidimensional programme. On the cost-effectiveness of rehabilitation interventions six studies were included. The interventions were inexpensive, as the average costs per patient ranged from €19 to €793. All interventions that were effective had favourable ICERs of €-17,000 (indicating cost-savings) to €11,000.
per QALY. It was concluded that in the evaluation of multidimensional interventions it is important to compare these against doing-nothing and to the included single interventions, in order to identify if adding more components also results in higher effectiveness. This is especially important as adding more components in the majority of cases results in higher costs. When mono-disciplinary cancer rehabilitation interventions are effective, they have a great potential for being cost-effective.

Chapter 3: Cost-effectiveness analysis of interventions to alleviate treatment-induced menopausal symptoms
Many breast cancer patients experience early, treatment-induced menopausal symptoms caused by cancer treatment. Two promising non-pharmacologic treatment options for this patient-group are cognitive behavioural therapy (CBT) and physical exercise (PE). The aim of chapter four was to evaluate these on their cost-effectiveness. The cost-effectiveness was evaluated from the Dutch health care perspective over a 5-year time horizon, comparing both interventions against usual care using a Markov model. The main outcomes were incremental treatment costs per significant reduction in endocrine symptoms and incremental treatment costs per QALY. The interventions were inexpensive, with costs of €190 for CBT and €197 for PE. The incremental costs for achieving a significant improvement in endocrine symptoms were €1,100 for CBT. PE was less effective than usual care. The ICER for CBT was €22,000 per QALY for CBT and €28,100 per QALY for PE. Thus, both interventions were cost-effective at a commonly accepted threshold of €30,000 per QALY. The conclusion of the analysis was that CBT is likely to be the most cost-effective intervention of the two. However, as CBT as well as PE are effective and cost-effective at the €30,000/QALY-threshold, both can be recommended. Thus, the choice for an intervention should be taken together with the patient and take into account his or her preferences.

Chapter 4: An approach for estimating if multicomponent interventions are cost-effective
For multicomponent interventions (MCIs), evidence of their added effectiveness over one of the included single interventions often is not available, which prohibits an economic evaluation with the standard methods. Therefore, the aim of chapter four was to develop a pragmatic approach that allows estimating if a multicomponent intervention is more cost-effective than the included single interventions in the absence of full data on costs and effects. First, the literature was reviewed for methods that aim at solving similar methodological problems. Second, the requirements that the
approach had to fulfil were identified by analysing the Dutch cancer rehabilitation guideline. Third, it was analysed which of the identified methods from the literature fulfilled the criteria. This applied to one approach, which subsequently was developed further into a fully suitable approach.

In the literature that was reviewed, six methods could be identified. These had to fulfil the following criteria: being able to estimate the cost-effectiveness of the single interventions vs. that of the MCI within a reasonable time frame, being able to estimate (cost-) effectiveness in the absence of full data, and being able to take into account carry-over and interaction effects. The only method that fulfilled all three criteria was headroom analysis, which was developed further into a fully suitable approach. The final approach starts by analysing the costs of all interventions, setting the willingness-to-pay, and choosing a common outcome measure for which the analysis is conducted. Subsequently, the minimum required effect for the MCI in order to be cost-effective, given its costs and the willingness-to-pay, is determined by headroom analysis. In the following, a qualitative but systematic assessment is conducted of how likely the MCI is to attain the minimum required effect. Finally, the MCI’s likelihood for being cost-effective is compared to the cost-effectiveness of the single interventions, which allows choosing which intervention is estimated to be the most cost-effective.

The approach was explicitly designed for use by decision-makers and hospitals for conducting a pragmatic and practical assessment that can be conducted within a short time frame and without advanced health economic expertise.

Chapter 5: Budget impact analysis of a multidisciplinary return-to-work intervention

As resuming work often is a very difficult process for cancer survivors, return-to-work interventions are designed to support them in this step. However, it is not clear whether these are affordable. Therefore, the first aim of chapter five was to analyse the budget impact of multidisciplinary return-to-work interventions. The second aim was to analyse the distribution of the costs and financial benefits of the intervention for several EU-countries, as this was expected to be an obstacle towards the implementation.

In the budget impact analysis the situation in which return to work is gradually implemented over 5 years from 2015 to 2020 was compared to the current situation. The analysis was conducted from the Dutch societal perspective and from that of a hypothetical large cancer centre. It is assumed that the intervention enables the participants to work 5.8 hours more per week than in usual care and that 12% of all cancer patients who are diagnosed per year are eligible for the intervention. For analysing the distribution of the costs and financial benefits of the multidisciplinary
return-to-work intervention among the stakeholders, a survey was conducted among the members of the Organisation of European Cancer Institutes. The average costs of the intervention were €1,500 per patient. From the Dutch societal perspective, the budget impact in 2020 would be €-71.1m. This indicated that the intervention is highly cost-saving, as the productivity benefits outweighed the costs. For a hypothetical cancer centre, the budget impact would be €1.1m in 2020, since for most participants the costs are not reimbursed. The results from the questionnaire showed that in most countries, a disincentive to provide reimbursement for return-to-work interventions existed. In order to make the implementation more viable, the misalignment of costs and financial benefits needs to be solved.

Chapter 6: Value of implementation analysis

As not all professionals are adherent to diagnosing and prescribing physical exercise as recommended by the Dutch cancer rehabilitation guideline, and as survivors who are prescribed an exercise intervention often only have an average compliance, implementation strategies (ISTs) to further increase adherence are needed. The aim of chapter six was to evaluate several ISTs on their total net benefit.

In four steps, seven ISTs directed at health professionals and two directed on patients were evaluated by (1) analysing the expected value of perfect implementation (EVPIM) that represents the maximum cost an IST may have in order to be considered cost-effective, (2) assessing the costs of the ISTs, (3) comparing the ISTs’ costs to that of the EVPIM in order to determine if these are cost-effective, and (4) evaluating the ISTs on their total net benefit (TNB) to identify which of them has the greatest value.

The EVPIM, the value that would be realised by increasing the adherence from the current level of 45% to 100% was high, with €293m over the 5-year period of guideline use. The costs of the ISTs ranged from €34k for printed educational materials to €120m for financial incentives for patients. Thus, all strategies could be considered cost-effective. The TNB of the strategies was lowest for printed educational materials with €5.7m and highest for a motivational programme for patients with €100.4m and a reminder system for professionals with €30.9m. Only financial incentives for patients had a negative TNB.

Based on the results, all ISTs, apart from financial incentives for patients, can unrestrictedly be recommended. The ISTs with the highest net benefits, the motivational programme and the electronic reminder system, also had the highest costs, which showed that large initial investments are worth their costs.
Discussion and conclusion

The results of this thesis showed that rehabilitation for cancer survivors in general can be assumed to be cost-effective. The interventions are relatively inexpensive with average per patient costs ranging from €190 to €1,500 for the typical interventions. Thus, when they are effective the chances are high that they also are cost-effective. When survivors are prescribed more than one intervention, in the absence of evidence of that multicomponent intervention’s cost-effectiveness, the intervention should be provided in the form of stepped care. The reason here fore is that multicomponent interventions were found to not always be more effective than a single intervention. However, costs often do increase, which leads to lower cost-effectiveness overall. Another option is to conduct a comparison of the multicomponent intervention’s cost-effectiveness against that of the single intervention using the approach that was developed in this thesis.

Considering the affordability of cancer rehabilitation, a multidisciplinary return-to-work intervention was found to be highly cost-saving in this thesis. Thus, rather than adding costs, the intervention saves costs from a societal point of view. As it is expected that other interventions, such as exercise, lead to savings in terms of productivity gains and reduced future health care costs as well, it can be expected that these also are highly affordable to society. Thus, the criteria of being cost-effective and affordable that are required for reimbursed health services can be considered fulfilled.

Still, an issue in the financing and further implementation of cancer rehabilitation interventions is the misalignment of their costs and financial benefits among the stakeholders. Financing interventions, especially return-to-work programmes, would become much more feasible when employers and pension funds would take a share of the costs, as these benefit the most when their employees/clients resume work faster. Although being expected to be cost-saving in the long-term, adding cancer rehabilitation into the insurance scheme would result in increased expenses in the short-run. Rather than increasing health insurance fees, cost-savings elsewhere in the field of cancer can be realised. Possibilities lie, for example, in the policy for reimbursing expensive cancer drugs. A re-thinking and societal and political debate about where the available resources should be spent on would need to take place in order to maximize the health gain that can be achieved with the available resources.
Samenvatting
Nederlandse samenvatting

Doordat de incidentie van kanker stijgt en steeds meer kankerpatiënten hun ziekte overleven neemt het aantal ex-kankerpatiënten binnen de bevolking toe. Naar schatting zijn dit 690.000 mensen in 2015, wat een verdubbeling sinds het jaar 2000 betekent. Helaas ervaren veel ex-kankerpatiënten na afloop van de behandeling late en lange-termijn symptomen die door de ziekte zelf of door de behandeling zijn veroorzaakt, zoals vermoeidheid, slecht fysiek functioneren, lage kwaliteit van leven, depressie, angststoornissen, cognitieve problemen en pijn. Hierdoor kunnen veel patiënten niet terugkeren naar hun dagelijks leven van voor de ziekte en lukt het hen vaak niet om het werk weer op te pakken. De symptomen kunnen goed verholpen worden door revalidatie, alleen zijn revalidatieprogramma’s voor ex-kankerpatiënten nog weinig beschikbaar. Omdat deze maar zelden door de zorgverzekeringen vergoedt worden verloopt de implementatie ervan moeizaam. Doordat de zorgkosten de laatste jaren snel gestegen zijn, moet zorg die in Nederland vanuit het basispakket vergoed wordt aan vier criteria voldoen. De zorg moet (1) nodig en (2) effectief zijn, maar ook (3) kosteneffectief en (4) betaalbaar zijn. Over de kosteneffectiviteit en betaalbaarheid van kankerrevalidatie was weinig bekend. Daarom was het doel van dit proefschrift om de kosteneffectiviteit en de budget impact van kankerrevalidatie te onderzoeken.

Hoofdstuk 2: Systematische literatuurreview

In dit hoofdstuk werd een systematische literatuurreview uitgevoerd waarin het bestaande onderzoek over twee onderwerpen samengevat en geanalyseerd is; de effectiviteit van multidisciplinaire revalidatie-interventies voor ex-kankerpatiënten en de kosteneffectiviteit van kankerrevalidatieinterventies voor (ex-)kankerpatiënten. Met betrekking tot de effectiviteit van multidisciplinaire interventies werden 16 geschikte studies gevonden. Afgezien van één studie lieten alle onderzoeken significante verbeteringen in de interventiegroep zien, in het bijzonder voor vermoeidheid, fysiek functioneren, spierkracht, en energielevels. Interessant is dat in de weinige studies waarin multidisciplinaire interventies vergeleken werden met monodisciplinaire interventies, er voor eerstgenoemde geen toegevoegde waarde gevonden werd. In het tweede gedeelte over de kosteneffectiviteit van kankerrevalidatie werden zes geschikte studies geïncludeerd. De kosten per interventie waren met €19 tot €793 redelijk laag. Alle effectieve interventies hadden een acceptabele incrementele kosteneffectiviteitsratio (ICER) tussen €-17.000 (wat een kostenbesparing betekent) en €11.000 per quality-
adjusted life year (QALY). Uit de review kwam naar voren dat het erg belangrijk is dat multidisciplinaire interventies met de aparte interventies waaruit ze bestaan vergeleken worden, om er op die manier achter te komen of de multidisciplinaire interventie daadwerkelijk een toegevoegde waarde heeft. Dit is bijzonder belangrijk omdat het toevoegen van een interventie aan al bestaande interventies in de meeste gevallen ook hogere kosten met zich meebrengt. Vanwege de lage interventiekosten is de kans groot dat, wanneer kankerrevalidatie effectief is, de interventie ook kosteneffectief is.

**Hoofdstuk 3: Kosteneffectiviteitsanalyse van cognitieve gedragstherapie en beweging**

Veel borstkankerpatiënten komen door hun behandeling vervroegd in de overgang en ervaren de daarmee gepaard gaande klachten, zoals hitteaanvallen en nachtzweten. Twee veelbelovende interventies voor deze patiëntengroep zijn cognitieve gedragstherapie (CGT) en beweging. Het doel van dit hoofdstuk was om deze twee interventies op hun kosteneffectiviteit te evalueren. Dit werd gedaan vanuit het perspectief van de Nederlandse gezondheidszorg over een tijdshorizon van vijf jaar, in vergelijking met een wachtlijstcontrolegroep. De uitkomstmaten waren onder andere incrementele zorgkosten per significante reductie in endokriene symptomen en incrementele kosten per QALY. De interventies hadden gemiddelde kosten per deelenemer van €190 voor CGT en €197 voor beweging. De incrementele kosten voor een significante reductie in de endokriene klachten waren €1.100 voor CGT. Voor deze klachten was beweging minder effectief dan de controlegroep. De ICER voor CGT en beweging bedroeg respectievelijk €22.000 en €28.100 per QALY. Beide interventies werden daarom kosteneffectief geacht bij een gebruikelijke drempelwaarde van €30.000 per QALY. Het is aan te bevelen de interventiekeuze ook op de preferenties van de patiënt te baseren.

**Hoofdstuk 4: Ontwikkeling van een benadering om multidisciplinaire interventies op kosteneffectiviteit te onderzoeken**

De toegevoegde waarde van een multicomпонентенинтервени у (MCI) ten opzichte van een mono-disciplinaire interventie is vaak onbekend, waardoor de standaardmethoden voor economische evaluatie niet gebruikt kunnen worden. In hoofdstuk 4 werd een methode ontwikkeld waarmee de kosteneffectiviteit van een MCI in vergelijking met een monodisciplinaire interventie op een pragmatische manier geschat kan worden. In een eerste stap werd de literatuur doorzocht naar methoden die soortgelijke beslisproblemen proberen op te lossen. Dit leverde zes methoden op. Om de criteria waaraan de methode moest voldoen vast te stellen werd de richtlijn voor oncologische
revalidatie geanalyseerd. Deze criteria waren: (1) in staat zijn om de kosteneffectiviteit binnen een redelijke tijdsperiode te schatten, (2) in staat zijn om de kosteneffectiviteit te schatten wanneer niet alle data beschikbaar is, en (3) in staat zijn om met carry-over en interactie-effecten rekening te houden. Vervolgens werd gekeken welke van de gevonden methoden aan deze criteria voldeden. Dit was het geval voor één methode—headroom analysis—die verder werd ontwikkeld, totdat ze helemaal geschikt was om het beslisprobleem op te lossen.

In de uiteindelijke methode worden als eerste de kosten van alle interventies in kaart gebracht. De betalings-bereidheid moet worden gekozen, alsmede één uitkomstmaat die voor alle interventies gebruikt wordt. Middels headroom analysis wordt het minimaal nodige effect dat de MCI moet halen om kosteneffectief te zijn vastgesteld, gegeven de kosten en de betalingsbereidheid. Vervolgens wordt een systematische, qualitative inschatting gemaakt van de waarschijnlijkheid dat de MCI dit effect bereikt. Aan het eind wordt deze waarschijnlijkheid vergeleken met de kosteneffectiviteit van de aparte interventies en kan geconcludeerd worden welke interventie volgens de schatting het meest kosteneffectief geacht wordt.

Deze methode is expliciet ontwikkeld voor het gebruik door beleidsmaker en ziekenhuizen. Deze kunnen hiermee op een pragmatische en praktische manier, binnen een korte tijdsperiode, een analyse uitvoeren die geen hele specifieke gezondheidseconomische expertkennis vereist.

**Hoofdstuk 5: Budget impact-analyse van een multidisciplinaire werkhervattings-interventie**

Omdat het veel ex-kankerpatiënten niet lukt om naar het werk terug te keren zijn er werkhervattings(RTW)-interventies ontwikkeld die patiënten hierin ondersteunen. Helaas is het onduidelijk in hoeverre deze betaalbaar zijn. Daarom was het eerste doel van dit hoofdstuk om dit middels een budgetimpactanalyse te onderzoeken. Omdat verwacht werd dat de verdeling van de kosten en financiële baten van de interventies tussen de betrokken stakeholders ongelijk is, was het tweede doel om dit voor een aantal Europese landen in kaart te brengen.

De multidisciplinaire RTW-interventie bestond uit counseling met een bedrijfsarts en beweging. De situatie waarin de interventie gradueel werd ingevoerd over vijf jaar (2015-2020) werd vergeleken met de huidige zorg. De analyse werd uitgevoerd vanuit het perspectief van de Nederlandse maatschappij en een groot fictief kankercentrum. Om de verdeling van de kosten en financiële baten van de interventie tussen de
stakeholders in kaart te brengen werd een enquete gehouden onder de leden van de Europese Organisatie van Kankercentra. De gemiddelde interventiekosten waren €1.500 per deelnemer. Vanuit het Nederlands maatschappelijk perspectief zou dit leiden tot een budget impact van €-71,1m. Dit betekent dat kosten bespaard worden omdat de toename in productiviteit meer dan opwekte tegen de interventiekosten. Omdat de kosten voor een groot gedeelte van de deelnemers niet vergoed worden, ontstaan er voor een fictief groot kankercentrum in 2020 kosten van €1,1m. De uitkomsten van de enquete lieten zien dat in de meeste landen een negatieve prikkel bestaat voor het uitbreiden van de interventie. Om de implementatie en vergoeding haalbaarder te maken is het daarom aan te raden de kostenverdeling te veranderen.

Hoofdstuk 6: Value of implementation-analyse
Het feit dat in Nederland een richtlijn voor o.a. beweging in het kader van oncologische revalidatie gepubliceerd werd betekent niet automatisch dat ex-kankerpatiënten die ervoor in aanmerking komen ook een bewegingstransitie voorgeschreven krijgen of dat de deelnemers volgzaam zijn aan de interventie. Het doel van hoofdstuk zes was om een aantal implementatie-strategieën (ISTs) die ervoor moeten zorgen dat de volgzaamheid van artsen en ex-kankerpatiënten omhoog gaat te onderzoeken op hun net benefit. Dit werd gedaan in vier stappen: (1) een analyse van de expected value of perfect implementation (EVPIM) die de waarde uitdrukt die behaald zou worden bij 100% volgzaamheid van professionals en patiënten, (2) het vaststellen van de kosten van de ISTs, (3) het vaststellen of de ISTs kosteneffectief zijn, en (4) het evalueren van de ISTs op hun total net benefit (TNB) om vast te stellen welke strategie het meest waardevol is. De TNB is de waarde die gecreëerd wordt door de IST door middel van het verhogen van de volgzaamheid. De EVPIM was hoog; €293m over de 5-jaarsperiode die in de richtlijn gebruikt wordt voor een jaarlijks aantal van 50.000 patiënten. De kosten voor de ISTs lagen tussen €34k voor geprint educatiemateriaal en €120m voor financiële prikkels voor patiënten. Daarom konden alle strategieën als kosteneffectief worden beschouwd. De TNB van de ISTs was het laagst voor het geprint educatiemateriaal en het hoogst voor een motivatieprogramma voor patiënten met €100,4m, gevolgd door een software-herinneringssysteem voor professionals met €30,9m. De ISTs met de hoogste waardes, het motivatieprogramma en het herinneringssysteem, hadden tegelijkertijd ook de hoogste kosten. Dit laat zien dat de duurdere ISTs hun geld waard zijn.
Discussie en conclusie

Op basis van de resultaten uit dit proefschrift kan ervan uitgegaan worden dat kankerrevalidatie kosteneffectief is. Met gemiddelde kosten per persoon van €190 to €1.500 voor de typische interventies zijn deze relatief goedkoop. Er kan geconcludeerd worden dat wanneer een interventie effectief is, deze met hoge waarschijnlijkheid ook kosteneffectief is. Voor multidisciplinaire interventies geldt dit niet, omdat deze niet altijd effectiever zijn dan monodisciplinaire interventies, maar meestal wel hogere kosten hebben. Daarom wordt aangeraden om multidisciplinaire interventies in de vorm van stepped care aan te bieden of deze voor de invoering op kosteneffectiviteit te onderzoeken door middel van de methode die in dit proefschrift zijn ontwikkeld. Wat betreft de betaalbaarheid van kankerrevalidatie kan gesteld worden dat in ieder geval de hier geëvalueerde interventie, multidisciplinaire werkhervatting, zichzelf meer dan terugverdient vanuit het maatschappelijk perspectief. Dit wordt ook voor andere interventies verwacht, zoals beweegprogramma’s, omdat deze ook kunnen leiden tot een snellere terugkeer naar werk en tot het voorkomen van toekomstige zorguitgaven. Daarom kan geconcludeerd worden dat in het geval van revalidatie voor ex-kankerpatiënten aan de criteria van kosteneffectiviteit en betaalbaarheid voldaan is. Wat betreft de implementatie ervan bestaan er negatieve prikkels voor de betrokken stakeholders in het financieren van de interventies, wat een obstakel vormt voor verdere implementatie. Daarom is het nodig om de financieringsstructuur zodanig aan te passen dat ook werkgevers en pensioenfondsen meebetalen, wat zou leiden tot een evenredigere kosten- en batenverdeling. Ook al wordt verwacht dat de brede invoering van kankerrevalidatie leidt tot kostenbesparingen op de lange termijn, onstaan er op korte termijn kosten bij het volwaardig implementeren van kankerrevalidatie die toch betaald moeten worden. Bij voorkeur kunnen kostenbesparingen elders in de zorg voor kanker gerealiseerd worden, die geen afbreuk aan de kwaliteit hoeven doen. Mogelijkheden liggen hier bijvoorbeeld in het vergoedingsbeleid van dure medicijnen. Er moet goed nagedacht worden over waaraan het geld dat ter beschikking staat voor de zorg wordt uitgegeven om een zo groot mogelijke gezondheidswinst te realiseren. Een maatschappelijke en politieke discussie is hiervoor onontbeerlijk.
Nederlandse samenvatting