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Exploring the Effectiveness of eHealth Interventions in Combating Cancer-Related Fatigue in Cancer Survivors: A Systematic Review

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Master's Thesis

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Introduction

One of the most prevalent side-effects when suffering from cancer is cancer-related fatigue (CRF), with a lifetime prevalence of 70 to 100 per cent. Many of those who finished treatment and were pronounced cancer-free, often display symptoms of cancer-related fatigue as well, such as lack of energy, or a decline in social or emotional lability. A recent approach toward CRF is using eHealth interventions to tackle symptoms of CRF, as well as other comorbid conditions. This paper is going to assess current research in the field, and is going to explore, whether there are eHealth interventions that are effective in combating CRF.

Method

Digital databases, namely Scopus, PubMed and Web of Science, were consulted on the topic of eHealth interventions in the context of CRF. It was searched for randomised controlled trials (RCTs), with participants having been cancer survivors, meaning that participants should have finished primary treatment, being disease-free, however showing fatigue symptoms because of the illness. As a guideline, the PRISMA scheme was used, paired with specific inclusion criteria. For the sake of recency, papers that were older than ten years at the time of search conduction, were excluded from the search.

Results

Eight studies were deemed suitable for further analysis. As mentioned, those studies were randomised controlled trials. While not all papers employed fatigue as the primary measure, it was at least always given as one of the measures. In total, seven out of eight papers reported statistically significant changes on at least the fatigue scales. Other domains that showed significant changes in some cases were for instance health-related quality of life, as well as symptoms of anxiety or depression.

Conclusion

It can be said that the selected eHealth interventions, especially guided interventions, appear to be a helpful tool in decreasing fatigue severity in cancer survivors. And while the field itself is still at an early stage, there is much room for innovation since technology is evolving fast. It will be interesting to see what researchers will come up with to further increase the positive effects in cancer-related fatigue.

Keywords: Cancer, cancer survivors, CRF, cancer-related fatigue, eHealth

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Introduction

When suffering from cancer, a person does not only have to deal with the physical symptoms that accompany the illness, but also a handful of psychological symptoms, such as anxiety, increased levels of stress, or depression, just to name a few. However, the most prevalent symptom is cancer-related fatigue (CRF). In cancer patients, CRF has a lifetime-prevalence of 70 to 100 per cent. During treatment, 61 to 99 per cent of patients complain about symptoms of fatigue. However, in post-treatment patients, this number still ranges from 20 to 40 per cent, even if patients have been disease-free for years after (van Weert et al., 2010). This purpose of this paper is to accumulate literature and assess, whether there are eHealth interventions that deem useful in combating CRF in cancer survivors.

But what exactly is cancer-related fatigue, and how does it show? Curt et al. (2000) have defined it along several dimensions. They presented fatigue, in relation to cancer, along three dimensions: (1) subjective energy, (2) mental capacity and (3) psychological status. Consequences of CRF can be impairments in daily functioning, for instance one's ability to care for themselves, but also damage to quality of life in general. If left unchecked, it may be detrimental to quality of life after surviving treatment. (Curt et al, 2000). And although fatigue is one of the most common complaints in cancer patients with an immense prevalence, it has mostly been overlooked or ignored (Stasi, Abriani, Beccaglia, Terzoli, & Amadori. 2003). Stasi et al. (2003) describe that this has only been due to doctors achieving increased control over other acute symptoms, such as nausea, emesis, or pain. Although it is by now understood that cancer patients experience fatigue, the underlying physiological and psychological factors remain mostly unclear. Cancer-related fatigue has also been defined in the ICD-10. Symptoms include, but are not limited to, diminished energy, increasing need for rest, diminished ability to concentrate, emotional lability, etc. It can thus be seen that patients who suffer from cancer-related fatigue, can experience a whole handful of symptoms, but it also shows that the fatigue can show itself differently from patient to patient.

Approaches toward cancer-related fatigue

Researchers suggest that there are nonpharmacological approaches that show at least some effect in tackling CRF (Berger, Gerber & Mayer, 2012). These have been divided into two major, clinically applicable strands, namely physical activity enhancement and psychosocial therapy. Pharmacological interventions are claimed to be hard to interpret, since certain medication may induce fatigue symptoms, or some medications may have interactions that have to be taken into account. Moreover, a deep dive into the effects of certain psychotropic drugs in the treatment of cancer-related fatigue is beyond the scope of this article.

Before going about this paper, it is important to pinpoint what the state of research regarding cancer-related fatigue is, and how researchers have been trying to combat it. What has been done already? Ever since the interest in cancer-related fatigue is growing, so is the research that is behind it. Systematic reviews on this topic already exist.

Finnegan-John, Molassiotis, and Richardson (2013) conducted a systematic review on the effect of complementary and alternative medicine (CAM) on cancer-related fatigue. CAM incorporates approaches that are outside of conventional medicine with the intention of increasing the number of options that are available in handling fatigue symptoms. They give a definition of CAM, which broadly states that it encompasses all approaches that are not prevalent in the dominant health system. The researchers consulted databases for randomised controlled trials (RCTs) that used treatment that would classify as complementary and alternative medicine. They used 20 papers for their review, in which they found that results were inconclusive. Some CAM treatments have shown promising results, while others have not shown positive effects. An issue of this study is that not all papers included were RCTs, only 15. It is thus not an optimal representation. Moreover, they used studies that were set in different points of treatment, such as during and following treatment. So it can be that one method that is effective during treatment, can be less useful post-treatment.

Another systematic review was conducted by Liu, He, and Feng (2019) on quality of life and cancer-related fatigue in survivors of lymphoma. They scanned databases for RCTs, focusing on observing evaluated health outcomes of exercise interventions, comparing a treatment group with a non-treatment control group. This study falls under strand one, physical activity enhancement. They concluded that short term exercise alone does not suffice in improving quality of life. Further analysis showed that routine physical activity, paired with mental exercise may be more beneficial. However, it is stated that the results must be taken with caution due to high heterogeneity in samples.

A new approach?

With the ever-rising dependence on technology in daily life, it should come to no surprise that it has also made its way into the health sector. Ever since the turn of the millennium, electronic health (or: eHealth) has gained more and more popularity. In the beginning, the term was used to loosely describe anything that was related to computers and medicine (Eysenbach, 2001). In his personal, more precise and scientific definition, the author stated that eHealth is referring to health services and information delivered or enhanced by technology or the internet (Eysenbach, 2001). By now, this definition is of course outdated. For that reason, it was revamped and extended in 2015 by Boogerd et. al, who also implemented an aspect of global thinking in health care, by collecting and implementing heath information collected worldwide by means of communication and information technology (Boogerd, Arts & van de Belt. 2015). To further understand eHealth as an up-and-coming topic in the field, Shaw, McGregor, and Barnet (2017) attempted to conceptualise eHealth using a qualitative approach. Based on their analyses, they divided eHealth into three overlapping domains: (1) Health in our Hands, which describes eHealth technologies used to monitor, track, and inform health, (2) interacting for health, meaning using technologies to enable health-related communication among practitioners and between professional and client or patient, and (3) data enabling health, which

encompasses collecting, managing, and using health data. These three domains can be used to classify eHealth in different ways. For this paper, the first domain will be the most relevant one, as interventions should have their participants use at least some form of technology.

Thus, eHealth can come in many different forms, such as technological devices, but also applications, such as apps or websites. However, there are also some more traditional approaches that might fall under the term eHealth, such as telemedicine or an electronic health record. It is debatable whether to like or dislike the idea of combining technology and personal data, nonetheless the concept eHealth has both advantages and disadvantages. Some advantages may be anonymity, easy access, and low cost of implementation (Andrews, Gavin, Titov & Nickolai. 2010). However, Musiat et al. (2014) have assessed the attitudes of the general population toward eHealth – and it can be said that in general, the attitudes are rather negative. Although they too named benefits of it for patients, such as more convenience regarding time and location of treatment, it was found that the population prefers traditional face-to-face therapy over the electronic pendant. That is, they believed that face-to-face therapy would meet most of their needs, including perceived helpfulness, intervention credibility, the ability to motivate the user, while they believed this is not the case for eHealth interventions.

Xu, Wang and Wu (2019) have conducted a systematic review on the effects of eHealth based self-management and its effects on cancer-related fatigue, self-efficacy and quality of life in cancer patients. For this they, researched digital databases for RCTs that fit their criteria. They identified 15 studies, with 2,337 participants in total. Their analysis showed that eHealth based self-management brings about statistically significant, yet low, effects on both symptoms of CRF and self-efficacy, however not on quality of life. Further analysis assumed that eHealth based self-management had a larger effect on fatigue compared to usual care or control conditions (Xu et al., 2019).

The research question for this paper is: ‘Are there eHealth interventions that show effectiveness in combating cancer-related fatigue in cancer survivors?’. To explore this

question, the objective will be to gather current literature and assess, whether there are specific types of interventions that show positive effects regarding CRF.

Methods

In 2009, David Moher presented a set of guidelines for conducting systematic reviews and meta-analyses. The 'preferred reporting items for systematic reviews' (PRISMA) will be used as a framework for this study.

Search Strategy

Digital databanks were consulted for the acquisition of literature. Searches were done using the databases Scopus, PubMed, and Web of Science. For each database, search terms were used to narrow down the list of results – terms, abbreviations and variations of the following were employed: (1) eHealth interventions, to define the kind of intervention, (2) cancer and cancer survivors, to define and narrow down the target group, (3) mental health problems, with a special focus on cancer-related fatigue and (4) if applicable, the search was narrowed down by implementing the desired type of study (randomised controlled trials) into the search. Finally, the search string "*Cancer AND surv* OR post-treatment AND eHealth OR eHealth app* AND cancer-related AND fatigue*" was employed. Since a first definition of eHealth has been given in 2001 already, and due to the rapid development of innovation in the sector of technology, articles were chosen to not be older than 10 years, thus released no earlier than 2011, in order to give an overview of contemporary technology and not list outdated tech. Only articles that were written in English language were employed.

Study Selection Criteria

Study Type

Study type of choice were randomised controlled trials employing any sort of eHealth intervention to tackle mental health complaints. The focus was put on RCTs, as they ensure thorough randomisation of participants as to not skew results. Furthermore, RCTs usually employ a control condition, which allows for comparison of effects between conditions.

Participants

Studies were selected in which the participants were above the age of 18 and have survived the treatment of any form of cancer. The type of treatments received when participants were still undergoing treatment of cancer were not relevant.

Interventions

The definition given in the introduction functioned as a broad guideline for the choice of intervention. Since eHealth can be defined as any technology that is used in the healthcare sector, to increase well-being of patients, any type of eHealth intervention was looked into, be it a webpage, a smartphone app, et cetera. No type was explicitly excluded.

Exclusion criteria

Studies older than ten years were not included in this paper. Studies were also excluded from the search when the participants of a study have not yet finished cancer treatment, meaning if, for instance, the target group were cancer patients mid-treatment, the study was omitted from the search.

Review Method

The databases were searched through using the relevant search terms. After screening for and removing duplicate studies, titles were screened for an initial fit with the guidelines and inclusion criteria. If studies fulfilled these, their abstract was inspected. If these were also in

line with the inclusion criteria, the full-text article was screened for the review. If its content held up with the desired guidelines and theme of this paper, it was included. The screening was done using the software EndNote X9 (released 2020).

Results

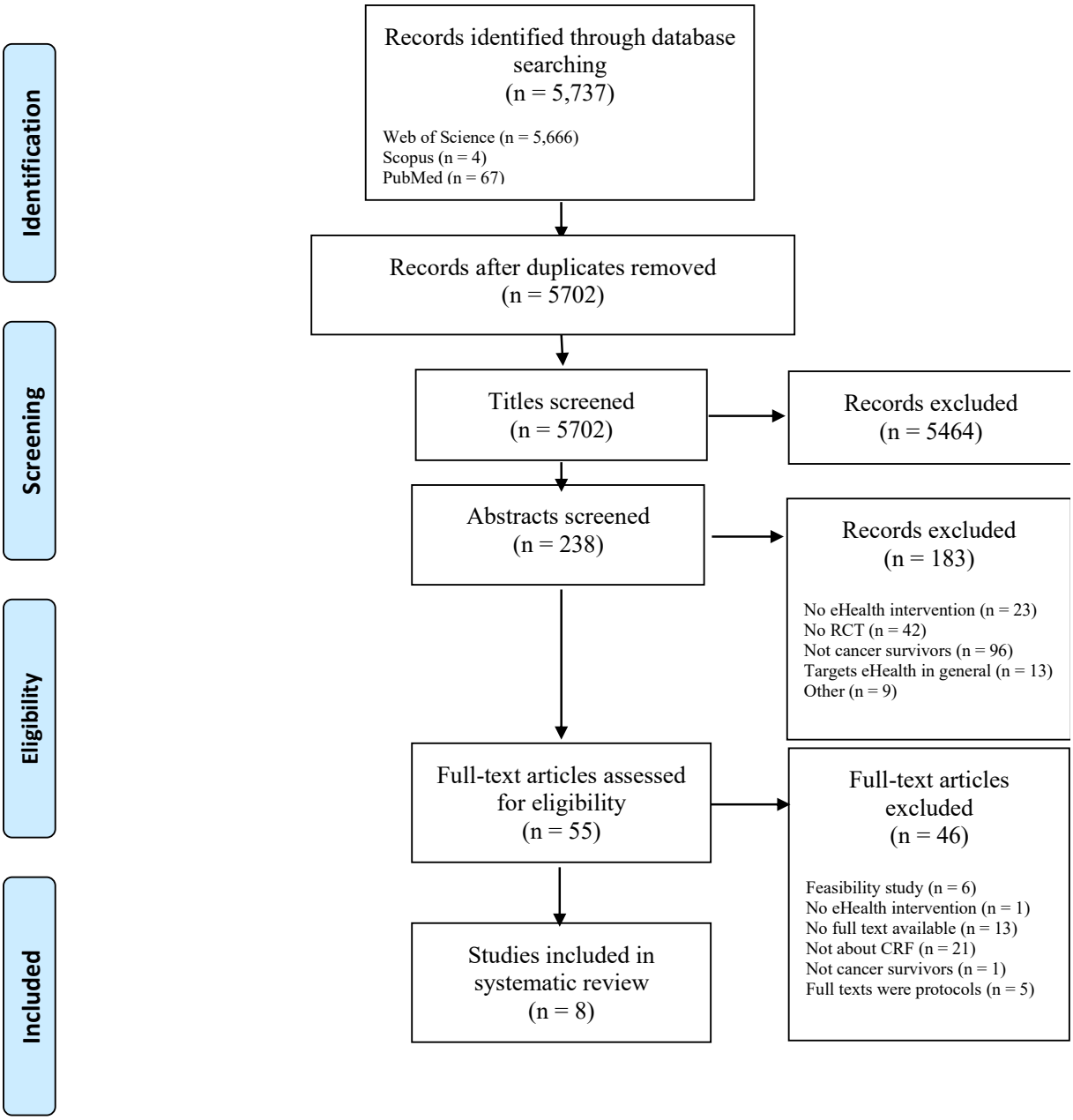

Figure 1. Elimination process as dictated by the PRISMA guidelines.

Study characteristics

After the elimination process, eight studies were deemed fitting for further analyses (see Table 1). Only one study [3] reported a sample size below one-hundred, four studies [2; 4; 6; 7] featured samples that were between one- and two-hundred and the remaining three studies experimented with sample sizes ranging from 462 to 799 participants. The mean age across studies was calculated to be 56.15 years. In all studies, there were more female than male participants. However, one study did not state an explicit mean age or age range for their studies. While some studies focused on one type of cancer only, such as breast cancer [3; 4; 6], there were also papers where there were two or more types of cancer represented. Next to breast cancer, papers featured participants with prostate or colorectal, but also cancer in head or neck, digestive organs, respiratory cancer, skin, bone (marrow) or eye cancer, cancer regarding the reproductive system, the urinary tract or the central nervous system [1]. Leukemia was also represented [2]. While those articles featured multiple types of cancer, breast cancer was a category in those as well, which may account for the high percentage of female participants across studies. A detailed overview of the demographic details, including mean age and standard deviation (SD), as well as the female percentage, if provided in the paper, and the types of cancer across samples is presented in Table 1.

Table 1.

Demographic characteristics of final studies

First Author (Year)	Type of Cancer (%)	% female	Mean Age (SD)
Spahrkäs (2020)[1]	Head/neck (3) Digestive Organs (8.3) Respiratory (3.4)	91.8	55.5 (9.79)

	Skin (2.1)		
	Bone (2.9)		
	Breast (61.3)		
	Reproductive organs (f) (9.1)		
	Reproductive organs (m) (1.9)		
	Urinary tract (2.9)		
	Hematology (8.8)		
	Endocrine glands (2.3)		
	Eye (0.3)		
	Central Nervous System (10)		
	Other (2.8)		
Bruggemann-Everts[1]	Breast (47.31)	83.2	54.8 (9.9)
(2017)	Blood, Bone marrow &		
	Hodgkin's (14.37)		
	Reproductive organs (14.97)		
	Digestive system (9.59)		
	Head and neck (6)		
	Urinary tract (5.4)		
	Leukemia (4.79)		
	Endocrine (2.4)		
	Skin (2.4)		
	Central Nervous System (1.8)		
	Bone (3)		
Vallance (2020)	Breast cancer (100)	100	62 (6.4)
Abrahams (2017)	Breast cancer (100)	100	51.5 (7.9)

Willems (2017)	Breast (70.6)	79.85	55.88 (11.4)
	Bladder (0.4)		
	Colorectal (14.1)		
	Esophageal (1.3)		
	Gynecologic (3.2)		
	Hematologic (5.6)		
	Kidney (0.9)		
	Liver (0.2)		
	Lung (1.1)		
	Prostate (1.2)		
	Stomach (0.6)		
	Testicular (0.6)		
	Thyroid (0.2)		
Freeman (2015)	Breast cancer (100)	100	55.43 (8.62)
Foster (2015)	Breast (59.1)	76.7	57.8 (9.95)
	Gastrointestinal (15.7)		
	Bladder/ Kidney (0.6)		
	Gynaecological (5)		
	Head and neck (9.4)		
	Lung (1.3)		
	Prostate (8.8)		
Willems (2017)	Breast (71.16)	80.93	56.27 (11.15)
	Other (28.84)		

[1]Cancer type and cancer treatment: Participants could have more than one cancer type and could have received more than one cancer treatment, therefore the respective percentages do not sum up to 100%.

Presentation of interventions

The selected papers employed different interventions. First, Spahrkäs et al. [1] employed the Untire mobile app, to reduce cancer-related fatigue. The second intervention was OncoActive [2], a computer-tailored physical activity intervention for prostate and colorectal cancer patients and survivors. Bruggemann-Everts et al. [3] tested two web-based interventions for chronic cancer-related fatigue in their "Fitter na Kanker" trial. In contrast, Vallance et al. [4] assessed the effects of the ACTIVity and TEchnology (ACTIVATE) intervention on health-related quality of life and fatigue in breast cancer survivors. Abrahams et al. [5] attempted to incorporate internet-based cognitive behavioural therapy (ICBT) as an intervention for severely fatigued survivors of breast cancer. Two of the papers at hand [6; 9] deal with the "Kanker Nazorg Wijzer", a web-based and tailored intervention for cancer survivors on social and emotional functioning, depression, and fatigue. Freeman et al [7] took a different approach and attempted to use an imagery-based behavioural intervention, to reduce symptoms in breast cancer survivors. Lastly, Foster et al. [8] designed the web-based intervention RESTORE to support self-management of cancer-related fatigue after primary treatment. Details about the interventions can be found in Table 2. For the sake of clarity, Table 2 only displays the scales that are related to measuring fatigue. To find a table with all scales and measures of all studies, Appendix A can be consulted.

Table 2.

Intervention descriptions of final studies

Author (year)	Intervention name (n)	Format (guidance)	Duration in weeks	Control group (n)	Follow-up from baseline in weeks	Outcome Measure(s) (p-values)[1]
Spahrkäs (2020)	"Untire" (n = 519)	Mobile App (No)	12	Waitlist (n = 280)	4; 8; 12	FSI (**<0.01**; n/a; n/a)
Bruggemann-Everts (2017)[2]	"Fitter na Kanker" (1) AAF (n_1 = 62) (2) eMBCT (n_2 = 55)	Web-based (Yes)	9	Psychoeducation (n = 50)	11; 24	CIS-FS (<**0.001**; **<0.001**; 0.22)
Vallance (2019)	"ACTIVATE" (n = 43)	Wearable Technology (Yes)	12	Waitlist (n = 40)	12; 24	FACIT-F (**0.02**; 0.452)
Abrahams (2017)	Internet-based CBT (ICBT) (n = 66)	Web-based and face-to-face (Yes)	24	Care as Usual (CAU) (n = 66)	24	CIS-FS (<**0.0001**) BSI (<**0.0001**)
Willems[2] (2017)	"Kanker Nazorg Wijzer" (n = 231)	Web-based (No)	24	Waitlist (n = 231)	24; 48	CIS (**0.048**; 0.661=
Freeman (2015)	"Envision the Rhythms of Life (ERL)" - LD (n_1 = 48)	Web-based and face-to-face (Yes)	12	Waitlist (n = 47)	12; 16; 24	SF-36 (PCS: 0.154) (MCS: **0.020**) FACIT-F (**0.002**) BSIGSI (0.051)

	- TD (n_2 = 23)					
Foster (2015)	"RESTORE" (n = 85)	Web-based (No)	6	Psychoeducation (n = 78)	6; 12	PSEFSM (0.09; 0.70) BFI (0.28; 0.50)
Willems (2017)[3]	"Kanker Nazorg Wijzer" (n = 231)	Web-based (No)	24	Waitlist (n=231)	12; 24; 48	CIS (**0.048**)

Abbreviations and other information: ***Intervention Names****:* AAF, Ambulant Activity Feedback; eMBCT, Web-based Mindfulness-based Cognitive Therapy; CBT, Cognitive Behavioural Therapy; LD, live-delivery group session; TD, technology-delivered group session; ***Outcome measures:*** FSI, Fatigue Symptom Inventory; CIS-FS, Clinical Isolated Syndrome – Fatigue Severity; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; BSI, Brief Symptom Inventory; CIS, Clinical Isolated Syndrome; SF-36, Medical Outcomes Study 36-item short form survey; PCS, Physical component summary; MCS, Mental component summary; BSIGSI, Brief Symptom Inventory Global Severity Index; PSEFSM, Perceived Self-Efficacy for Fatigue Self-Management; BFI; Brief Fatigue Inventory; ***Duplicate measures have been marked for easier identification.***
Bold p-values describe statistical significance.

[1] *Multiple p-values in brackets resemble follow-up measures from baseline in the described time frame (if provided).*
[2] *Multiple p-values in brackets resemble the respective interventions.*
[3] *Values were provided per construct, not per scale.*

The "Untire" Mobile App

The study by Spahrkäs, Looijmans, Sanderman & Hagedoorn (2020) attempted to approach cancer-related fatigue with their Untire mobile app. The app was comprised of four modules, namely (1) My themes, (2) My exercises, (3) Physical activity, and (4) Tips. In the My themes module, the app should tackle dysfunctional thoughts via psychoeducation, in the My exercise module, it was attempted to reduce stress and improve sleep via mindfulness-based stress reduction (MBSR), the physical activity module should help enhance physical fitness through exercise instructions and lastly, the tips module should empower the user via Positive Psychology. Moreover, quick scans allowed to participants to get a weekly insight into their fatigue levels, burden, their happiness, satisfaction, and energy leaks over time. While daily use was recommended, the intervention group was instructed to use the app at their own pace.

In their paper, fatigue reduction was the primary objective, thus also the primary measure. The researchers employed multiple analyses to prove the effectiveness of their intervention. The reduction of fatigue severity was most prominent in those with high (≥9 days) and medium use (≥3 days). With a p-value of <0.01 in the FSI, there was a significant difference in fatigue between users of the app and the control condition. However, after twelve weeks, the levels of fatigue in low and nonusers did not differ from the control group. The second measure, quality of life, deemed no statistical significance, meaning there were no notable differences between groups that could be traced back to the intervention.

The "Fitter na kanker" intervention

The "Fitter na kanker" intervention was conducted by Bruggemann-Everts et al. [2] and assessed the effectiveness of two web-based interventions for chronic cancer-related fatigue (CCRF) compared to control conditions. The Ambulant Activity Feedback (AAF) consists of a home-based and physiologist-guided protocol, in which participants used an accelerometer to

gain insight into their physical activity patterns and increase or balance their daily activities. This should be done in ways that improve their energy levels. It involved noticing, and responding to, Personal Digital Assistant messages, changing activity as a reaction, and reading the weekly feedback from the physiotherapist. The web-based mindfulness-based cognitive therapy (eMBCT) intervention aimed at changing the participant's behavioural and cognitive reactions to cancer-related stressors, including fatigue itself. The intervention's time investment involved weekly information, doing mindfulness exercises while listening to MP3 files that were provided, filling out logs, reading therapist feedback and replying to this feedback via email.

Primary outcome measure of the study was fatigue severity. Analyses showed effectiveness in both interventions, that both AAF and eMBCT were significantly more effective in reducing fatigue severity than psychoeducation alone (CIS-FS: P<.001; P<.001; P=.22). There were also significant differences in anxiety levels across all conditions (HADS: P<.001; P<.001; P<.001, See Appendix A). Differences in both positive and negative affect were also significant (PA: P<.001; P<.001; P<.001 / NA: P=.003; P=.03; P=.004, See Appendix A). In the AAF condition, 66 per cent of participants improved, in the eMBCT condition the number was 49 per cent, and for psychoeducation alone, this number was 12 per cent.

The ACTIVATE intervention

This intervention was conducted by Vallance et al. [3]. Over time, participants received (1) behavioural feedback and goal setting in a single face-to-face session at a cancer council with two trained research assistants, (2) a wrist-worn activity monitor which they were asked to wear for twelve weeks, and (3) five telephone-delivered behavioural counselling sessions from a trained assistant. During the twelve-week span of the interventions, participants retained their wrist monitors, but there was no mandatory wear-time.

Primary measures were health-related quality of life and fatigue. Differences in fatigue levels compared from baseline to end of intervention were significant (P=0.02). This significance was lost however, when values from end of intervention were compared to follow-up measures (P=0.452). All in all, though, when baseline and follow-up were compared, values too were significant (P=0.04). For health-related quality of life, p-values deemed no statistical significance across none of the compared measures and points in time (P=0.217; P=0.68; P=0.087).

Internet-based Cognitive Behavioural Therapy

The intervention carried by Abrahams et al. [4] aimed at employing internet-based cognitive behavioural therapy (ICBT) for severely fatigued survivors of breast cancer. ICBT consisted of a total of three face-to-face sessions and a maximum of eight web-based modules.

The first module contained setting one's treatment goals. Second, participants worked on fatigue-perpetuating factors that were applicable to them, such as (1) poor coping with breast cancer (treatment), (2) high fear of cancer recurrence, (3) dysfunctional fatigue-related cognitions, (4) a deregulated sleep-wake rhythm, (5) a deregulated activity pattern, and/or (6) negative social interactions and low social support. Each of these six factors corresponded with one of the modules, thus modules two to seven. In module eight, participants realised their treatment goals. The intervention was tailored to the individual participant, since it was determined at baseline what each participant deemed relevant to them.

Primary outcome measure was fatigue severity. Compared to the control condition, participants in the ICBT condition reported significantly less fatigue (P<0.0001), with a large effect size and the majority showing clinically significant and self-rated improvement. In general, the differences in all of the explored measures, meaning functional impairment (SIP-8), psychological distress (BSI-18), as well as quality of life (EORTC-QOL-C30) were significant (P<0.0001 for all scales, see Appendix A).

Envision the Rhythms of Life (ERL)

This study conducted by Freeman et al. [6] attempted to tackle symptoms in breast cancer survivors via what they termed the "Envision the Rhythm of Life" intervention. Both intervention groups had five, four-hour weekly group sessions and received brief weekly phone calls to encourage at-home practice, ranging from treatment start until three months post-treatment. The groups met in a community centre, with either the therapist present (LD), or an assistant present setting up videoconferencing software (TD). The first four sessions were separated into three modules each comprised of 25 minutes of didactic education followed by 25 minutes of interaction with fellow group members in triads to discuss and practice materials. During the fifth session, each participant presented her long-term plan after the intervention, with other participants providing feedback and suggestions.

The didactic aspect focused on educating on the mind-body connection and presented research on the impact of mental imagery on bodily processes. The interactive part of the sessions enabled the participants to apply what was learned. Also, participants received 20-30 minutes of guided imagery on a CD, weekly. They were instructed to engage in daily practice also after treatment.

Many determinants were measured, such as HRQOL, perceived cognitive function, but also fatigue. Analyses show statistically significant improvements in perceived fatigue in both intervention conditions, when compared to the control condition ($P=0.002$). Differences in cognitive functioning, as well as spiritual well-being were also significant ($P=0.002$ and $P=0.001$ respectively). Additionally, participants reported much better sleep ($P<0.001$). For the other measures, the differences were not statistically significant.

The RESTORE intervention

The RESTORE intervention was a web-based intervention conducted by Foster et al [7]. It consisted of five sessions, with one session per week. Sessions one and two were mandatory

and introduced cancer-related fatigue as a concept, and goal setting. The three weeks after this consisted of participants dealing with three topics, namely (1) diet, sleep, exercise, home and work life; (2) thoughts and feelings, and (3) talking to others. Participants could either complete all available session or focus more on those that they deemed most important. Structured activities were available, such as goal setting, automated tailored feedback on goal achievement and fatigue level, and videos of patient stories. Next to the main body of the RESTORE intervention, participants were also encouraged to make use of a fatigue diary.

Next to feasibility and acceptance of the intervention itself, the potential of the program to tackle cancer-related fatigue was measured. More precisely, it was attempted to measure perceived self-efficacy when combating fatigue. Different measures were taken, and while there were differences in values, such as in fatigue efficacy (P=0.09; P=0.70), none of the measures showed statistically significant differences.

The "Kanker Nazorg Wijzer"

The "Kanker Nazorg Wijzer" (KNW) intervention was employed in two studies [5; 8]. The intervention was executed as a stand-alone intervention, meaning that participants managed it themselves. The intervention was conducted the same way in both studies, meaning that there were eight modules of which seven were self-management training modules. Those modules covered the topics of returning to work, fatigue, anxiety and depression, social relationship and intimacy issues, physical activity, diet, and smoking cessation. The eighth module provided some general information about common residual symptoms. Prior to beginning the intervention, participants filled out a baseline questionnaire, with which tailoring was enabled. The contents of the modules were based on both problem-solving theory (PST) and cognitive behavioural therapy (CBT). PST principles included into the intervention were problem identification, goal selection and goal setting, action planning, and evaluation. These four aspects were divided into four sessions. CBT principles incorporated were psychoeducation,

assignments such as monitoring of behaviour or cognitions, and relaxation exercises. While one study [5] investigated whether short-term effects of the KNW, that means six months from baseline, remained on the long-term as well, meaning twelve months, the other study [8] assessed mediating effects of both problem-solving skill and personal control on depression and fatigue.

The KNW proved useful in combating depression and fatigue in cancer survivors, showing reduction in symptoms, although only personal control was shown to be a mediator for those effects, while the role of problem-solving skills was not significant [8]. It was also found that the effects of the intervention remained stable, when short-term and long-term were compared [5]. In both studies, the HADS and the CIS scales showed significant differences (HADS: P=0.048 [5]; P=0.012 [8]; CIS: P=0.048 [5;8]).

Discussion

Objective of this paper was to find out, whether there are eHealth interventions that are effective in combating cancer-related fatigue in cancer survivors. This systematic review suggests that most of the presented eHealth interventions have statistically significant effects on CRF when compared to given control groups or conditions, except for one. While effects were statistically significant, they were not long-lasting for the most part, as can be seen by the fact that in four of the eight studies, the effects flattened out when the intervention and control group were compared. It can thus be said that most interventions do you have short-term effects, but those effects lack longevity.

The interventions with the highest effectiveness, when looking at the statistics behind them, are “Fitter na Kanker” and internet-based cognitive-behavioural therapy. In the “Fitter na Kanker” intervention, participants reported significantly less fatigue severity than the control condition, being only psychoeducation. Considering the AAF condition, an explanation for the changes in those aspects might be enhanced physical activity. That is, because enhanced

physical activity is said to be a useful tool in combating a handful of mental illnesses (Monteiro Peloso, Guerra de Andrade, 2005). Moreover, physical activity and exercise have shown to at least have moderate effects on cancer-related fatigue as well (Ehlers, DuBois & Salerno, 2020). It is thus very likely that employing mechanisms that enhance participants' physical activity levels may deem positive outcomes. Since this is paired with supervision through psychologists and physiologists, the outcome is as positive as it is. The second intervention condition employed mindfulness as the working mechanism. Mindfulness, and all surrounding facets too, have already been proven to be effective in tackling various forms of mental illness, as well as psychiatric comorbidities (Wielgosz et al., 2019). To be more precise, Xunlin, Lau, & Klainin-Yobas (2020) have found that mindfulness-based approaches significantly lowered fatigue complaints in cancer survivors. Moreover, they also found significant effects on anxiety, depression, stress and quality of life. However, they focused on traditional face-to-face approaches, not on eHealth approaches. In the context of eHealth and online interventions, Matis et al. (2020) conducted a systematic review on mindfulness-based programs for patients via eHealth and mHealth. While they reported vast heterogeneity in results, it was still found that eHealth applications may serve as a suitable channel for mindfulness-based approaches. And since a part of mindfulness deals with paying attention to your body and the here and now, it might have helped patients to shift the mind away from negativity and fatigue toward what is going on right now, eventually even helping them wind down and relax.

The other intervention that can be deemed extraordinarily effective is internet-based CBT. The intervention managed to significantly reduce fatigue severity in participants – in general, all measures taken deemed statistically significant changes, fatigue severity being of the most interest. This study employed the already well-established and widely used cognitive-behavioural therapy and attempted to transfer traditional and functioning elements of it into the digital environment. However, these outstanding effects may also be explained by the fact that this intervention could also be classified as a sort of "hybrid", since it entailed both web-based

and traditional face-to-face therapy sessions. It can be assumed that these "hybrid" properties might be in part responsible for the positive outcomes. Wilhelmsen et al. (2013) investigated into blended care by interviewing participants of another ICBT intervention about aspects of it. They found that next to the effects of the eHealth intervention as such, the in-person factors came to play a big role as well, such as feedback and acknowledgement by a qualified therapist during meetings. It provided participants with a sense of connectedness toward the intervention as a whole, which also might explain the results of this study here, since internet-based CBT was paired with occasional face-to-face therapy sessions.

The overall findings are in line with what Seiler et al. (2017) have found in their systematic review. They also only were able to use a small number of papers, nine in total, for their review, strengthening the idea that the application of eHealth onto tackling CRF is still at a very early stage. They employed papers with dates ranging from 2011 to 2016, thus also having an approximate timeframe of five years. There was one overlap in the papers analysed between this paper and the paper of the colleagues, namely the paper by Freeman et al. (2015). Some of the interventions they looked into are also featured in the paper at hand, for instance web-based mindfulness therapy, the RESTORE intervention and the "Kanker Nazorg Wijzer". The analysed papers were taken at different points in time than those featured in this paper. A meta-analysis of the papers was conducted by the researchers, deeming statistically significant results with $P<0.01$. They found that six out of the nine studies showed significantly reduced fatigue levels, with the remaining three showing no significant differences between conditions. This too is in line with this paper, where the interventions for the most part did significantly reduce fatigue levels in participants. Moreover, they found that therapist-guided interventions were more effective than self-guided interventions, which is also in line with this paper's results. However, the fact that there is some overlap might skew the results in a way that they might be more in line than they actually are. Readers must proceed with caution. And while the results are in line with those of this paper, the review by Seiler et al. too has its limitations, as

stated by the authors themselves. Some of those can also be applied to this paper. They stated that gathering papers was difficult due to the subjectivity of the concept of CRF – this was circumvented by looking exclusively for validated and standardised measures. In the case of this paper, it was attempted to work with a reliable definition, as well as standardised scales for measuring fatigue. Another point of criticism was that only three of the selected papers measured CRF pre-treatment.

This goes to show in what early stage the research into eHealth in the context of CRF still is, with a research field being this early and small, it should come to no surprise that there is an overlap between studies, as well as yet to be perfected methodologies – yet, this also demonstrates the rapid development of interventions, as there already are multiple studies featuring the same intervention, with eventual tweaks and changes, but also investigating into other facets of the illness, exploring how to best approach it. While the research behind eHealth is ever-rising, so is the number of meta-analyses and systematic reviews in the field of cancer-related. However, the phenomenon of CRF is still not fully explored, thus, every attempt at conceptualising and gathering state of the art research in the field of eHealth is important to fully understand all facets of it, and how to best tackle it. And since technology is constantly evolving, at a fast pace as well, it is important to keep up with it. This study has achieved just that by gathering literature that has only been published very recently, with the least recent paper having been published in 2015. In general, it can be said that recent times have only paved the way for eHealth interventions further, not only in the context for cancer or cancer-related fatigue. Bennett et al. (2020) have investigated into the role of eHealth during the COVID-19 pandemic. Since many people worldwide were more or less “forced” to stay at home and social distance, and many institutions closed because of the pandemic, there needed to be a shift in approaching the matter. The loss of actual face-to-face contacts severely impacted psychotherapists and patients. The new challenges and barriers need to be overcome somehow. The researchers presented eHealth as an opportunity to not only overcome the barriers posed

by the pandemic, but also as a prospect for future endeavours (Benett et al., 2020). However, while the concept itself was deemed promising and showed effects on common problems in psychotherapy it is still not perfectly clear which type of eHealth intervention is the go-to solution.

All in all, it can thus be stated that eHealth interventions across the board have shown to be effective in combating CRF, this has been proven in multiple instances. On a sidenote, there is definitely more research required in the field of mHealth. The lack thereof might be due to smartphone being a more recent innovation than computers are, with computers being around for decades already, and personal computers making their ways into people's homes for at least 15 to 20 years.

Strengths and Limitations

A strength of this study is that, especially when comparing to the other two reviews presented prior, that it exclusively focused on RCTs. Having one methodological approach only has a clarifying effect, since one does not need to discriminate between different approaches and can rate and analyse in one coherent way. Another strength is the recency of the reviewed papers. With the least recent paper having been published six years ago, it can be stated that it accurately represents contemporary eHealth technologies. And since both eHealth, and technology in general, are steadily and rapidly evolving, it is only reasonable to assess recent papers only.

While this paper is in line with the studies presented prior, it too has its limitations. First, it became apparent that two articles had to be removed from the list mid-analysis. This was due to the fact that while initially screened, even full text, they were considered viable, but an even more in-depth look during analysis phase deemed that two sources were, retrospectively, unsuitable. In one case that was due to the paper being a feasibility study, which did not become apparent until the end of the reading process. In the other case, the researchers simply presented a design prototype, talking about the design process and what an RCT could look like and what

effects could be present, thus not deeming actual results. More care has to be taken in future attempts, when trying to conceptualise eHealth effectiveness. Secondly, the collection has been done by one person only, thus, it could not be fully controlled for bias. While the PRISMA scheme was employed, which in a sense does provide an objective framework, it is not guaranteed that bias may influence in- or exclusion of one article over another, albeit very strict criteria were provided. What could also be seen was the overrepresentation of females in the samples, especially seeing that three of the studies at hand explicitly focused on breast cancer, thus having fully female samples. It is definitely recommended to incorporate different types of cancers to get a clearer picture to see if interventions that work for one cancer type work for another as well. While studies like this do of course exist, exploring the variety of cancer types, as well as just how subjective the symptoms of CRF are, it would be adequate.

A last point of concern might be that the data collected is very heterogeneous in nature. This can be seen as both an advantage and a drawback. While it does provide a large spread in what was investigated, meaning many different facets and types of disease, it also provided a larger overview about the state regarding just these different facets and types. This merely goes to show the subjectivity of the concepts at hand, as well as the perception of them by participants. There are also unmistakable differences in study outcomes, however, this again just provides a more whole and collected image of the issue at hand.

Increasing eHealth Uptake

This review, and the other reviews as well for that matter, have shown just how limited the research in this field truly is. Moreover, research in this field should constantly be evaluated and revamped because innovative technologies arise at a faster pace than ever before. Thus, researchers must give it their best efforts to keep up with the development of new technology. However, developing new technology is one thing, but distributing and having people use technology, especially new technologies, is the other thing.

In 1985, Gould & Lewis coined the term Human-Centred Design, to describe a design process, in which the needs, expectations, interests and motivations of prospective users are taken as focal design points. This was done in order to ensure user-friendlier designs, which in turn should increase adherence to technology, as well as facilitate implementation of technology. Van Gemert-Pijnen et al. (2011) attributed difficulties in distributing technologies to issues such as a lack of financial incentives, lack of stakeholder support, or a lack of motivation and ability to use a certain technology within the population.

The focus here will be on elderly people, since when growing older, one's risk to get certain diseases, for instance a type of cancer, rises drastically (World Health Organisation, 2014). Also, it should come to no surprise that the younger generations, those who group up with the internet, or advanced technology in general, are both more familiar and more literate when it comes to using said technology, as well as more ready to adopt new technologies. And in the generational clash, one can often hear a certain aversion or reluctance toward technology coming from older folks, although there has been a steady increase in health-related internet usage among elderly people (Sheng & Simpson, 2013). In the context of eHealth interventions, age too is a factor that may influence readiness to participate in or incorporate eHealth technology into one's life. Age is, however, not the only factor, others include biological sex, socioeconomic status, as well as current technology already in use (Ware et al, 2017). While the risk of suffering from cancer rises with age, it should be known, what would make the target group more likely to adopt such technologies into their lives.

Ware et al. (2017) attempted to uncover themes within the interests, preferences, and concerns of older populations, that is 65 and older, regarding the internet and eHealth technologies – and while the population is not cancer patients, it still provides a broad overview, from which one may derive behavioural patterns. They found five emerging themes, (1) difficulty of identifying credible and relevant sources of information, (2) ownership, access, and responsibility for medical information, (3) peer communication and support, (4)

opportunities to enhance health care interactions, and (5) privacy concerns. A main way to deal with most of these issues could be in-depth education about the topics these people are so concerned about. Sheng & Simpson (2013) stated that professionals should make use of the level of internet literacy that elderly people already possess to distribute information properly. Moreover, in the cases where the literacy or willingness is low, professionals should search for alternatives, such as designing disease management programs that incorporate and eventually incentivise using the internet or eHealth applications as such. Bolle et al. (2016) found that once elderly people were invested with online health information, they came to appreciate it. In their think-aloud study, the researchers found that their target group, aged between 70 and 79, saw health-related internet content as a useful tool to gain knowledge. However, the researchers went into detail about how, if elderly people should use online sources, these sources should be designed in a user-friendly manner, paying attention to eventual struggles and problems the target population might have.

In general, it was found by Tennant et al. (2015), that if older folks, in their study they surveyed the generation of "baby boomers" (People born between approximately 1946 and 1964), were to already use the Web 2.0, meaning the more interactive part of the internet, such as social media, they were reported to have more eHealth literacy than those of their age group that have not used Web 2.0 before. This should come to no surprise, as those with increased eHealth literacy already have a history of internet use and are thus more familiar with the internet as a virtual space, but also have more experience in navigating through it.

All in all, professionals should try to educate about the benefits of eHealth applications and health-related content on the internet – however, when distributing such contents, or when designing an intervention, special attention should be paid toward known struggles and problems, as well as age-related cognitive issues.

Conclusion and Recommendations

This paper has provided insight into the state of the art of eHealth technologies in the context of cancer-related fatigue in cancer survivors. It has shown the effectiveness of certain eHealth interventions on fatigue severity – especially guided eHealth interventions. This can be used as an orientation for further research, both into new, innovative interventions, and for keeping track of said research by conducting systematic reviews and meta-analyses. The research in this area is still in its early stage.

In designing eHealth applications, a human-centred design can be desirable, as it can attempt to counterplay certain drawbacks that currently exist in the implementation of new technologies. Moreover, the application should be adequately tailored. As the example of elderly people showed, one should keep specific issues in mind, such as a lack of eHealth literacy or a decline in certain cognitive abilities. If such things are taken into account, the innovation might be able to set foot. Nonetheless, also due to the current situation the world is in, with the pandemic still going on, there will most likely be an increase in eHealth technologies as a sort of transition until things return to normal. What needs to be kept in mind however, is that humanity should not get lost in technology, meaning that in order to have the biggest impact, a mix of technology and humanity is most desirable.

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Appendix A: Intervention descriptions with all scales

Intervention descriptions of final studies

Author (year)	Intervention name (n)	Format (guidance)	Duration in weeks	Control group (n)	Follow-up from baseline in weeks	Outcome Measure(s) (p-values)[1]
Spahrkäs (2020)	"Untire" (n = 519)	Mobile App (No)	12	Waitlist (n = 280)	4; 8; 12	FSI (**<0.01**; n/a; n/a) EORTC-QLQ-30 (0.07; n/a; n/a)
Bruggemann-Everts (2017)[2]	"Fitter na Kanker" (1) AAF (n_1 = 62) (2) eMBCT (n_2 = 55)	Web-based (Yes)	9	Psychoeducation (n = 50)	11; 24	CIS-FS (<**0.001**; **<0.001**; 0.22) PA (**<0.001**; **<0.001**; **0.001**) NA (**0.003**; 0.03; **0.004**) HADS (**<0.001**; **<0.001**; **<0.001**)
Vallance (2019)	"ACTIVATE" (n = 43)	Wearable Technology (Yes)	12	Waitlist (n = 40)	12; 24	FACT-B (0.217; 0.68) FACIT-F (**0.02**; 0.452)
Abrahams (2017)	Internet-based CBT (ICBT) (n = 66)	Web-based and face-to-face (Yes)	24	Care as Usual (CAU) (n = 66)	24	CIS-FS (<**0.0001**) SIP-8 (<**0.0001**) BSI (<**0.0001**) EORTC-QLQ-C30 (<**0.0001**)

Willems[2] (2017)	"Kanker Nazorg Wijzer" (n = 231)	Web-based (No)	24	Waitlist (n = 231)	24; 48	EORTC-QLQ-C30 (EF: **0.049**; 0.384) (SF: **0.048**; 0.580) HADS (**0.048**; 0.454) CIS (**0.048**; 0.661=
Freeman (2015)	"Envision the Rhythms of Life (ERL)" - LD (n_1 = 48) - TD (n_2 = 23)	Web-based and face-to-face (Yes)	12	Waitlist (n = 47)	12; 16; 24	SF-36 (PCS: 0.154) (MCS: **0.020**) FACT-B (0.076) FACIT-F (**0.002**) FACT-Cog (**0.001**) FACIT-Sp-Ex (**0.049**) BSIGSI (0.051) PSQI (<**0.001**)
Foster (2015)	"RESTORE" (n = 85)	Web-based (No)	6	Psychoeducation (n = 78)	6; 12	PSEFSM (0.09; 0.70) CS-SES (0.90; 0.43) FACT-G (0.19; 0.10) PWI (0.76; 0.94) PHQ-9 (0.50; 0.40) BFI (0.28; 0.50)
Willems (2017)[3]	"Kanker Nazorg Wijzer" (n = 231)	Web-based (No)	24	Waitlist (n=231)	12; 24; 48	HADS (**0.12**) CIS (**0.048**) SPSI-R IPQ-R

Abbreviations and other information: ***Intervention Names****:* AAF, Ambulant Activity Feedback; eMBCT, Web-based Mindfulness-based Cognitive Therapy; CBT, Cognitive Behavioural Therapy; LD, live-delivery group session; TD, technology-delivered group session; ***Outcome measures:*** FSI, Fatigue Symptom Inventory; EORTC-QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; CIS-FS, Clinical Isolated Syndrome – Fatigue Severity; PA/NA, Positive Affect/ Negative Affect; HADS, Hospital Anxiety and Depression Scale; FACT-B, Functional Assessment of Cancer Therapy – Breast; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; SIP-8, Sickness Impact Profile 8; BSI, Brief Symptom Inventory; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EF, Emotional Functioning; SF, Social Functioning CIS, Clinical Isolated Syndrome; SF-36, Medical Outcomes Study 36-item short form survey; PCS, Physical component summary; MCS, Mental component summary FACT-Cog, Functional Assessment of Cancer Therapy – Cognitive Function; FACIT-Sp-Ex,

Functional Assessment of Chronic Illness Therapy – Spiritual Well-Being – Expanded Version; BSIGSI, Brief Symptom Inventory Global Severity Index; PSQI, Pittsburgh Sleep Quality Index; PSEFSM, Perceived Self-Efficacy for Fatigue Self-Management; CS-SES, Cancer Survivors' Self-Efficacy Scale; FACT-G, Functional Assessment of Cancer Therapy – General; PWI, Personal Well-Being Index; PHQ-9, Patient Health Questionnaire 9; BFI; Brief Fatigue Inventory; SPSI-R, Social Problem-Solving Inventory – Revised; IPQ-R, Illness Perception Questionnaire – Revised; ***Duplicate measures have been marked for easier identification.*** *Bold p-values describe statistical significance.*

[1] *Multiple p-values in brackets resemble follow-up measures from baseline in the described time frame (if provided).*
[2] *Multiple p-values in brackets resemble the respective interventions.*
[3] *Values were provided per construct, not per scale*