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**Protocol amendment submitted to RSEC July 6, 2017 (long-term follow-up) is highlighted in green.**

# FEASIBILITY AND EFFICACY OF AN INTERNET-DELIVERED COGNITIVE-BEHAVIORAL INTERVENTION FOR INSOMNIA IN A NATIONAL COHORT OF DANISH BREAST CANCER SURVIVORS

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## BACKGROUND AND AIMS

Insomnia is usually defined as: a) difficulties in falling asleep and maintaining sleep or experiencing non-restorative sleep for at least one month, resulting in b) daytime sleepiness and lack of energy with significant implications for social, occupational or other functions. In addition, c) the sleep problems should not be due to other sleep-related pathologies, e.g. narcolepsy or apnea (1). The sleep problems can be difficulties in falling asleep (long sleep latency), involuntary awakenings during the night, early morning awakenings, or poor sleep quality resulting in feelings of being non-refreshed after sleep (2). Common causes of primary insomnia include psychological and behavioral factors such as anxiety, depressive symptoms, and inadequate sleeping habits, inappropriate thoughts about sleep, and stressful life events. Such causes can induce physical and mental stress reactions that impair sleep. Secondary insomnia stems from mental or physical problems and illnesses such as depression or pain (3).

Reviews of the literature conclude that insomnia is the most common sleep problem, with 9 - 30% of the general population experiencing symptoms of primary insomnia, and 6 - 10% meeting the diagnostic criteria for primary insomnia (2;4). The risk of experiencing sleep difficulties appear to increase with old age and women seem to be at greater risk for developing insomnia (2). Sleep problems are even more prevalent among people with current or previous physical illness. For example, 23 -63% of cancer patients and cancer survivors report specific symptoms of insomnia (5-7). Our own data from a national cohort of 3343 Danish women treated for breast cancer revealed that 58% of women experienced clinically significant sleep problems three months after surgery (8). Preliminary data, from this study, further indicate that more than half (51.5%) of the women continue to experience significant sleep difficulties 7-10 years later. Sleep and sleep quality are related to both mental and physical health. In the aforementioned cohort of women, sleep problems thus explained approximately 35% of the variation in depressive symptoms one year after surgery (unpublished data). Sleep is also a restorative process of importance to the immune system (9) and experimentally induced sleep deficiency has been found to induce effects on the immune system similar to the effects found among patients with depression (10). Other studies have found evidence suggesting that a significant proportion of the variation in the relationship between stress and effects on immune function can be explained by impaired sleep quality (9). Furthermore insufficient sleep has been associated with increased caloric intake and obesity (11;12) and with increased secretion of pro-inflammatory cytokines (10); all known risk factors for a number of diseases, including heart disease, diabetes, and cancer. Although the precise causal relationship between sleep quality, biological processes, and health is still unclear (13), a number of cohort studies have explored associations between sleep and mortality. A recent meta-analysis of data for more than 1.3 million participants in 27 studies suggests that both many (> 8 h) and few hours of sleep (<6 h) are associated with increased mortality (14). Other studies have assessed more specific sleep quality measures. For example, in a prospective study of healthy elderly, it was found that both increased sleep latency and reduced sleep efficiency (hours of sleep/hours in bed) were associated with

increased risk of dying during the investigation period (15). Although sleep quality thus appears to be related to physical health and survival in general, the specific role of sleep and sleep quality for the prognosis of diseases such as cancer is still unknown.

It is recommended that insomnia is treated non-pharmacologically, whenever possible (16;17) though studies suggest that sedative medication, hypnotics and over the counter sleeping medication are the most frequently used method to combat insomnia in cancer survivors (18). Several meta-analyses have confirmed the efficacy of various behavioral interventions for sleep disorders (19-21). In particular cognitive behavioral therapy (CBT) has been deemed as efficient as pharmacological treatment but with durable post-treatment effects (22;23). However, as is the case for most behavioral interventions, limited availability of trained practitioners and the costs associated with face-to-face interventions limit their implementation.

Computerized internet-based delivery of cognitive behavioral therapy for insomnia (CCBT-I) could be a method to improve the dissemination and implementation of interventions for sleep-related problems. This fairly new approach enables treatment of a larger proportion of people at a lower cost and at the same time ensures personalized treatment via algorithms. In a recent comprehensive meta-analysis[1] of the usability and efficiency of Internet based cognitive behavioral therapy six randomized controlled trials (24-29) were identified (30). The six studies applied similar and hence comparable CCBT-I components, and two studies implemented the same CCBT-I program (24;25). Out of the six studies only one small study (N = 28) investigated the effect of CCBT-I on insomnia in cancer survivors with promising results (24). The meta-analysis reports statistically significant improvements on most sleep measures post-treatment and effect sizes ranging from small to large: sleep quality *d*= 0.41, sleep efficiency *d*= 0.40, number of awakening *d*=-0.45, sleep onset latency *d*=-0.55, insomnia severity index (*see under measures*) *d*=-0.86 (30; p. 210). The effect of treatment on total sleep time (*d*=0.22) was only near significant (*p*=.08) whilst the total minutes in bed (*d*=-0.25) was non-significant. Generally, larger effect sizes were seen in programs wherein more components of CBT were included and where the duration of therapy was prolonged to last at least six weeks (24;25). Since the publication of the review one additional randomized controlled trial has been published (31) employing both an intervention group and a treatment as usual control group and a scam imagery relief therapy group. This study also reported small to large effect sizes post treatment as well as at eight weeks follow-up.

Overall, the utilization of CCBT-I is promising though the results, especially pertaining sleep problems in relation to cancer, must be regarded as preliminary.

In summary, the available research indicates that: 1) a significant proportion of cancer patients and cancer survivors experience sleep problems, 2) sleep problems are associated with impaired quality of life and may have negative consequences for mental and physical health, 3) non-pharmacological treatments should be preferred to pharmacological when possible, and 4) cognitive behavioral interventions for insomnia are effective, but the availability is limited. However, a small number of recent studies suggest that 5) Internet-based treatments for insomnia can be effective, but 6) there is to date only a single preliminary study with cancer patients.

Our aim is therefore, in a randomized controlled trial, to test the feasibility and evaluate the efficacy of an internet-based treatment for insomnia, previously tested in a group of 28 US cancer patients, ~~in a large sample of Danish breast cancer survivors who are experiencing significant sleep problems 7-10 years after treatment.~~ (Change in protocol prior to recruitment and data collection: "in a large sample of Danish breast cancer survivors who are experiencing significant sleep problems 6 months to 3 years after surgery"). We

[1] The meta-analysis covered publications between 1990- Marts 2011 in English language in the databases: PUBMED, PsychINFO, EMBASE, CINAHL, Cochrane Library, Social Sciences Citation Index, and Pub med. Search terms applied were: concept 1 [ internet, web, online, computer-aided, computer-assisted, computer-guided, computerized OR computerised ] concept 2 [CBT, cognitive therapy, behavioral therapy, OR behaviour therapy] AND concept 3 [insomnia, sleep disorders OR sleeping problem]. P. 207-208 (30)

aim to test the following hypotheses: That a group receiving Internet-delivered cognitive-behavioral therapy (CCBT) for insomnia (CCBT-I) will experience reduced sleep latency, more hours of sleep, fewer awakenings during the night, improved sleep efficiency, increased subjective sleep quality, and improved quality of life after the intervention, when compared to a waiting list control group. We also aim to explore a number of possible moderators of the effect (comorbidity, depression, fear of cancer recurrence tendency to ruminate) and mediating mechanisms (changes in sleep habits and sleep-related lifestyle factors).

**METHODS**

PARTICIPANTS

~~Women from a national cohort of Danish women treated for primary breast cancer between autumn 2001 and spring 2004, who responded to a follow-up questionnaire in August 2011~~ (Change to protocol prior to recruitment and data collection: Danish women surgically treated for breast cancer according to Danish Breast Cancer Group (DBCG) guidelines for loco-regional breast cancer between June, 2011 and December, 2013) and who meet the following criteria:

Inclusion criteria: 1) Reported moderate-to-severe sleep disturbances, defined as a score> 5 on the Pittsburgh Sleep Quality Index (PSQI) (32;33) (see below), and 2) are found to be disease free. Furthermore, participants 3) are required to have access to the Internet.

Exclusion criteria: 1) Recurrence of breast cancer, 2) a second cancer, 3) and other serious physical or psychological comorbidity (e.g. depression, cardiovascular disease, and COPD), 4) shift work schedule, 5) other sleep disorders (sleep apnea, narcolepsy)

**PROCEDURE**

INFORMATION AND REQUEST TO PARTICIPATE

Women who fulfill the inclusion criteria receive an information folder by mail informing them of the study (Appendix 3-4) and requesting them to return either a) a “no thank you”- form if they are not interested in participating (Appendix 5), or b) an interest-form (Appendix 6) stating their phone number, email-address, and a list of dates on which they can be reached by telephone for further verbal information, and instruction before they decide whether to participate. The following information about the phone call is stated on the interest form: that it lasts approximately 20 minutes, and that they are advised to chose a date, and time of day for the call where there is a minimum of distractions, and if possible to take the call in a quiet location. They are also informed about their right to have a lay representative present in which case they are encouraged to phone the project coordinator themselves with the phone on speaker.

The information folder (Appendix 4) informs about the background, purpose, and target group of the study, who planned, initiated and funded the study, and the overall procedures and risks involved with the study. Also, they are told, that for practical reasons, they will be randomly assigned to one of two groups after completion of the questionnaires and sleep dairies: either a group that begin the intervention straight away or a group who begins the intervention after 15 weeks. Non-respondent women receive a reminder after one week (Appendix 7) containing the information folder, the no-thank you form, and the interest-form. The women who return a completed interest form receive a phone call undertaken by trained research assistants under the supervision of the project coordinator. During the approximately 20 minute phone call they receive verbal information about the study and the procedures. If the women are still interested in participating after the verbal information is given, they are screened via a semi structured interview in terms of exclusion criteria to ensure that they are eligible for the intervention (appendix 8). ~~Finally, they are informed that they have 48 hours to electronically sign (via NemID) a consent form (appendix 9) sent to their e-mail address if they are interested in participating. The email also informs about the procedure of signing via NemID (appendix 10).~~ (Change to protocol prior to recruitment and data collection: the electron-

ic signing (NemID) of the consent form is for technical and economic reasons replaced with signing a paper consent form and returned the consent form by mail).

Phone calls as opposed to face-to-face conversations are a necessary means of delivering the verbal information about the project as the women are part of an existing national cohort of cancer survivors, and thereby not pre-selected in terms of geographical location. Hence, we expect women from all parts of the country, to be interested in participating. Making the journey to Aarhus may pose an inconvenience and preclude some from participating thereby having a detrimental effect on the study quality.

BASELINE MEASURES

After receiving the consent form, log-on details (username and password) to the www.shut-i.org site alongside information about technical support and PC requirements (appendix 11-12) is e-mailed to the participants. They are advised to logon to the site within five days, and commence filling out the baseline questionnaires (appendix 13) and the sleep diary (appendix 14-15) available through the SHUTi interface. Non-respondents are e-mailed a reminder after three days. The baseline questionnaires (see below for detailed descriptions) include questions about sleep quality, fatigue, depression, anxiety, quality of life, sleep habits and sleep-relevant lifestyles, together with use of health care services, sleep medication, and use of alternative medicine with the aim of treating sleep problems. They are also asked to complete questions about physical and mental comorbidity, rumination, and fear of recurrence of cancer. They are then asked to complete an Internet-based sleep diary (appendix 15) for a minimum of 10 days during the following 2-week period. They will be sent reminders to fill in the diary via email. (Change to protocol prior to recruitment and data collection: while sleep diaries will be completed through the SHUTi program, the remaining questionnaires at baseline, post-intervention, and follow-up will for practical reasons be completed as online questionnaires using the Qualtrics platform (Qualtrics, Provo, Utah)).

RANDOMIZATION

After completion of the baseline measures and sleep diaries, the participants are randomized ~~using an established computerized randomization procedure (provided by the Department of Experimental Clinical Oncology, Aarhus University Hospital)~~ to: a) internet-delivered cognitive behavioral therapy of insomnia (CCBT-I) or b) a waiting list control group for whom CCBT-I is delayed for 15 weeks. The participants are informed of group allocation via email (appendix 16-17) (Change to protocol prior to recruitment and data collection: The women are allocated to CCBT-I and waitlist control using randomization lists generated using the software package Power And Sample Size (PASS) version 12 (Kaysville, UTAH, USA: NCSS, LLC.; 2013.)

INTERVENTION

The intervention program is designed to be completed in 6 weeks. To ensure that all participants have opportunity to complete the program they are granted access to the program for 9 weeks (see below for details of the intervention).

POST-INTERVENTION

After the intervention, participants in both groups are asked to complete a post-intervention questionnaire package and then to fill in the sleep diary for a 2-week period (see below for details and appendix 18-19)

FOLLOW-UP (1)

After an additional 4 weeks both groups complete two sleep questionnaires (PSQI and the Insomnia Severity Index (ISI), see below for details and appendix 20-21) after which the waiting list group is offered the intervention (The procedure is summarized in **figure 1**)

FOLLOW-UP (2)

Approx. two years after completion of the first follow-up (December 2017) we will ask both groups to complete the PSQI and ISI to assess the stability of the effects.

INTERVENTION DETAILS

The Internet intervention offered is the SHUTi program (Sleep Healthy Using The Internet), which is based on the existing consensus concerning non-pharmacological treatment of insomnia and builds on previous validated CBT's for insomnia (CBT -I) (34). The method has been tested and validated with insomnia patients (25;35) as well as in a small group of cancer survivors in the U.S. (24). The program consists of 6 interactive modules: 1) "Overview" - an introduction to the program, 2) "Behavior 1" which focuses on sleep restriction, i.e. reducing the time spent in bed, with the aim of improving sleep efficiency (number of hours of sleep / number of hours in the bed), 3) "Behavior 2" which focuses on stimulus control with the aim of strengthening the associations between the bedroom/bed and sleep (e.g. by eliminating activities in bed not associated with sleep), 4) "Education" which focuses on establishing appropriate bed-time habits, 5) "Sleep thoughts" which helps the participant identify and modify inappropriate thoughts about sleep. 6) "Problem prevention" focuses on minimizing the risk of relapse.

After the first two modules, participants will have access to a new module every week after having completed the previous module. Each module takes approx. 60 minutes to complete, and participants subsequently have free access to this and the previous modules. Participants are recommended to fill in the sleep diary during the entire course of the intervention and receive individualized feedback and instructions based on the results of their sleep diary. Automated e-mails inform the participants about the next step in the program and provide information with the aim of increasing adherence. Technical support via email and telephone contact with research assistants will be available throughout the intervention period. ~~One week after the intervention has commenced all participants in the intervention group will receive a phone call to ensure that they have started the intervention and to answer any questions they may have.~~ (Change to protocol prior to recruitment and data collection: The participants will not receive any phone calls). The intervention is based on a model of factors found to promote the effect of Internet-delivered interventions aimed at behavior change (24).

CONTROL GROUP

Participants randomly assigned to the control condition are told that for practical reasons, they will have to wait 15 weeks before partaking in the intervention. The term "*waitlist control*" is not used in an attempt to alleviate some of the methodological issues related to the waitlist control condition and strengthen the design of the study. Some of the issues related to the waitlist conditions are: a) increased drop-out rates, b) reduced motivation as a result of disappointment, c) increased likelihood of seeking other treatment or treatment information thereby distorting the treatment effects of the intervention. Such issues can have a detrimental effect on the study quality and results. The waitlist control group completes the same measures as the intervention group and is offered CCBT-I at the end of the assessment period (see figure 1).

**MEASURES**

Below all measures are listed. A summary can be found in **table 1** at the end of this section. Copies of the baseline questionnaire package can be found in appendix 13, the post-intervention questionnaire package in appendix 19, and the follow-up questionnaire package in appendix 21. ~~All questionnaires are solely ad-~~

~~ministered through the SHUTi interface and is username/password protected.~~ (Change to protocol prior to recruitment and data collection: With the exception of the sleep diaries, which are integrated in the SHUTi program, all remaining questionnaires will be completed using the Qualtrics platform assigning the participants a personal, unique ID. Anonymity is ensured by keeping user IDs and files with personal information separate).

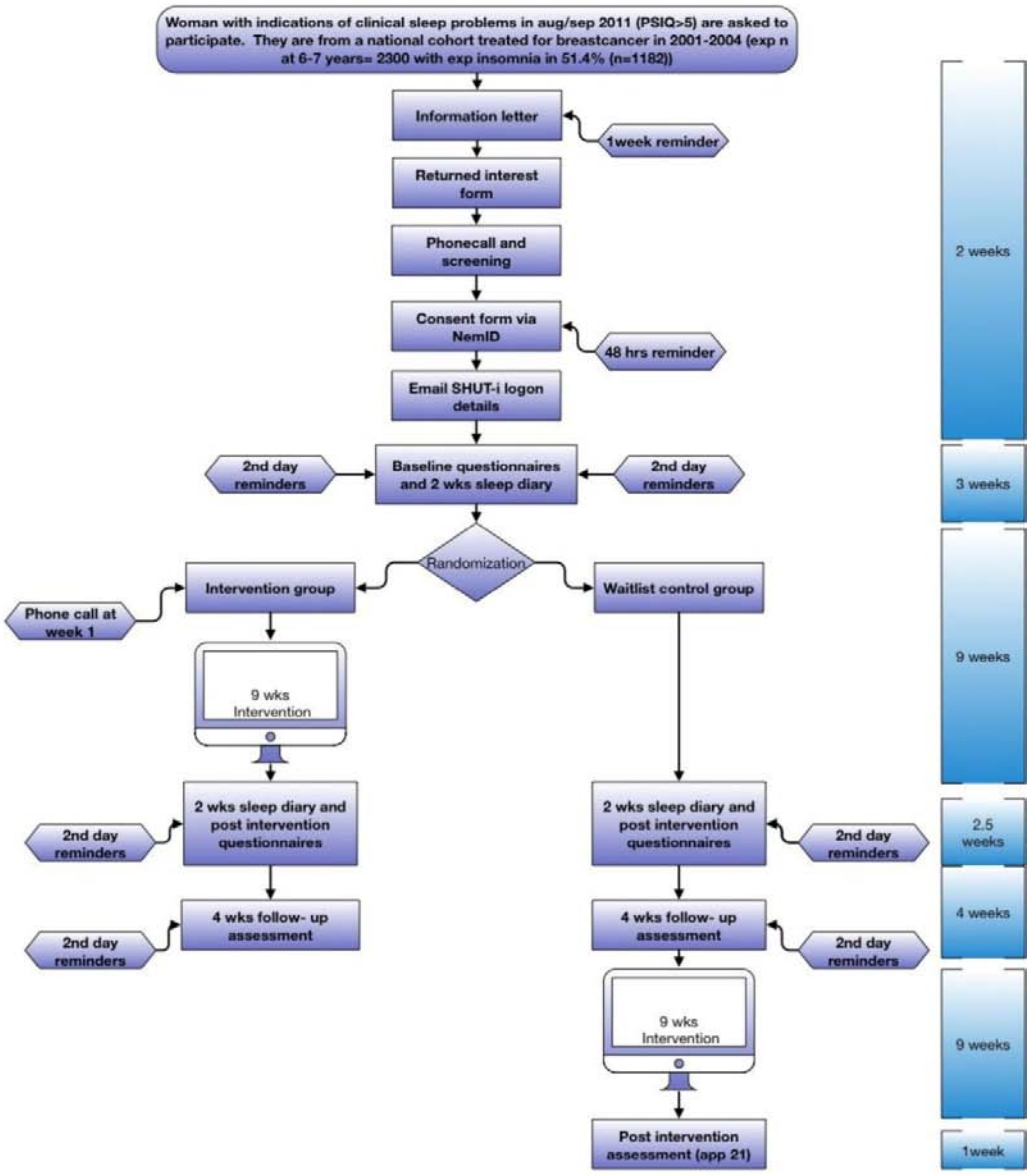


**Figure 1 Study flow**

PRIMARY ENDPOINTS

1) Sleep diary (See appendix 15). To assess the severity of sleep disturbance, an online sleep diary is to be completed daily for at least 10 out of 14 days before initiation of the intervention (24;25). The sleep diaries includes 10 standard questions including information about bedtime, sleep onset latency, number of awakenings, total length of awakenings, wake time, arising time, daytime naps, rating of soundness of previous night's sleep, rating of refreshed feeling upon morning awakening, and information about sleep aids (medication and/or alcohol use).

2) The Pittsburgh Sleep Quality Index (PSQI; appendix 13 p.14-15; appendix 19 p. 4-5; appendix 21) (33). This scale is a recognized and widely used instrument for assessing sleep quality (36;37), which has been validated in studies of cancer patients (32). We have previously used the Danish version in several studies, including a study of young and older Danes (38) and in previous studies of the cohort of women treated for breast cancer (8). The PSQI consists of 19 questions covering seven components, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medications, and daytime dysfunction. The total PSQI score ranges from 0 to 21. A total PSQI score> 5 is considered to be indicative of primary insomnia both in the general population (36) and among cancer patients (32). Comparisons with sleep laboratory-based data and sleep diaries have shown a total PSQI score of > 5 to have both high sensitivity (98.7%) and high specificity (84.4%) (32) in identifying individuals with insomnia. A higher cut-off of 6 yielded higher specificity (100%), but a somewhat lower sensitivity (93.4%). In the present context, high sensitivity (low number of false negatives) has been given higher priority than high specificity (low number of false positives).

3) The Insomnia Severity Index (ISI; appendix 13 p.11; appendix 19 p. 11; appendix 21) is a 7 item questionnaire assessing subjective experience of sleep onset time, sleep maintenance, early morning awakenings, degree of sleep satisfaction, reduction of daytime functioning as a result of sleep difficulties, distress caused by sleep problems and conspicuousness of sleep problems as estimated by others (39). The scale has been validated in both paper and pencil (40) and web-based formats (41) and has been successfully applied to assess the prevalence of insomnia in cancer patients (42).

SECONDARY ENDPOINTS

1) Fatigue is assessed with the 13-item Functional Assessment of Chronic Illness Therapy (FACIT; appendix 13 p. 16; appendix 19 p. 8) Fatigue Scale (Version 4). This scale is developed to assess cancer related levels of fatigue during daily activity (43) and is available in a validated Danish version.

2) Depressive symptoms are assessed with Beck's Depression Inventory (BDI-II; appendix 13 p. 33-34; appendix 19 p.18-19) (44). A Danish version has been used and validated in several studies, including the cohort of women treated for breast cancer (45). (Change to protocol prior to recruitment and data collection: to reduce participant burden, this questionnaire is omitted at post-intervention and follow-up).

~~3) Anxiety is measured by the State-Trait Anxiety Inventory (STAI; appendix 13, p. 31-32; appendix 19 p 16-17) (46), which was previously used in several Danish studies, for example (47).~~ (Change to protocol prior to recruitment and data collection: to reduce participant burden, this questionnaire is omitted at all time points).

~~4) Quality of life (QoL) is measured with the SF-12 (48; appendix 13 p. 12-13; appendix 19, p.6-7), a short version of the SF-36, available in a validated Danish version (49).~~ (Change to protocol prior to recruitment and data collection: to reduce participant burden, this questionnaire is omitted at all time points).

5) Self-reported cognitive function is assessed with the Cognitive Failures Questionnaire (CFQ; appendix 13 p. 27-30; appendix 19 p.12-15) (50), which measures subjective cognitive difficulties such as impaired memory, difficulties concentrating, etc. A Danish version of the CFQ is currently being validated in a group of cancer patients and patients attending the dementia clinic, Aarhus University Hospital.

6) Sleep habits and sleep-relevant lifestyle is assessed by adapting, further developing, and testing in the first phase of the study an existing instrument (27; appendix 13 p.17-18; appendix 19 p.9-10), that measures: activities before bedtime, eating habits before bedtime, use of stimulants (coffee, tea, softdrinks), alcohol, activities in the bedroom, exercise, thought patterns concerning sleep, etc.

7) A brief questionnaire has been developed to assess the use of health services, self-help methods, sleep medication,fatigue, morningness-eveningness type, and complementary and alternative medi-

cine/treatment (appendix 13 p. 1-6; appendix 19 p. 1-3; appendix 21). (Change to protocol prior to recruitment and data collection: to reduce participant burden, this questionnaire is omitted at post-intervention and follow-up).

8) A brief questionnaire assessing pain is included (appendix 13 p. 6-7; appendix 19 p.2-3; appendix 21)

POSSIBLE MODERATORS

Baseline factors that could be hypothesized to moderate the effect of the intervention include:

1) Fear of recurrence of cancer, which is measured with the Fear of Cancer Recurrence (FCR; appendix 13 p.20) Questionnaire that has been developed in collaboration with Australian partners and tested in the cohort of women treated for breast cancer (data not yet published).

2) Depressive symptoms (BDI-II, see above and appendix 13 p. 33-34; appendix 19 p.18-19)

3) The tendency to ruminate, as measured with the Rehearsal subscale of the Emotional Control Scale (ECQ-R; appendix 13 p.21) (53). We have previously used a Danish version and found correlations between rumination and sleep quality (PSQI) (38).

4) A short questionnaire has been developed to assess the expected effects of and motivation to complete the intervention (appendix 13 p. 19).

5) A short questionnaire has been developed to assess the use of health services, self-help methods, sleep medication, and complementary and alternative medicine/treatment (appendix 13 p. 1-7; appendix 19 p.1-3; appendix 21).

6) A brief questionnaire assessing pain is included (see above).

8) The Impact of Event Scale-Revised (appendix 13 p.22-23;25-26) (54) is included as a measure of subjective response to a specific traumatic event. This scale approximates the DSM-IV criteria for posttraumatic stress disorder. Subjective response to both breast cancer and one other self-chosen traumatic event is assessed. The delineation of the self-chosen traumatic event is based on the traumatic life event questionnaire (see below)

~~9) Traumatic Life Events Questionnaire (TLEQ; appendix 13 p.24) (55) is an inventory consisting of 22 different, potentially traumatic events where the participants are asked to identify the one event, that they have experienced and found the most traumatic. The inventory has been adapted and modified to suit the Danish population.~~ (Change to protocol prior to recruitment and data collection: to reduce participant burden, this questionnaire is omitted).

POSSIBLE MEDIATORS

Possible mediating mechanisms of the effect of the intervention on sleep include:

1) Changes in sleep habits and sleep-related lifestyle from baseline to post-intervention (see above and appendix 13 p.17-18; appendix 19 p.9-10)

2) The experience of and satisfaction with the intervention (intervention group only), as measured by the instrument developed in the first trials of the SHUTi intervention (35; see appendix 19, p.20)

**Table 1**. Summary of measures and assessment times:

| Measures | Baseline | Post intervention | FUP | Type |
|---|---|---|---|---|
| Sleep diary (SHUTi) | X | X | | Outcome |
| The Pittsburgh sleep quality index | X | X | X | Outcome |
| Insomnia Severity index | X | X | X | Outcome |
| FACIT Fatigue Scale | X | X | X | Secondary endpoint |
| Becks depression inventory | X | ~~X~~ (-) | | Secondary endpoint, moderator |
| State-trait anxiety index | ~~X~~ (-) | ~~X~~ (-) | | Secondary endpoint |
| SF-12 | ~~X~~ (-) | ~~X~~ (-) | | Secondary endpoint |
| Cognitive failures questionnaire | X | X | | Secondary endpoint |
| Sleep-related behavior index | X | X | | Secondary endpoint mediator |
| Fear of Cancer Recurrence | X | | | moderator |
| The Rehearsal subscale of the Emotional Control Scale | X | | | moderator |
| Pain questionnaire | X | X | X | Secondary endpoint, moderator |
| Expectations about the intervention questionnaire | X | | | Mediator |
| The impact of event scale-revised | X | | | Mediator |
| Traumatic Life Events Questionnaire | ~~X~~ (-) | | | Mediator |
| Use of health services, and general health questionnaire | X | X | x | Secondary endpoint, moderator |
| Expected effects and motivation | X | | | Moderator |

(Change to protocol prior to recruitment and data collection: to reduce participant burden, questionnaires marked with (-) are omitted. FACIT fatigue is included at follow-up).

SUPPLEMENTARY DATA

Registry- and questionnaire data available 7-10 years, 6-8 years and 1 year prior to the intervention study include: Socio-economic status (education, income, wealth), disease characteristics (tumor size, number of involved lymph nodes, estrogen receptor status), treatment (type of surgery, chemotherapy, radiation, and hormone therapy), health and health-related behaviors (comorbidity, pain and sensory disturbances, smoking, alcohol, physical activity, physical function (SF-36), psychological characteristics and symptoms (depressive symptoms, post-traumatic stress symptoms, concerns about relapse of cancer, social support, religiosity), and use of health services/medication (antidepressants, sleep medication, psychosocial support, and complementary and alternative treatment). Furthermore, seasonal effects will be included as a variable upon interpretation of the results by registering the photoperiod throughout the study. All data are based on Danish national longitudinal registries or validated questionnaires, and are described in previous publications, e.g. (8;45;56;57) and present, in an international context, a unique opportunity for drop-out analyses, enabling us to evaluate the generalizability of the results.

**ANALYSIS**

Dropout analyses: Available socio-demographic, disease-and treatment-related, and psychosocial data for participants and non-responders will be compared to evaluate the generalizability of results. If differences are found, adjustments will be made in subsequent analyzes.

Comparison of groups at baseline: A preliminary comparison of baseline data for the two groups at baseline will be conducted using t- tests and $chi_2$ tests with the aim of evaluating the result of randomization. If differences are found, they will be statistically adjusted for in the subsequent analysis.

Main effects: The main effect of the treatment on primary and secondary outcome variables will be assessed using mixed-model repeated-measures ANOVA's (Group x Time). If statistically significant group x time interactions are found, the data will be further analyzed with post-hoc-tests/planned contrast analyses adjusting for multiple comparisons. If group differences are found at baseline, the relevant variables will be included as covariates.

Moderator analyses: The influence of possible moderators will be analyzed using interaction analyses, as suggested by Baron and Kenny (58;59), with the aim of assessing whether individual differences in various baseline variables (e.g. comorbidity, expectations, etc.) influence the effects of the intervention. The extensive background data available to us will allow us to explore other potential moderators (e.g., disease and treatment-related variables).

Mediator analyses: Mediation analysis, as proposed by Sobel and Baron & Kenny (58;60;61) will be used to examine mediation, i.e. whether changes in certain variables (e.g. sleeping habits) can explain the changes after intervention in the primary endpoints. If needed, moderated mediation analyses will be applied (62).

NUMBER OF PARTICIPANTS

The combined effects found in the meta-analysis of published randomized trials of Internet-based treatment for insomnia (30) are: sleep quality (d=0.41), sleep efficiency (d=0.40), number of awakenings (d=-0.45), sleep onset latency (d=-0.55), total minutes slept (d=.22), time spent in bed (d=.25). If we aim to detect an effect corresponding to an average of the effects above (d = 0.38) with 80% statistical power, at least 2 x 109 participants are required. If we, again based on existing studies, expect an uneven dropout rate of 30% in the intervention group and 15% in the control group, at least 142 participants should be randomized to the intervention group and at least 126 to the control group.

In our national cohort of women previously treated for breast cancer who had completed a follow-up questionnaire in August 2011 (N: 2085 = 84% of eligible women), 51.5% had a total PSQI score >5. This indicates that we can expect that approx. 1000 women will show evidence of primary insomnia. Data from Statistics Denmark (63) indicate that only half of those aged 65-89 years are Internet users. In our cohort, approx. half of the women are over 65 yrs old. Therefore, we can estimate that approximately 75% of the sample can be expected to have access to and be able to use the Internet. This results in an expected number of 750 eligible participants. Based on these numbers, a response rate of at least 36% is needed to recruit the 268 women needed to obtain a satisfactory statistical power (80%). This is considered a realistic goal. In an earlier national intervention study of women treated for breast cancer, we thus achieved a response rate of 50% (64). (Change to protocol prior to recruitment and data collection: the population of breast cancer survivors from which we will recruit is changed from the original cohort who have received surgery between 2001 and 2004 to a cohort of women surgically treated for breast cancer according to Danish Breast Cancer Group (DBCG) guidelines for loco-regional breast cancer between June, 2011 and December, 2013. Prevalence of sleep problems, eligibility and response rates, and statistical power calculations remain unchanged).

STUDY GROUP

The responsibility and day-to-day running of the project is undertaken by The Unit for Psychooncology and Health Psychology, Aarhus University Hospital/University of Aarhus. The intervention program that we plan to use in the study (SHUTi), has been developed and tested by a U.S. research group (University of Virginia Health System) in people with insomnia (25;35), including 28 cancer patients with insomnia who had completed their treatment at least 1 month earlier (24). We have established contact with University of Virginia

Health System, who has agreed to collaborate with us in developing and testing a Danish version of the program. This collaboration is noncommercial.

FUNDING

The project has received funding kr. 500.000 from the Danish Cancer Society (Kræftens Bekæmpelse) and DKK 2.077366 has been applied for at the TRYG foundation (appendix 22). None of the researchers involved are affiliated with nor have financial or other interests in the funding bodies. The participants will not receive any financial compensation for participation in the study.

**ETHICAL CONSIDERATIONS**

~~The national cohort study has previously been approved by the relevant research ethics committees and the Danish Data Protection Agency~~. (Change to protocol prior to recruitment and data collection: The national cohort of women treated for breast cancer from which we will recruit is changed from the original cohort who have received surgery between 2001 and 2004 to a cohort of women surgically treated for breast cancer according to Danish Breast Cancer Group (DBCG) guidelines for loco-regional breast cancer between June, 2011 and December, 2013). Prior to data collection, the protocol will be submitted to: a) an international database for planned clinical trials (e.g., clinicaltrials.gov), b) the local research ethics committee. We will adhere to the general ethical guidelines for human trials. All participants receive oral and written information about the project. They are informed that they can withdraw at any time from the study with no consequence for their current or future treatment. To ensure that the participants have equal opportunity to benefit from the intervention, a telephone help line is established which participants can call concerning both technical questions about the program. In addition, they receive weekly reminders per e-mail to remember to access the interface. If a participant, based on her responses, is estimated to require treatment (e.g. for depression), they will be encouraged to and assisted in seeking appropriate medical or psychological help. Participants are advised to continue any medical treatment for insomnia, and to consult a doctor before changing medical regimen. As the intervention is not introduced as a substitute for any other treatment, we do not consider the waiting list condition per se to pose a specific ethical challenge.

PRIVACY AND DATA SECURITY

Participants access the SHUTi interface using a personal, unique user name and password. The SHUTI program stores any personal information in a separate one-way system that cannot be accessed from the Internet but only locally by the SHUTi administrators. Connections between personal information and other data are encrypted. Data is stored physically on servers in locked facilities, in the United States. Participants are encouraged to continuously update their antivirus software on their personal computers for the duration of the project. Combined, these measures ensure an acceptable level of data security. After completion of the study, the data is stored and processed according to "Act on Processing of Personal Data". The data is only useful for the interpretation of this trial and will therefore be unattractive to any third party. (Addition to protocol prior to recruitment and data collection: All other questionnaires will be completed using the Qualtrics platform assigning the participants a personal, unique ID. Anonymity is ensured by keeping user IDs and files with personal information separate).

DIGITAL COLLECTION OF PATIENT CONSENT FOR RESEARCH PROJECT

~~Collection of consent forms can be signed digitally. This makes it easy and safe for patients to sign and to file the consent form. Once the consent form has been digitally signed, it can be traced to all involved signatories, it is assigned a time stamp and the signature is legally binding.The electronically signed consent forms are secured on a server at Nets. Nets have a vast experience with archiving sensitive documents for organizations such as banks, insurance companies and public institutions. They comply with the most stringent requirements in relation to uptime, encryption, availability and security. NemID meet the Danish stat-~~

~~utory requirements for data security in accordance with Datatilsynet. Nets is responsible for the public digital employee signature, company signature and NemID.~~ (Change to protocol prior to recruitment and data collection: the electronic signing (NemID) of the consent form is for technical and economic reasons replaced with signing a paper consent form and returned the consent form by mail).

ADVERSE EFFECTS, INCONVENIENCES, BENEFITS, AND RISKS

We do not expect Internet-based cognitive behavioral therapy to be associated with any adverse health effects or risks as no adverse effects has been reported for conventional CBT for insomnia.

At the level of the individual participant we expect treatment benefits of the Internet-based intervention to be comparable to conventional cognitive behavioral therapy for insomnia. Hence, we expect participants to experience improved sleep quality and improved sleep efficiency post-intervention. Minimally, they will have better knowledge of their own sleep patterns and sleep hygiene. We expect that sleep improvements lead to better day time functioning with decreased daytime fatigue, reduced subjective experience of cognitive dysfunction, depression, and anxiety and overall increased quality of life. The time invested in the projected may pose an inconvenience in a busy schedule but this seems outweighed by the potential benefits of the intervention.

The study will contribute to both the research area of insomnia and of long-term symptoms after cancer treatment. Sleep problems are associated with impaired quality of life and can adversely affect physical and mental health. Non-pharmacological treatments for insomnia have been shown at least as effective as drug therapies, and are without adverse effects. If it is confirmed that an Internet- delivered intervention is effective against sleep problems among women previously treated for breast cancer, this treatment could without significant costs be implemented immediately as a rehabilitation service for cancer patients, survivors as well as other groups with significant sleep problems. ~~A particular strength of the proposed study lies in our use of our ongoing national cohort of Danish women treated for breast cancer with high data quality. This allows us to conduct a population-based study with high generalizability of the results.~~ (Change to protocol prior to recruitment and data collection: The national cohort of women treated for breast cancer from which we will recruit is changed from the original cohort who have received surgery between 2001 and 2004 to a cohort of women surgically treated for breast cancer according to Danish Breast Cancer Group (DBCG) guidelines for loco-regional breast cancer between June, 2011 and December, 2013). We also consider the results to be generalizable to other groups with sleep problems. Hence, we expect the study to bring forth new beneficial knowledge to many people.

PUBLICATION AND DISSEMINATION

Positive, negative and inconclusive results will be published in international peer-reviewed journals and the current guidelines for good scientific practice (Vancouver (65), CONSORT (66)) will be adhered to.

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