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Digital Cognitive-Behavioral Therapy for Insomnia in Cancer Survivors: Protocol for a Pragmatic Clinical Trial

Intervenção Digital para o Tratamento da Insónia em Sobreviventes de Cancro: Protocolo de um Ensaio Clínico Pragmático

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ABSTRACT

Introduction: Insomnia is one of the most prevalent, persistent, and distressing conditions associated with cancer, affecting almost half of all cancer survivors. Although cognitive-behavioral therapy for insomnia is well established as the gold-standard treatment for insomnia, its accessibility is very limited in routine care. We aim to examine the real-world effectiveness and acceptability of a digital cognitive-behavioral therapy for insomnia for cancer survivors with insomnia symptoms through a randomized controlled trial in Portugal.

Methods and Analysis: Our cancer trial will test the effects and acceptability of an accessible internet-delivered self-administered cognitive-behavioral therapy for insomnia digital intervention with clinician support, OncoSleep. This online program includes six interactive, personalized weekly sessions featuring evidence-based techniques targeting psychophysiological hyperarousal and maladaptive conditioning, tailored for cancer survivors. Research study procedures include screening for eligibility in the general population and randomization into one of two arms: the digital CBT-I program or a waitlist control group. Insomnia severity (primary outcome), fatigue, sleep diary outcomes, psychological distress, and quality of life (secondary outcomes) will be assessed at baseline and post-intervention.

Keywords: Cognitive Behavioral Therapy; Digital Health; Neoplasms/complications; Sleep Initiation and Maintenance Disorders

RESUMO

Introdução: A insónia é um dos sintomas associados ao cancro mais prevalentes, persistentes e debilitantes, afetando quase metade das pessoas sobreviventes. Embora a terapia cognitivo-comportamental para a insónia esteja bem estabelecida como o tratamento de referência para a insónia persistente, permanece praticamente inacessível na prática clínica. Pretendemos examinar os efeitos clínicos e a aceitabilidade de uma intervenção digital de terapia cognitivo-comportamental para a insónia para pessoas sobreviventes de cancro com sintomas de insónia através de um ensaio clínico em Portugal.

Métodos e Análise: O nosso ensaio oncológico vai testar os efeitos clínicos e aceitabilidade de uma intervenção digital de terapia cognitivo-comportamental para a insónia com apoio clínico oferecido *online*, o programa OncoSleep. O programa *online* inclui seis sessões semanais, interativas e personalizadas, que envolvem técnicas baseadas na evidência para reduzir a hiperativação psicofisiológica e condicionamentos maladaptativos, adaptadas à sobrevivência oncológica. O recrutamento será realizado na população geral e, após triagem, os participantes elegíveis serão aleatoriamente alocados a um de dois braços: o grupo de intervenção da terapia cognitivo-comportamental para a insónia ou um grupo em lista de espera. A gravidade da insónia (indicador primário), fadiga, indicadores de sono, sofrimento psicológico, e a qualidade de vida (indicadores secundários) serão avaliados pré- e pós-intervenção.

Palavras-chave: Distúrbios do Início e da Manutenção do Sono; Neoplasias/complicações; Saúde Digital; Terapia Cognitivo-Comportamental

INTRODUCTION

More people are surviving cancer than ever before, despite a surge in cancer incidence, particularly early-onset.[1-3] Cancer is increasingly recognized as a chronic condition, with ongoing unmet needs after primary treatment and throughout the cancer journey. Insomnia emerges as a prevalent complaint linked to cancer and its treatments, and tends to persist, affecting between 29% to 64% of cancer survivors months or years after treatment completion.[4-6] Insomnia has been associated with deleterious consequences, including heightened fatigue and pain sensitivity, and reduced quality of life and immune functioning.[7,8] Untread cancer-related insomnia may also contribute to poorer treatment response, increased risk of cancer recurrence, and reduced survival.[9-11]

Insomnia is, however, highly treatable with cognitive-behavioral therapy for insomnia (CBT-I), a behavioral medicine intervention well-established as the treatment of choice for cancer-related sleep disturbances due to its efficacy, long-lasting benefits, and security profile.[12,13] Among people diagnosed with cancer, CBT-I improves key sleep parameters (i.e., insomnia, sleep diary outcomes), while also yielding benefits in psychological well-being, cancer-related symptoms (i.e., fatigue), and quality of life.[14] Cognitive-behavioral therapy for insomnia may be beneficial in addressing insomnia symptoms even when they do not reach the clinical threshold, acting as an important preventative measure against the development of

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more severe insomnia disorder.[15]

Current guidelines recommend CBT-I as the first-line treatment for insomnia, either offered in-person or digitally.[13] However, the accessibility to CBT-I remains extremely limited, particularly in cancer care.[16] As insomnia affects nearly half of all patients diagnosed with cancer, the need for CBT-I far exceeds available resources.[17] Consequently, pharmacotherapy, a second-line intervention, remains the most pragmatic resource,[4] filling the cancer-related insomnia treatment gap despite limited evidence for long-term efficacy, not being curative, side effects (including abuse, dependence, and tolerance), and security profile (e.g., drug-drug and drug-disease interactions).[18] Along with system-level barriers, practical barriers (i.e., travel/disease burden) affect cancer survivors' access to in-person CBT-I, emphasizing the need for more accessible interventions for cancer-related insomnia.[16]

The European Cancer Manifesto for 2024 - 2029 highlights the need to translate available clinical evidence into healthcare systems to support its sustainability and resilience, recognizing the value of comprehensive care models, the pressing need for treatment optimization, and the potential of digital for providing high-quality cancer care for all.[19] Digital CBT-I (dCBT-I) has been proposed to optimize insomnia treatment within cancer care, presenting a promising approach to address the needs of cancer survivors, offering patient convenience, opportunities for efficiency gains, and enhanced access to evidence-based, guideline-concordant insomnia treatment.[16]

The European Society for Medical Oncology (ESMO) clinical practice guideline recommends CBT-I as the standard of care for treating insomnia in cancer survivors (level of evidence I, grade of recommendation A), and offering dCBT-I when in-person CBT-I is not available (II, A). Subsequent treatment options include brief CBT-I or mindfulness-based therapies (II, B) and pharmacological intervention (II, C).[20] The guideline highlights that despite few studies have been conducted, dCBT-I shows highly promising effects for survivors, underscoring the need for high-quality trials to strengthen the evidence base for dCBT-I in people living with and beyond cancer.

By being focused on improving the accessibility of evidence-based digital therapeutics providing care for insomnia and expanding research on dCBT-I for cancer survivors, our goal is to test the real-world effectiveness and acceptability of a web-supported self-administered CBT-I intervention with clinician support, OncoSleep, on insomnia symptom severity in cancer survivors through a clinic-randomized hybrid effectiveness-implementation trial, in Portugal. Our primary aim is to test the clinical effects and acceptability of an accessible internet-delivered CBT-I by comparing post-test outcomes of insomnia severity between the intervention and a waitlist control group for cancer survivors experiencing subclinical or clinically significant insomnia symptoms. Our primary hypothesis is that, compared to the control group, the intervention group will show significantly lower insomnia symptom severity by the end of the intervention, and that the dCBT-I will be a well-accepted treatment for insomnia among cancer survivors.

The daytime consequences of insomnia, including fatigue and mood impairments that affect the quality of life, typically motivate survivors to seek specialized help.[4] Therefore, we will also test if the intervention produces clinically meaningful benefits on these psychosocial outcomes. We will also examine secondary between-group outcomes: sleep diary parameters, fatigue, psychological distress, and quality of life. We hypothesize that, compared to the waitlist control group, participants in the intervention group will report significantly better sleep after treatment, better health-related quality of life, and lower psychological distress and fatigue after treatment.

METHODS AND ANALYSIS

Participants

Survivors, recruited from the general population, will be eligible if they are aged 18 years or older; have a history of cancer, solid or blood malignancy(ies); have completed primary cancer treatment (survivors who are on hormone and/or other long-term maintenance therapies are eligible), and report having at least subclinical symptoms of insomnia [severity scores ≥ 8 in the Insomnia Severity Scale (ISI)],[21,22] emphasizing the unmet needs of this subgroup. Exclusion criteria: inability to read/write in Portuguese, pregnancy, breastfeeding, nightshift work, psychotherapy for insomnia, and self-reported untreated psychiatric condition or a formal diagnosis of another untreated sleep disorder (e.g., sleep apnea syndrome). These criteria were selected to be the most representative of real clinical settings, where it may not be feasible to systematically conduct diagnostic interviews or polysomnographic assessments to confirm insomnia disorder or exclude other sleep disorders. Patients can be on sleep medication if it has been stable for four weeks.

Screening, randomization, and assessments

In this two-armed parallel randomized controlled trial (RCT), the experimental group (dCBT-I via OncoSleep) will be compared to a waitlist control using treatment as usual from baseline to post-treatment. Survivors will complete surveys

at baseline (T0) and post-treatment (T1: eight weeks after randomization). Potential participants will be asked to complete an online screening assessment [including the ISI and the Hospital and Anxiety and Depression Scale (HADS)] to assess eligibility.[23,24] Survivors exhibiting severe psychological distress in the screening assessment (score of 21 - 41 in the HADS) will be advised to consider seeking specialized help but are welcome to participate in the study. After informed consent, eligible survivors will be sent links to complete the baseline assessment, including sociodemographic and clinical data, through a brief questionnaire developed for the study (Table 1).

Participants will then be randomized by an automated system either to the intervention group or a waitlist through a computer-generated randomization scheme using randomly varying block sizes (of two and four). Randomization will be stratified according to insomnia severity [based on the Insomnia Severity Index (ISI)] cutoff points[21,22]: sub-threshold insomnia (ISI score 8 - 14), moderate insomnia (15 - 21), severe insomnia (22 - 28), sleep medication use ("yes" if using medication at least two times per week, "no" if otherwise), psychological distress ("yes" if HADS score 22 - 42, "no" if < 22),[23,24] and time since completion of cancer treatment ("up to five years", "five or more years").

All outcomes will be assessed online using surveys consisting of a battery of validated questionnaires administered through a secure platform provided by the University of Coimbra. The OncoSleep program integrates an automated online collection of sleep diaries. Researchers remain blind to the allocation until after study completion.

Primary outcome: insomnia severity

Insomnia will be measured using the ISI,[21,22] consisting of seven items rated on a five-point Likert scale. Scores range from 0 - 28, categorized as no insomnia (0 - 7), subthreshold (8 - 14), moderate (15 - 21), and severe insomnia (≥ 22).

Secondary outcomes

Psychological distress

The HADS is a 14-item self-reported questionnaire assessing anxiety and depression (seven items each).[23,24] Psychological distress in the past week will be gauged using the two subscale scores, ranging from 0 - 21. Scores ≤ 7 indicate non-cases, 8 - 10 indicate mild symptoms, 11 - 14 moderate symptoms, and ≥ 15 severe symptoms.

Quality of life

Health-related quality of life in the past two weeks will be evaluated using the World Health Organization Quality of Life–Brief (WHOQOL-BREF),[26,27] covering four domains (physical health, psychological health, social relationships, and environment). Higher scores indicate better quality of life. Cancer-related quality of life will be assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30).[28,29] Scores range from 0 - 100, with higher scores indicating better functioning/global health status, and higher scores on symptom/single-item scales indicating more significant symptoms.

Fatigue

Fatigue in the preceding week will be assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF),[30,31] with higher scores indicating more fatigue.

Sleep diary

Sleep diaries capture waking and sleeping time, sleep onset latency (SOL: time it takes to fall asleep after turning off the lights), number of awakenings, total time awake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), and sleep efficiency (SE: percentage of time someone slept while in bed).[32] The diary also measures respondents' sense of morning refreshment (0 = "not at all" to 4 = "very"), sleep quality (0 = "very poor" to 4 = "very good"), and the use of sleep medication/alcohol. Post-test differences in sleep diary estimates between the intervention and control groups will be assessed. Baseline and post-treatment outcomes (weekly averages of daily mean SE, sleep quality, TST, WASO, and SOL) will be established from the week before the intervention and the week of intervention completion. The program will guide behavior change based on participants' SE by suggesting a sleep window.

Intervention

OncoSleep is a web-based CBT-I with six interactive, self-guided weekly sessions (approximately 35 minutes each) plus remote clinician support. OncoSleep is a fully automated program but includes support from a licensed psychologist as an additional feature: after each session, participants receive an email with additional feedback. Participants are also

informed they can contact the clinician if they have questions or difficulties.

The treatment was modeled after a well-established protocol but features disease-specific adaptations to target survivor-specific perpetuating factors and address factors that could interfere with treatment adherence.[16,33] Table 2 provides a detailed overview of the sessions' content. The initial session provides psychoeducation on sleep and cancer-related insomnia. Participants learn strategies to manage cancer-related symptoms affecting sleep (e.g., fatigue, night sweats). The second session covers sleep hygiene and relaxation techniques. Relaxation techniques, tailored to accommodate cancer-related effects, are recommended as a strategy to manage the stress that exacerbates cancer-related symptoms, thereby alleviating these symptoms. The third session introduces behavioral techniques stimulus control therapy (SCT) and sleep restriction therapy (SRT). Sleep restriction therapy seeks to restrict sleep opportunity (curtailing TIB based on the current sleep pattern, but not to less than a minimum of five hours) while leveraging heightened sleep pressure to consolidate and regularize sleep. Time in bed is then gradually adjusted weekly (indexed by a SE > 85%) until optimal sleep duration (and daytime functioning) is achieved. SRT is presented as adjusting the sleep window to emphasize the goal is to optimize sleep efficiency rather than limiting sleep. Sleep restriction therapy decreases arousal and improves sleep continuity and sleep depth.[13] Stimulus control therapy strengthens the association between sleep and the conditions under which it typically occurs by eliminating sleep-incompatible activities, minimizing awake TIB (e.g., going to bed only when sleepy and getting up when unable to sleep), and regulating the sleep schedule. Behavioral techniques are applied flexibly for participants who have difficulty complying due to illness burden and to prevent sleep loss, which could produce a hyperalgesic response). Adaptations also include addressing unhelpful sleep-related beliefs aiming to overcome resistance to behavioral strategies. The next session focuses on restructuring sleep and cancer-related beliefs (e.g., worry about the impact of insomnia on cancer progression) to decrease cognitive-cortical arousal and short-circuit the self-perpetuating cycle of insomnia. The fifth session features additional cognitive techniques to prevent (daytime) and cope (nighttime) with the racing mind (e.g., "worry time" is taught to reduce the interference of cancer-related worry during nighttime). Entering sleep diary information is a prerequisite for advancing to the next session, guiding personalized techniques, and tracking weekly progress.

Acceptability

Acceptability will be assessed through an online survey using quantitative measures (satisfaction, helpfulness, usability, odds of future technique use, willingness to recommend, and overall enjoyableness, rated on Likert-type scales), along with qualitative insights garnered from an open-ended question inviting participant feedback and suggestions for improvement. To assess satisfaction, the Consumer Report Treatment Satisfaction scale was adapted[25]: "How much do you feel the OncoSleep program has helped you in the following areas?" Items (well-being, coping with stress, energy levels, mood, insomnia, performance) will be rated from "a lot worse" = 0 to "a lot better" = 4. Format, clinician support, and complementary material helpfulness will be rated from "not helpful at all" = 0 to "very helpful" = 3. Usability, odds of future technique use, and willingness to recommend will be rated from "very low" = 0 to "very high" = 3 and overall enjoyableness will be rated from "very dissatisfied" = 0 to "very satisfied" = 3.

Ethical considerations and data management plan

This pragmatic trial, approved by the Deontology Committee for Research of the Faculty of Psychology of the University of Coimbra, is prospectively registered at ClinicalTrials.gov (NCT04898855), follows the Helsinki Declaration, and adheres to both the CONSORT[34] and SPIRIT reporting guidelines.[35] All data that may indirectly identify the participants will be deleted five years following the end of the study, as instructed by Resolution no. 1704/2015 of the Portuguese National Commission for the Protection of Data, enforceable to the treatment of personal data for clinical research.

Power analyses

Based on prior research,[14] we expect a moderate-to-large effect size. To detect a statistically significant ($p < 0.05$) effect of $d = 0.5$ with a statistical power of 80%, the required sample is 64 for each group. Adjusting for an anticipated attrition rate of 20%,[36] the total enrolment goal is 154 participants, 77 per arm. Sample size calculations were carried out in the pwr package in R version 4.4.0.

Statistical analysis plan

Mixed effects models based on an intent-to-treat approach will be used to assess between-group changes over time. All statistical tests will be two-sided. An eight-point clinical margin is considered clinically significant based on previous

research.[37] Cohen's *d* will be calculated based on absolute between-group differences post-treatment. Dropouts will be defined as participants failing to complete questionnaires at post-treatment and adherence as the number of sessions completed. Acceptability ratings will be analyzed using descriptive statistics.

DISCUSSION

There is a pressing need to adopt sustainable and innovative care delivery models to alleviate the burden of cancer, aiming to ensure that the rights outlined in the European Code of Cancer Practice are upheld: equal access to affordable and optimal cancer care through multidisciplinary within cancer networks. Considering insomnia tends to adopt a chronic course and has detrimental effects for survivorship and recovery, optimal treatment for cancer-related insomnia should be included in routine care. This article details the study design and protocol for a pragmatic RCT testing a dCBT-I to deliver guideline care in cancer survivorship. We aim to determine if dCBT-I is effective in a diverse setting for cancer survivors with complaints of insomnia and whether it can lead to improvements in patient's psychological distress, fatigue, and quality of life.

To improve equity in access to guideline treatment for insomnia in cancer care, we developed a dCBT-I for cancer survivors. Committed to delivering evidence-based, quality cancer care, we aim to examine its real-world effectiveness and acceptability. Certain limitations are anticipated. First, a self-referred sample of cancer survivors will be recruited, introducing potential selection bias. Our focus is on creating an interactive, user-friendly program with professional support to minimize attrition rates. Second, albeit comparable in efficacy to face-to-face CBT-I, self-guided interventions may result in smaller treatment effects.[14,37,38] To address this limitation and enhance treatment effects, self-administered CBT-I may be supplemented by clinician support,[39,40] helping patients implement treatment strategies, stay engaged in sessions, personalize treatment based on cancer experiences, and reinforce their self-efficacy.[41] A recent meta-analysis suggested clinician support is preferred when CBT-I is administered digitally.[42] This is in line with another meta-analysis that evaluated various delivery CBT-I formats and found in-person therapies and digital therapy with clinician support to be the most effective approaches.[43] Hence, our choice to include clinician support is informed by this evidence. Lastly, we opted for a wait-list control group to avoid withholding treatment unethically, making long-term between-subjects comparisons unfeasible. Notwithstanding such limitations, our pragmatic cancer trial will offer clinical practice guideline care for insomnia to cancer survivors in Portugal, in a community setting, generating broadly applicable evidence while simultaneously contributing to improved patient outcomes. Currently, pharmacotherapy, a second-line intervention for insomnia, stands as the prevailing treatment despite concerns around its efficacy, side effects, and safety profile, largely due to its accessibility. Telemedicine may be leveraged to enhance access to CBT-I for survivors who would otherwise be limited to pharmacotherapy, a less effective, second-line intervention. Our clinical trial aims to shed light on opportunities for facilitating optimal access to guideline-concordant insomnia treatment in cancer care and translating innovative, evidence-based approaches into clinical practice.

Effective and well-accepted digital therapeutics delivering CBT-I may result in clinical guideline care becoming routine in oncology settings, improving sleep and insomnia daytime consequences, and alleviating cancer burden. Evidence-based digital therapeutics may be integrated into a comprehensive survivorship plan, allowing for a personalized care pathway supported by an interconnected digital ecosystem aimed at enhancing the cancer healing journey.[16]

AUTHOR CONTRIBUTIONS

MIC: Conceptualization, writing – original draft.
AVS: Writing – original draft, review & editing, supervision.
MCC: Writing – review & editing, supervision.
AAG: Conceptualization, writing – original draft, review & editing, supervision.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. World Cancer Research Fund International. Cancer survival statistics. 2022. [cited 2023 Dec 20]. Available from: https://www.wcrf.org/cancer-trends/cancer-survival-statistics/.
2. American Association for Cancer Research. Cancer progress report. 2022. [cited 2023 Dec 20]. Available from: https://cancerprogressreport.aacr.org/progress/.
3. Ugai T, Sasamoto N, Lee HY, Ando M, Song M, Tamimi, et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. Nat Rev Clin Oncol. 2022;19:656-73.
4. Reynolds-Cowie P, Fleming L. Living with persistent insomnia after cancer: a qualitative analysis of impact and management. Br J Health Psychol. 2021;26:33-49.
5. Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol. 2010;28:292-8.
6. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001;19:895-908.
7. Lis CG, Gupta D, Grutsch JF. The relationship between insomnia and patient satisfaction with quality of life in cancer. Support Care Cancer. 2008;16:261-6.
8. Blask DE, Hill SM, Dauchy RT, Xiang S, Yuan L, Duplessis T, et al. Circadian regulation of molecular, dietary, and metabolic signaling mechanisms of human breast cancer growth by the nocturnal melatonin signal and the consequences of its disruption by light at night. J Pineal Res. 2011;51:259-69.
9. Innominato PF, Spiegel D, Ulusakarya A, Giacchetti S, Bjarnason GA, Lévi F, et al. Subjective sleep and overall survival in chemotherapy-naïve patients with metastatic colorectal cancer. Sleep Med. 2015;16:391-8.
10. Marinac CR, Nelson SH, Flatt SW, Natarajan L, Pierce JP, Patterson RE. Sleep duration and breast cancer prognosis: perspectives from the women's healthy eating and living study. Breast Cancer Res Treat. 2017;162:581-9.
11. Trudel-Fitzgerald C, Zhou ES, Poole EM, Zhang X, Michels KB, Eliassen AH. Sleep and survival among women with breast cancer: 30 years of follow-up within the Nurses' Health Study. Br J Cancer. 2017;116:1239-46.
12. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165:125-33.
13. Riemann D, Espie CA, Altena E, Arnardottir ES, Baglioni C, Bassetti CL, et al. The European Insomnia Guideline: an update on the diagnosis and treatment of insomnia 2023. J Sleep Res. 2023;32:e14035.
14. Squires LR, Rash JA, Fawcett J, Garland SN. Systematic review and meta-analysis of cognitive-behavioural therapy for insomnia on subjective and actigraphy-measured sleep and comorbid symptoms in cancer survivors. Sleep Med Rev. 2022;63:101615.
15. Denis D, Eley TC, Rijsdijk F, Zavos HM, Keers R, Espie CA, et al. Is digital cognitive behavioural therapy for insomnia effective in treating sub-threshold insomnia: a pilot RCT. Sleep Med. 202;66:174-83.
16. Clara MI, Canavarro MC, Miller-Mendes M, Allen Gomes A. Insomnia in cancer survivors: a precision behavioral sleep medicine approach. Eur Psychol. 2023;28:2.
17. Garland SN. A step in the right direction: making cognitive-behavioral therapy for insomnia more accessible to people diagnosed with cancer. Sleep. 2021;44:zsab202.
18. National Cancer Institute. Sleep disorders. 2022. [cited 2023 Dec 20]. Available from: https://www.cancer.gov/about-cancer/treatment/side-effects/sleep-disorders-hp-pdq.
19. European Cancer Organisation. Time to accelerate: together against cancer. 2023. [cited 2023 Dec 20]. Available from: https://www.europeancancer.org/manifesto.
20. Grassi L, Zachariae R, Caruso R, Palagini L, Campos-Ródenas R, Riba MB, et al. Insomnia in adult patients with cancer: ESMO Clinical Practice Guideline. ESMO Open. 2023;8:102047.
21. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34:601-8.
22. Clemente V, Ruivo Marques D, Miller-Mendes M, Morin CM, Serra J, Allen Gomes A. The European Portuguese version of the insomnia severity index. J Sleep Res. 2021;30:e13198.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.
24. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007;12:225-35.
25. Seligman ME. The effectiveness of psychotherapy: The consumer reports study. Am Psychol. 1995;50:12.
26. Vaz Serra A., Canavarro MC, Simões MR, Pereira M, Gameiro S, Quartilho ML, et al. Estudos psicométricos do instrumento de avaliação da qualidade de vida da Organização Mundial de Saúde (WHOQOL-Bref) para Português de Portugal. Psiq Clín. 2006;27:41.
27. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998;28:551-8.
28. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-76.
29. Pais-Ribeiro JL, Pinto C, Santos C. Validation study of the Portuguese version of the QLC-C30- V3. Psicol Saúde Doenças. 2008;9:89-102.
30. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. J Pain Symptom Manage. 2004;27:14-23.
31. Clara MI, Stein K, Canavarro MC, Allen Gomes A. European Portuguese version of the multidimensional fatigue symptom inventory-short form: validation study. Acta Med Port. 2023;36:723-30.
32. Morin CM, Espie CA. Insomnia: a clinical guide to assessment and treatment. New York: Springer; 2013.

33. Clara MI, Canavarro MC, Severina A, Ramos S, Rafael C, Allen Gomes A. Assessment of cancer-related fatigue expression: comparing the expression of fatigue in patients with a history of cancer, patients with other chronic diseases, and healthy individuals. Psycho-Oncologie. 2024;18:49-57.
34. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res. 2011;13:e126.
35. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34:601-8.
36. Savard J, Ivers H, Savard MH, Morin CM. Is a video-based cognitive behavioral therapy for insomnia as efficacious as a professionally administered treatment in breast cancer? Results of a randomized controlled trial. Sleep. 2014;37:1305-14.
37. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200-7.
38. van Straten A, Cuijpers P. Self-help therapy for insomnia: a meta-analysis. Sleep Med Rev. 2009;13:61-71.
39. Ho FY, Chung KF, Yeung WF, Ng TH, Cheng SK. Weekly brief phone support in self-help cognitive behavioral therapy for insomnia disorder: relevance to adherence and efficacy. Behav Res Ther. 2014;63:147-56.
40. Kaldo V, Jernelöv S, Blom K, Ljótsson B, Brodin M, Jörgensen M, et al. Guided internet cognitive behavioral therapy for insomnia compared to a control treatment - a randomized trial. Behav Res Ther. 2015;71:90-100.
41. Savard J, Ivers H, Savard MH, Morin CM. Is a video-based cognitive behavioral therapy for insomnia as efficacious as a professionally administered treatment in breast cancer? Results of a randomized controlled trial. Sleep. 2014;37:1305-14.
42. Hasan F, Tu YK, Yang CM, James Gordon C, Wu D, Lee HC, et al. Comparative efficacy of digital cognitive behavioral therapy for insomnia: a systematic review and network meta-analysis. Sleep Med Rev. 2022;61:101567.
43. Gao Y, Ge L, Liu M, Niu M, Chen Y, Sun Y, et al. Comparative efficacy and acceptability of cognitive behavioral therapy delivery formats for insomnia in adults: a systematic review and network meta-analysis. Sleep Med Rev. 2022;64:101648.

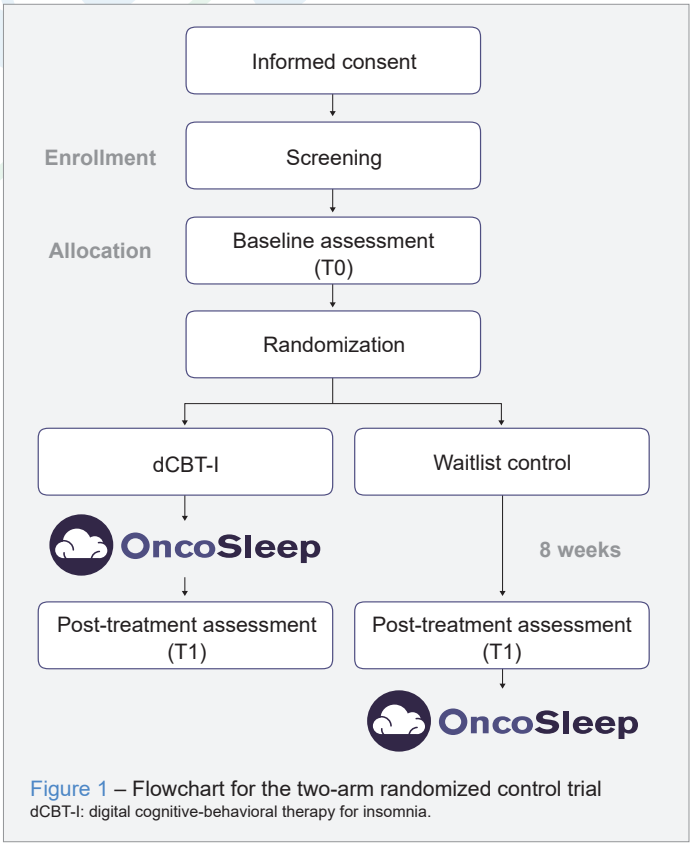

Figure 1 – Flowchart for the two-arm randomized control trial
dCBT-I: digital cognitive-behavioral therapy for insomnia.

Table 1 – Sociodemographic and clinical questionnaire

Sociodemographic and cancer questions	Questions on insomnia and digital treatment
Name and e-mail	Use of sleep medication
Sex	Insomnia symptoms: duration and frequency
Year of birth	Impact of cancer diagnosis in insomnia
Marital status	Daytime complaints
Education level	Known non-insomnia sleep disturbances/other major conditions
Occupational status	Current psychological treatment for insomnia (yes/no)
Working shifts (if applicable)	Digital literacy (0 = very bad to 4 = very good)
Year of cancer diagnosis	
Cancer type	
Cancer treatment(s) and end of active treatment (if applicable)	
Other health conditions (mental or physical)	

Table 2 – Structure of the intervention

Session	Content	Handouts and resources
1	Overview of the intervention Psychoeducation Defining goals	Understanding sleep Cancer-related insomnia: associations with cancer-related fatigue, night sweats
2	Sleep hygiene Relaxation	Sleep hygiene Relaxation audios
3	Stimulus control Sleep consolidation	Sleep efficiency Sleep window
4	Restructuring dysfunctional beliefs about sleep	Thought record Cognitive distortions (mind traps) Reframing thoughts
5	Restructuring dysfunctional beliefs about cancer Additional adapted cognitive techniques (e.g., cognitive control, paradoxical intention therapy, acceptance and commitment-based strategies)	Mind map Dealing with a racing mind
6	Insomnia relapse prevention	Insomnia cycle overview Personal plan