

# A guided internet-delivered individually-tailored ACT-influenced cognitive behavioural intervention to improve psychosocial outcomes in breast cancer survivors (iNNOVBC): Study protocol

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## ABSTRACT

**Background:** Internet-delivered interventions can provide remarkable opportunities in addressing breast cancer survivors' unmet support care needs, as they present an effective strategy to improve care coordination and provide access to efficacious, cost-efficient and convenient survivorship care. Nevertheless, research focusing on improving survivors' psychosocial needs using internet-based tools is scarce and its practical implementation is limited.

**Objectives:** To study the acceptability, feasibility, efficacy and cost-effectiveness of iNNOVBC, a 10 weeks guided internet-delivered individually-tailored Acceptance and Commitment Therapy (ACT)-influenced cognitive behavioural (CBT) intervention developed to improve mild to moderate anxiety and depression in Breast cancer survivors when compared to treatment as usual (TAU) in a waiting list control group (WLC).

**Methods:** A two-arm, parallel, open label, multicentre, waiting list randomized controlled trial will be conducted to investigate the efficacy and cost-effectiveness of iNNOVBC. The primary outcomes in this research will be anxiety and depression. Secondary outcomes will include psychological flexibility, fatigue, insomnia, sexual dysfunction and Health Related Quality of Life (HRQoL).

**Ethical approval:** This study has been reviewed and approved by *Comissão Nacional de Proteção de Dados*; *Instituto Português de Oncologia do Porto Francisco Gentil*; *Unidade Local de Saúde de Matosinhos, EPE*; *Centro Hospitalar de São João* and *Ordem dos Psicólogos* ethical committees.

**Expected results:** It is anticipated that iNNOVBC will show to be an efficacious and cost-effective program in improving the outcomes of interest in this study, as opposed to a WLC under TAU. The results of this research will be published in accordance with CONSORT-EHEALTH guidelines.

**Conclusions:** This study will inform on the acceptability, feasibility, efficacy and cost-effectiveness of iNNOVBC, in improving psychosocial outcomes in breast cancer survivors when compared to TAU in a WLC. Its conclusions will contribute to understand the idiosyncrasies of designing and implementing internet-delivered interventions in breast cancer survivors.

Trial Registration code: iNNOVBC (NCT03275727).

## 1. Background

Breast cancer is the second most common cancer in the world and the most frequent among women, with 2.1 million incident cases

estimated in 2018 and 6.9 million women living with cancer within 5 years of diagnosis. Breast cancer is the fourth cause of death from cancer overall and the leading cause of cancer deaths for women. However, due to major advances in early diagnosis, improvements in

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treatment and cancer management, survival has increased steadily over time in the developed countries. In Portugal, particularly, 5-year prevalence is estimated to be 26,329 in 2018, which translates into a high and growing number of breast cancer survivors in the country (Bray et al., 2018). Breast cancer survivors are a heterogeneous group in terms of personal and tumour characteristics, as well as treatments performed. Most literature focusing on Health-related Quality of Life (HRQoL) reports high levels of functioning and HRQoL in breast cancer survivors (Mols et al., 2005). Nevertheless, a “significant minority” of 20%–30% of survivors, experience sequelae of treatment, late effects and unmet support care needs, including physical, psychosocial or practical problems, that can occur immediately to several years after primary treatment ends and cause clinically significant levels of disruption (Beckjord et al., 2016). Among the potential psychosocial late and long-term effects breast cancer survivors may experience are: anxiety (Burgess et al., 2005; Hodgkinson et al., 2007); depression (Burgess et al., 2005; Maass et al., 2015; Kim et al., 2008); fear of cancer recurrence (Simard et al., 2013; Ellegaard et al., 2017; Koch et al., 2014); cancer related fatigue (Kim et al., 2008; Goldstein et al., 2012; Abrahams et al., 2016; Reinertsen et al., 2017); sleeping problems (Lowery-Allison et al., 2017) and sexual dysfunction (Boquiren et al., 2016; Panjari et al., 2011; Paterson et al., 2016; Raggio et al., 2014). Reports on the prevalence and degree to which these difficulties affect breast cancer survivors vary in the literature.

Recent reviews by Zainal et al. (2013) and Maass et al. (2015) determined that the prevalence of depression and anxiety in breast cancer survivors varies from 6% to 56% and 17,9% to 33,3%, respectively. When compared to the general female population, the prevalence of depression was found to be higher and persistent over > 5 years after diagnosis, while the prevalence of anxiety was considered equivalent to results exhibited by the general female population. On the contrary, a study by Hodgkinson et al. (2007) aiming at identifying long-term outcomes and supportive care needs in disease-free breast cancer survivors, documented higher rates of anxiety 2–10 years after diagnosis, but depression scores consistent with age-adjusted community prevalence rates. Moreover, clinically anxious survivors reported over three times as many unmet needs as those with no anxiety. The field of most frequently reported unmet needs was *existential issues* and the most prevalent unmet need identified in this research was related to *managing concerns about the cancer coming back*, which is consistent with literature findings focusing on fear of cancer recurrence (Ellegaard et al., 2017). Fear of cancer recurrence is highly prevalent among breast cancer survivors (rates ranging from 52% to 86%) and seems to remain stable over the survivorship trajectory (Simard et al., 2013; Koch et al., 2014). Higher levels of fear of cancer recurrence have been associated with younger age, psychological distress, lower HRQoL, presence and severity of physical symptoms (Simard et al., 2013), higher health costs and lower surveillance rates, compromising breast cancer survivors health outcomes (Thewes et al., 2012).

Along with fear of cancer recurrence, cancer related fatigue has been reported as one of the most frequent, persistent and disruptive adverse events experienced by breast cancer survivors. Prevalence rates vary from 25% to 99% depending on the type of treatment received and method of assessment (Bower, 2014), and although its highest prevalence is during chemotherapy (CT), around 30% of breast cancer survivors experience enduring cancer related fatigue symptoms more than five years into survivorship (Reinertsen et al., 2017). A recent meta-analysis (Abrahams et al., 2016) focusing on cancer related fatigue related risk factors identified higher disease stages, CT and receiving the combination of surgery, radiotherapy (RT) and CT with or without hormone therapy (HT) as risk factors of severe fatigue in this population. Conversely, having a partner, performing surgery alone or surgery plus RT decreased the risk. Other studies have found an association between fatigue and pre-treatment fatigue (Bower, 2014), pain (Kim et al., 2008), dyspnea, depression, physical inactivity and high body mass index (Bower, 2014), significant disability and health care

utilization (Goldstein et al., 2012) and poor HRQoL (Kim et al., 2008).

Sleep disturbance is also a long-term concern in this population. Experienced over 5–10 years post-treatment it has been associated with cancer related fatigue, depression and anxiety (Otte et al., 2010), lower HRQoL, greater severity of pain, fear of cancer recurrence and increased vasomotor symptoms (Lowery-Allison et al., 2017). Its prevalence is higher in breast cancer survivors than in the general population and other cancer groups ranging from 38% to 73% (Lowery-Allison et al., 2017; Otte et al., 2010; Carpenter et al., 2004).

Another major, but often neglected, problem breast cancer patients may experience during survivorship is sexual dysfunction. Breast cancer treatments and associated side-effects can impair different areas of sexual function via a myriad of mechanisms, such as disrupting ovarian function, body image, intimacy and relationships (Paterson et al., 2016; Seav et al., 2015). Sexual dysfunction prevalence rates vary in the literature, ranging from 45% to 83% (Boquiren et al., 2016; Panjari et al., 2011; Safarinejad et al., 2013) being higher than in the general female population and persisting for several years after treatment completion (Raggio et al., 2014) compromising survivors' HRQoL (Safarinejad et al., 2013). Breast cancer survivors of younger age; presenting negative or body image disturbance, low perceived sexual attractiveness, poorer marital/relationship satisfaction or relationship distress, facing partner's fear of sexual intercourse, depression, psychological distress, vasomotor symptoms, lymphedema, weight gain, tiredness and pain; having performed a combination of RT, CT and HT, treatment with aromatase inhibitors, and bilateral mastectomy, are at higher risk of developing sexual dysfunction (Boquiren et al., 2016; Panjari et al., 2011; Raggio et al., 2014; Safarinejad et al., 2013).

Given the above, addressing breast cancer survivors' supportive care needs is key to improve their adjustment and well-being (Hodgkinson et al., 2007). However, providing such care depends on the ability of the healthcare systems to deliver comprehensive, highly coordinated, patient-centred care, which may prove difficult to operationalize in a context of competing priorities and constrained health and social care budgets. Additionally, many survivors will no longer attend follow-up appointments as often as in the initial stages of survivorship and innovative intervention strategies capable of reaching those in need and controlling costs without diminishing quality of service such as, interventions delivered by primary care workers, the Internet and self-help groups may be required (Hodgkinson et al., 2007). In this context, *internet-delivered interventions*, can provide remarkable opportunities in overcoming some of the aforementioned constraints, as presenting an effective strategy to improve care coordination and provide access to efficacious, cost-efficient and convenient breast cancer survivorship care (Post and Flanagan, 2016).

Internet-delivered interventions consist of self-help interventions, implemented as a prescriptive online program operated via a secure platform/website or mobile application (app) and used by consumers seeking health and mental-health related assistance (Andersson et al., 2008; Andersson and Titov, 2014). Internet interventions are often based on psychotherapy models - most commonly cognitive-behavioural therapy (CBT) - adopt a schedule and length that is similar to face to face treatment protocols (usually, 5 to 15 weeks) and can include a guided or unguided structure, involving or not therapist/clinician contact. Guided interventions can be further divided into those including synchronous interaction (e.g. real-time contact via telephone, video, or messenger services), asynchronous interaction (e.g. encrypted e-mail communications) or both types of interaction with patients. The amount of time therapists devote to work with patients varies between studies, but is often significantly reduced when compared to face-to-face psychological treatments (Andersson et al., 2008; Andersson and Titov, 2014). The beneficial impact of guided internet-delivered interventions has been shown in several studies (Andersson and Cuijpers, 2009). Nevertheless, automated reminders and other features may be included in guided interventions and the type and amount of contact between patient and therapist should be adjusted to the condition in

question, since some conditions require more guidance and support than others (Andersson, 2016).

During treatment, patients login regularly to a secure website, where the online environment is similar to online banking or an e-learning platform. Systems are encrypted, and double authentication procedures and one-time passwords are required at login (Andersson, 2016). Once logged in, patients have access to text, audio and/or video content, interactive programs and e-mail based individualized instructions that may be read/streamed online or downloaded/printed. The online materials are organized into a series of lessons or treatment modules (Andersson and Titov, 2014) – the equivalent to a face-to-face psychotherapy “session”. Treatment usually starts with psychoeducation content, continues with modules that are based on treatment manuals and established psychotherapy methods for specific disorders (Carlbring et al., 2011) and ends with a relapse/prevention module. It can include fixed modules and follow a linear structure or comprise optional modules and be individually-tailored. In the latter case, treatment is organized according to a case formulation, client preferences and/or characteristics and a transdiagnostic perspective is frequently adopted. Tailored interventions are particularly relevant when addressing comorbidity or overlapping conditions, since the patient has the power of determining which problems or symptoms are more urgent to deal with (Carlbring et al., 2011). On the course of treatment, homework assignments are prescribed. Patients are expected to complete those assignments before the next treatment module is made available and the use of mobile technology enables real-time submission of homework assignments. Furthermore, during treatment, patients are asked to complete computer administered questionnaires adequate to their condition and appropriate to monitor their progress, safety and outcomes. The addition of other interactive features such as, discussion forums, messaging services (chats), video-conference, quizzes and SMS reminders is also a possibility (Andersson and Titov, 2014; Andersson, 2016).

Over the last years, various controlled trials, systematic reviews and meta-analysis have been published supporting the efficacy and effectiveness of internet interventions (Andersson and Cuijpers, 2009; Andersson, 2016; Richards and Richardson, 2012; Olthuis et al., 2016; Barak et al., 2008). They have been found to be more effective than treatment as usual (TAU) or as effective as face-to-face therapies for a wide range of disorders, namely anxiety and depression. Nevertheless, research in the breast cancer survivorship setting is scarce. Most studies focusing on this population reported on the efficacy of CBT protocols (Amidi et al., 2018; Hummel et al., 2017; Zhang et al., 2017). A recent integrative review (Post and Flanagan, 2016) identified 15 studies on the matter, with 46,66% of the studies being published from 2015 onwards. Of these, 5 studied CBT and psychosocial interventions (Carpenter et al., 2014; Damholdt et al., 2016; Bruggeman Everts et al., 2015; Lepore et al., 2014; Berg et al., 2015); 3 implemented physical activity and lifestyle interventions (De Cocker et al., 2015; Lee et al., 2014; McCarroll et al., 2015); 2 addressed symptom management (Wheelock et al., 2015; Bock et al., 2012) and; 5 were pilots and exploratory studies (Haq et al., 2013; Hill-Kayser et al., 2013; Johnson-Turbes et al., n.d.; Pauwels et al., 2013; Wen et al., 2012). Self-efficacy, empowerment, working memory, reduced fatigue, distress (Carpenter et al., 2014; Damholdt et al., 2016; Bruggeman Everts et al., 2015; Berg et al., 2015), depression (Lepore et al., 2014), exercise frequency, weight change, fruit/vegetable intake (De Cocker et al., 2015; Lee et al., 2014; McCarroll et al., 2015), reported time on symptom management (Wheelock et al., 2015; Bock et al., 2012), patient satisfaction, usability and acceptability (Haq et al., 2013; Hill-Kayser et al., 2013; Johnson-Turbes et al., n.d.; Pauwels et al., 2013; Wen et al., 2012) were the primary outcomes in these studies. Overall, the findings of these research suggest that internet-delivered survivorship interventions are feasible and acceptable to breast cancer survivors and most studies reported improvements in their intended outcomes. However, many limitations can be appointed to these studies (Post and Flanagan, 2016):

many studies lacked on a control or comparison group; there was limited information on the cost-effectiveness of the internet-interventions and; none of the studies reported on longitudinal patient outcomes such as HRQoL. These limitations highlight the need for additional research in this field.

Within the Third Wave of cognitive behavioural therapies, Acceptance and Commitment Therapy (ACT), due to its model of healthy adaptation to difficult circumstances and transdiagnostic approach, may be particularly useful in addressing the high levels of psychological and medical comorbidities that manifest in cancer populations (Fashler et al., 2018). ACT's efficacy has been studied in several conditions, namely anxiety, depression and chronic pain and its application to the cancer setting is increasing (Hulbert-Williams et al., 2015). More recently, ACT-based internet-interventions are emerging and some positive preliminary results have been published (Low et al., 2016; Köhle et al., 2015; Arch and Mitchell, 2016; Mujcic et al., 2018; Köhle et al., 2017). Nevertheless, stronger evidence of efficacy and cost-effectiveness is needed. Thus, the present research intends to contribute to close the abovementioned research gaps by assessing the feasibility, efficacy and cost-effectiveness of iNNOVBC – a 10 weeks guided internet-delivered individually-tailored ACT-influenced CBT intervention developed to improve mild to moderate anxiety and depression in Breast cancer survivors when compared to TAU in a waiting list control group (WLC).

## 2. Objectives and hypotheses

This research aims at exploring the acceptability, feasibility, efficacy and cost-effectiveness of iNNOVBC - a 10 weeks guided internet-delivered individually-tailored ACT-influenced CBT intervention developed to improve mild to moderate anxiety and depression in Breast cancer survivors when compared to TAU in WLC. This research also aims at assessing iNNOVBC's efficacy in improving psychological flexibility, fatigue, insomnia, sexual dysfunction and HRQoL in breast cancer survivors when compared to TAU in a WLC; and examining iNNOVBC's cost-effectiveness, from a societal perspective.

We hypothesise that iNNOVBC will prove to be more efficacious in improving the above-mentioned outcomes in breast cancer survivors when compared to TAU in a WLC. We also expect iNNOVBC to show to be a cost-effective method to deliver psychosocial care to breast cancer survivors when compared to TAU in a WLC.

## 3. Methods

### 3.1. Study design

A two-arm, parallel, open label, multicentre, waiting list randomized controlled trial will be conducted to investigate the efficacy and cost-effectiveness of iNNOVBC when compared to TAU in a WLC. A Pilot study, mirroring the conditions of this trial will be performed to: evaluate the feasibility of the parent study; identify potential weaknesses of the study design; test the structure, format and content of the study intervention; test the data collection process; and obtain preliminary data for the primary outcome measures, in order to attest/correct the previous calculated sample size. Results from this Pilot study should be appraised after randomization of 30 participants to the study and inform execution of the main trial (c.f. Fig. 1). If the assessment does not indicate changes to be made in the study design or procedures, the pilot study will proceed to the main study. An economic evaluation of iNNOVBC will be undertaken from a societal perspective.

### 3.2. Study population

The study population includes female individuals diagnosed with primary breast cancer, who have completed primary adjuvant treatment from 6 months up to 10 years before enrolling in the study and

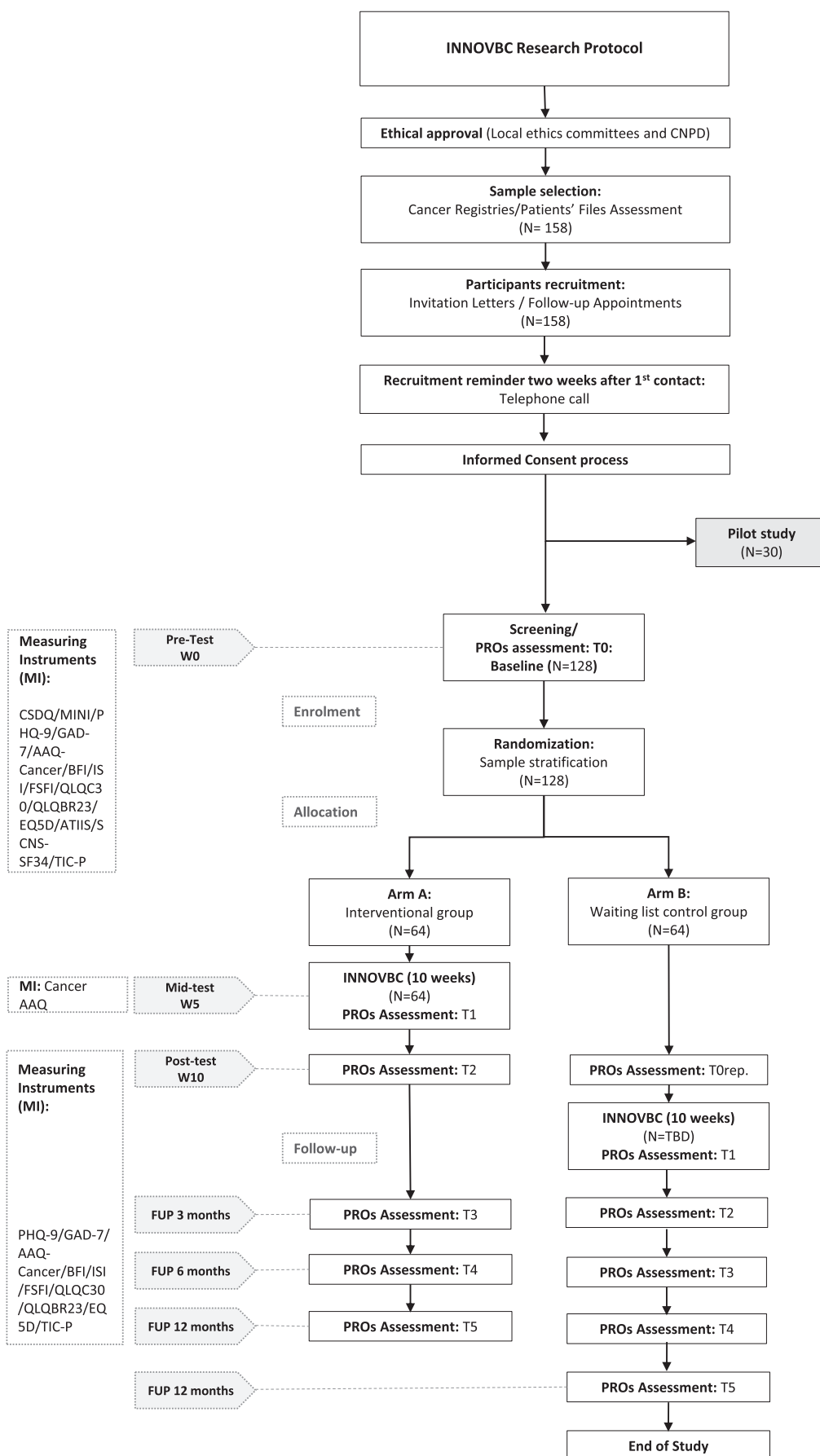


Fig. 1. Study design.

**Table 1**  
Eligibility criteria INNOVBC RCT.

Inclusion criteria	<ul style="list-style-type: none"> <li>• Signed written informed consent.</li> <li>• Age <math>\geq</math> 18 years;</li> <li>• Ability to read and write in Portuguese.</li> <li>• History of histologically or cytologically confirmed breast cancer with no evidence of metastatic disease.</li> <li>• An interval <math>\geq</math> 6 month from primary adjuvant treatment completion (surgery, chemotherapy and/or radiotherapy), except for hormonal therapy.</li> <li>• Clinically significant symptoms of mild to moderate anxiety (GAD-7 scores from 5 to 14) and/or moderately to moderately severe depression (PHQ-9 scores from 6 to 14). Patients can or not present clinically significant symptoms of insomnia, fatigue or sexual dysfunction.</li> <li>• Ongoing regular psychoactive medication only accepted if dosage has been stable during the last 3 months.</li> <li>• Daily access to the Internet by computer and/or smartphone.</li> <li>• Ability to use a computer and/or smartphone and the internet.</li> <li>• No participation on any other interventional study or clinical trial.</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Age <math>\leq</math> 18 years;</li> <li>• Inability to co-operate and give informed consent.</li> <li>• Breast cancer not histologically or cytologically confirmed.</li> <li>• History of other malignancy within the last 5 years.</li> <li>• Metastasized breast cancer.</li> <li>• Current severe, uncontrolled systemic disease or mental disorder.</li> <li>• Absence of clinically significant symptoms of mild to moderate anxiety (GAD-7 scores <math>&lt;</math> 5) and/or moderately to moderately severe depression (PHQ-9 scores <math>&lt;</math> 5) or presence of severe anxiety (GAD-7 <math>&gt;</math> 15) and severe depression (PHQ-9 <math>&gt;</math> 15). The presence of clinically significant symptoms of insomnia, fatigue or sexual dysfunction as stand-alone conditions does not fulfil the necessary requirements to be enrolled in the trial.</li> <li>• Parallel ongoing psychological treatment.</li> <li>• Ongoing regular psychoactive medication if dosage has been changed during the last 3 months.</li> <li>• No access to the internet.</li> <li>• Inability to use a computer and/or smartphone and the internet.</li> <li>• Parallel ongoing participation in other interventional study or clinical trial.</li> <li>• Assessment by the investigator to be unable or unwilling to comply with the requirements of the protocol.</li> </ul>

show no evidence of disease. For this project, the sample will be collected in Portugal. The following criteria should be used to check eligibility for participation in the study (c.f. Table 1).

### 3.3. Research sites

To increase the generalizability of results, this project will adopt a multicentric design. Sites invited to participate were selected due to its treatment standards and resources.

### 3.4. Study intervention

INNOVBC is a guided, self-management, individually-tailored, internet-delivered ACT-influenced CBT program composed of 10 treatment modules, namely 5 mandatory modules – *Introduction: Living with breast cancer and beyond; Depression; Anxiety, worries and fear of recurrence; Relaxation and; Conclusion: Key points summary and Planning for the future* - and 5 optional modules – *Behavioural activation Parts I and II; Sleep problems; Fatigue and; Interpersonal relationships, sex and intimacy* - to be completed from 5 to 10 weeks. Its structure and content build on prior research interventions developed by the Department of Behavioural Sciences and Learning at Linköping University (Carlbring et al., 2011; Jasper et al., 2014; Andersson et al., 2013; Buhrman et al., 2013) that have been considered effective for various outcomes such as depression, anxiety, chronic pain and tinnitus. The applicable previously available content was translated from Swedish and English to Portuguese and validated by external experts. Additional content was developed considering several peer-reviewed sources (NCCN, 2017a; NCCN, 2017b; NCCN, 2017c; Andersson, 2014; Hayes et al., 2012) and validated by multidisciplinary external experts. The program adopts a transdiagnostic structure, featuring treatment strategies considered relevant for the different conditions at interest in this research. Its central components are: psychoeducation, acceptance, cognitive defusion, connecting with values, committed action, exposure, behavioural activation and relaxation. By cultivating the abovementioned processes through experiential exercises, metaphors and homework assignments considered appropriate for breast cancer survivors, the intervention aims at diminishing patients symptoms and increasing psychological flexibility. For participants selecting the optional modules, the mentioned core processes will be adjuvated by one or more of the following

techniques: sleep management, energy conservation techniques, problem solving and sensate focusing.

At the onset of the intervention participants should tailor their treatment with the support of their assigned therapist and according to their baseline assessment. The completion of a module by the participant, triggers the access to the next. Each module takes approximately 60 min to complete and comprises short texts, images, videos, audio-files and calendar features matching the modules' themes; quizzes; ACT and CBT based exercises, homework assignments and respective worksheets. Professional feedback and guidance will be provided by certified psychologists and psychology trainees under supervision, asynchronously, and once a week, unless a supplementary e-consultation is requested by the participant. Integrated two-way communication features such as e-mail, chat, SMS and video-conference will support this process. Therapists will be instructed to use approximately 15 min per participant per week. This period should be used to monitor and assess participants' progress, read messages and write answers. Therapists feedback should be based on the following guidelines (Paxling et al., 2012): validation of participants' work and reported difficulties; problem-solving and clarification on the implementation of treatment techniques; therapeutic alliance bolstering; task prompting; progress reinforcement and; encourage continued work. A referral algorithm will be in force throughout the program ensuring participants referral to the study sites respective Psychiatric/Psycho-oncology Department in case of acute aggravation of their condition. The intervention will be delivered via iTerapi, a web-based treatment platform developed at Linköping University. Further details on the platform features, including its security features, are described elsewhere (Vlaescu et al., 2016).

#### 3.4.1. Treatment as usual (TAU)

In this study, TAU corresponds to the routine care participants would receive when diagnosed with any of the conditions under study at the recruitment sites. Thus, TAU can vary from site to site and among participants and is likely to include pharmacologic treatment and/or psychosocial support. The type of TAU received will be monitored through patients' records and self-report measures (e.g. TIC-P). WLC participants will be informed that they are free to access any form of support/TAU during the study. They will also be instructed to seek professional support, in case they experience symptomatic deterioration

**Table 2**  
Outcome measures.

Outcome measure	No. of Items/modules	Dimensions	Rating scale	Cut-off points	Psychometric properties	Translation/adaptation to Portuguese and/or cancer population
Demographics: Clinical and Socio-demographic Questionnaire (CSDQ) – Version A (patients)	40	Not applicable (NA)	NA	NA	NA	Original version developed in Portuguese (Portugal) by the research team
Mini-International Neuropsychiatric Interview (MIND) (Sheehan et al., 1998)	16 modules (branching tree logic items)	Multidimensional	Dichotomous rating scale	NA	Cohen's k = 0.7	Translated and adapted to Portuguese (Portugal)
Attitudes Towards Internet Interventions Survey (ATTIS) - Version A (patients)	35	Multidimensional	Dichotomous and Likert scale	NA	To be determined in this research	Original version developed in Portuguese (Portugal) by the research team
Support Care Needs Survey Short-Form (SCNS-SF34) (Boyes et al., 2009)	34 + 8	Multidimensional	5-point Likert scale	NA	$\alpha = 0.86$ to $0.96$	To be translated and adapted in the context of this research. Methodology to be used will include: a preliminary forward translation from English to Portuguese (Portugal); a back translation from Portuguese to English; a second forward translation from English to Portuguese (Portugal); pre-testing and cognitive interviewing. Translated and adapted to Portuguese (Portugal)
Patient Health Questionnaire (PHQ-9) (Torres et al., 2016)	9	Unidimensional	4-point Likert scale	Mild depression (< 5); Moderate depression (6–10); Moderately severe (11–15); Severe depression (> 15)	$\alpha = 0.86$	Translated and adapted to Portuguese (Portugal)
Generalized Anxiety Disorder Screener (GAD-7) (Souza et al., 2015)	7	Unidimensional	4-point Likert scale	Normal anxiety (< 5); Mild anxiety (5–9); Moderate anxiety (10–15); Severe anxiety (15–21)	Primary care setting ( $\alpha = 0.92$ ); General population ( $\alpha = 0.89$ )	Translated and adapted to Portuguese (Portugal)
Acceptance and Commitment Questionnaire for Cancer Patients (Cancer AAQ) (Arch and Mitchell, 2016)	18	Unidimensional	7-point Likert scale	NA	$\alpha = 0.91$ – $0.95$	To be translated and adapted in the context of this research. Methodology to be used will include: a preliminary forward translation from English to Portuguese (Portugal); a back translation from Portuguese to English; a second forward translation from English to Portuguese (Portugal); pre-testing and cognitive interviewing. Translated and adapted to Portuguese (Portugal)
Brief Fatigue Inventory (BFI) (Mendoza et al., 1999)	9	Unidimensional	10-point Likert scale	Mild (1–3); moderate (4–6); severe fatigue (7–10)	$\alpha = 0.96$	Translated and adapted to Portuguese (Portugal)
Insomnia Severity Index (ISI) (Bastien et al., 2001)	7	Unidimensional	5-point Likert scale	Absence of insomnia (0–7); sub-threshold insomnia (8–14); moderate insomnia (15–21); severe insomnia (22–28)	Clinical setting ( $\alpha = 0.74$ ); research settings ( $\alpha = 0.76$ to $0.78$ ).	Translated and adapted to Portuguese (Portugal)
Female Sexual Function Index (FSFI) (Rosen et al., 2000)	19	Multidimensional	0–5 or 1–5 numeric rating scales	$\leq 26$ expresses risk of sexual dysfunction	$\alpha > 0.9$ for all domains	Translated and adapted to Portuguese (Portugal)
EORTC QLQ30 (Pais-Ribeiro et al., 2008)	30	Multidimensional	4-point Likert scale and 7-point linear analogue scale	NA	$\alpha \geq 0.70$	Translated and adapted to Portuguese (Portugal)
EORTC QLQBR23 (Sprangers et al., 1996)	23	Multidimensional	4-point Likert scale	NA	$\alpha = 0.46$ to $0.94$	Translated and adapted to Portuguese (Portugal)
EuroQol-5D-5 L (Ferreira et al., 2016)	6	Multidimensional	5-point Likert scale and 100-point linear analogue scale	NA	Not specified	Translated and adapted to Portuguese (Portugal)
Questionnaire on Medical consumption and Productivity losses associated with Psychiatric Illness (TIC-P) (Bouwmans et al., 2013)	26	Multidimensional	Dichotomous rating scale	NA	Cohen's k = $0.492$ to $0.839$	TIC-P Part I will be translated and adapted to Portuguese (Portugal) in the context of this research, as the iPCQ has already been translated and adapted to Portuguese (Portugal) by IMTA.

or other difficulties over the course of the study. Participants in the WLC will be offered the same treatment protocol applied to the experimental group after completion of the program (approximately 3 months from baseline).

### 3.5. Outcome variables and outcome measures

All variables and assessments will be collected online and via iTerapi. Outcome measures selection was based on psychometric properties, feasibility and frequency of use in both oncology and internet interventions domains to ensure data comparability. A compilation of the outcome measures to be used in this research is available in Table 2.

#### 3.5.1. Socio-demographic and medical information

The following socio-demographic and medical information variables will be assessed in this study: Age; education; marital status; occupation; area of residence; distance between residence and cancer centre; comorbidities; history of prior psychological/psychiatric treatment; menstrual status; body mass index (BMI); BC diagnosis date (biopsy or cytology date); type of BC; date of BC surgery; number of BC related surgeries; type of surgery; breast reconstruction; history of neoadjuvant treatment; neoadjuvant treatment start and end dates; type of neoadjuvant treatment; history of adjuvant treatment; adjuvant treatment start and end dates; type of adjuvant treatment; TNM status; ECOG; and concomitant psychoactive medication. These variables will be collected using a customized, brief, self-report, socio-demographic and clinical questionnaire developed for this purpose. Missing clinical data will be provided by the local study team at each site and will be collected through the analysis of patients' files.

#### 3.5.2. Primary outcomes and measures

The primary outcome variables in this research are anxiety and depression. The Patient Health Questionnaire (PHQ-9) (Torres et al., 2016) and Generalized Anxiety Disorder Scale (GAD-7) (Sousa et al., 2015) will be used to measure anxiety and depression, respectively, throughout the study.

#### 3.5.3. Secondary outcomes and measures

Psychological flexibility, fatigue, insomnia, sexual dysfunction and HRQoL are considered secondary outcome variables in this research. Changes in ACT-processes will be measured with Cancer Acceptance and Action Questionnaire (Cancer AAQ) (Arch and Mitchell, 2016). Fatigue, insomnia and sexual dysfunction will be evaluated with the Brief Fatigue Inventory (BFI) (Mendoza et al., 1999), Insomnia Severity Index (ISI) (Bastien et al., 2001) and Female Sexual Function Index (FSFI) (Pechorro et al., 2009) respectively and EORTC QLQC30 and QLQBR23 corresponding items. HRQoL will be measured with QLQC30 (Pais-Ribeiro et al., 2008), QLQBR23 (Sprangers et al., 1996) and EuroQol-5D-5 L (Ferreira et al., 2016).

#### 3.5.4. Exploratory outcomes and measures

Participants' attitudes towards internet interventions, breast cancer patients' unmet support needs, and intervention feasibility and cost-effectiveness will also be explored. Participants' attitudes towards internet interventions will be investigated with ATIIS – a short, self-report questionnaire developed in the context of this research, to assess participant's perceived usefulness, ease of use and attitudes towards internet interventions. Due to the scarcity of adequate instruments to evaluate this construct in the target population, a customized questionnaire was developed based on a literature review (Topooco et al., 2017; Schröder et al., 2015; Jansen et al., 2015) and enquiries of healthcare professionals. Its psychometric properties will be assessed during this research.

Breast cancer patients' unmet support care needs will be assessed with the Supportive Care Needs Survey Questionnaire (SCNS-SF34)

(Boyes et al., 2009).

Intervention feasibility will be assessed considering: *demand* (expressed by participants' unmet needs, recruitment rates and initial iINNOVBC uptake), *acceptability* (given by BC survivors' attitudes towards internet interventions, the perceived appropriateness of the treatment program and participants' satisfaction with iINNOVBC), *implementation* (analysed based on adherence to iINNOVBC/treatment modules completion, retention and attrition rates, amount and type of resources needed to implement the program and factors affecting the implementation), *practicality* (reporting on usability, efficacy, and cost-effectiveness of iINNOVBC), *integration* (evaluating the perceived fit within different sites and potential costs to sites and policy bodies) and *expansion* (based on healthcare providers' attitudes towards internet interventions, perceived fit with organizational goals and culture, positive or negative effects on sites and potential disruption due to expansion of the program). iINNOVBC specific feasibility measures include: recruitment rates, screening failure logs, iINNOVBC initial uptake rates, adherence rates, attrition and retention rates, iTerapi users' activity logs and single-item questions assessing participants' perceived appropriateness, usability and satisfaction with iINNOVBC treatment modules and program. ATIIS and SCNS-SF34 results, efficacy and cost-effectiveness analysis will also be used to assess iINNOVBC *demand*, *practicality*, *integration* and *expansion* feasibility components.

Finally, iINNOVBC associated costs will be assessed based on direct medical costs - all healthcare utilization of the participants will be collected, regardless of the cause or reason for using the service (e.g., visits to general practitioner, to mental health care, hospital admissions, etc.) - direct non-medical costs (e.g., direct out-of-pocket expenses such as, travelling, lodging and home services) and productivity losses (absenteeism and presenteeism). These variables will be collected using the Questionnaire on Medical consumption and Productivity losses associated with Psychiatric Illness (TIC-P) (Bouwman et al., 2013).

### 3.6. Study procedures

#### 3.6.1. Compliance with laws, regulations and ethical requirements

This study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996) and the following Portuguese Decree-laws: *Lei n.º 67/98, de 26 de Outubro (Lei de Protecção de Dados Pessoais)*; *Lei n.º 21/2014 (Lei da Investigação Clínica)*, de 16 de Abril; *Regulamento n.º 258/2011 (nos termos do artigo 77.º do Estatuto da Ordem dos Psicólogos Portugueses, aprovado pela Lei n.º 57/2008, de 4 de Setembro, a Ordem elabora, mantém e actualiza o Código Deontológico da Ordem dos Psicólogos Portugueses)*; and *Deliberação n.º 1704/2015 (Deliberação da Comissão Nacional de Protecção de Dados Aplicável aos tratamentos de dados pessoais efectuados no âmbito de Investigação Clínica)*. This study will also comply with EU Regulation 2016/679 of The European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

This research protocol has been reviewed and approved by Comissão Nacional de Protecção de Dados; Instituto Português de Oncologia do Porto Francisco Gentil, Unidade Local de Saúde de Matosinhos, EPE; Centro Hospitalar de São João and Ordem dos Psicólogos ethical committees.

#### 3.6.2. Study initiation

The study will be initiated in January 2019. The study duration will be approximately 22 months including a recruitment period of approximately 6 months.

**3.6.2.1. Study initiation visit and study therapists' training.** A study initiation visit will be performed to present the research protocol, train the local study teams and adjust the study procedures to sites'

idiosyncrasies. A training course targeting the study therapists will be delivered prior the onset of the recruitment period with the purpose of harmonizing knowledge between therapists included in the study team. This course will focus on BC clinical and psychosocial aspects, ACT, internet-delivered psychosocial programs, good clinical practices, the research protocol, the study Instruments and iTerapi. The course will be taught by certified oncologists and psychologists, who are also co-investigators in this study and should be delivered online and/or in loco over 12 h.

### 3.6.3. Recruitment

Potential study participants will be identified, with the support of local study team members, by reviewing cancer registration databases and patient files at each site. While long term follow-up patients will be mainly invited to participate via post mail since they may not have an appointment scheduled at the sites during the recruitment period, participants ongoing treatment or short-term follow up will be invited to participate at the study sites during medical, surgical and multi-disciplinary appointments. In the latter case, patients will be approached by their clinician or by other element of the local study team, trained for this purpose. Subjects requesting to participate, but not directly invited by the study team (e.g., self-referral patients finding about the study through the study website or by a third person, such as other participant, etc.) may be allowed to participate if their treatment/follow-up is ensured by any of the participating sites.

**3.6.3.1. Consent process.** A written informed consent must be obtained for all participants and prior to any study specific assessments and procedures are performed. Regardless of the implemented recruitment method – post mail or face-to face – the first contact should be performed by a local study team member to obtain patients' permission to be approached by the researchers and copies of the Study Information Sheet and Informed Consent Form (ICF) should be provided for analysis. After reading the study documents, if a patient is interested in participating in the trial, an appointment – face to face or teleconference/videoconference - should be scheduled with the purpose of detailing the study objectives and procedures, answering to queries raised by the patient, confirming her interest in participating, determining eligibility and signing the ICF. The signature of the ICF should be obtained, whenever possible, in the presence of one of the research team members. For patients recruited via post mail and/or refusing to meet the researchers at the study site, the ICF may be returned via post mail. After the signature of the ICF, study procedures may be initiated. If and whenever an updated version of the ICF is enforced, a reconsent must be obtained. ICF will be stored at the Clinical Research Unit or Breast Clinic of each site by a Clinical Research Coordinator or Clinical Nurse Manager, respectively.

**3.6.3.2. Participants recruitment strategies.** In order to guarantee the success of this research, the following recruitment strategies should be applied: an *Invitation flyer* describing the study to potential participants should be made available at the reception areas, examination rooms and multidisciplinary meeting rooms at the study sites and at BC patients associations; a web banner linking to the study website should be advertised in the study sites' website, whenever possible; healthcare providers such as, nurses, psychologists, oncologists, surgeons and radiation oncologists should be informed about the study and be encouraged to refer patients meeting the eligibility criteria; and a reminder telephone contact should be performed two weeks after the first contact with the patient. All advertisement material targeting the public should comply with study sites' regulations and the Portuguese regulation on the matter as it is enforced in articles 2°, 40° and 42° of the Decree-law n°21/1014, de 16 de Abril.

### 3.6.4. Screening and pre-assessment procedures

Following the participants' consent to participate in the study, the

screening procedures should be initiated. Participants fulfilling the initial screening criteria should be invited to a diagnostic interview, to establish their eligibility for the study. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) will be used for this purpose. MINI should be performed by a certified psychologist or by psychologist students/trainees participating under the supervision of a certified psychologist. Subjects diagnosed with severe mental disorders or suicide risk will be referred to the respective Psychiatric/Psycho-oncology Department at the study sites. Baseline pre-assessment procedures should be completed online, via iTerapi, starting from the day ICF is signed. Access to a computer or mobile device should be provided for patients completing the pre-assessment at the sites.

### 3.6.5. Enrolment and randomization

Following registration, randomization procedures will be conducted in two steps. Firstly, the method of minimization will be applied to ensure treatment arms are balanced with respect to the severity of anxiety and depression, as well as for the number of patients in each group. A random element will be incorporated, and allocation will be concealed. Subsequently, participants in the experimental arm will be randomly assigned to one of the four therapists providing support to participants during the trial. Simple randomization will be used at this stage. Randomization procedures will be performed by an independent statistician collaborating with the research team and that has no contact with the study subjects. A computerized program will be used in these procedures. After randomization, all participants will receive an e-mail with a link to login into iTerapi and get to know the outcome of randomization: Arm A – Experimental condition or Arm B – WLC condition. Participants in Arm A will receive immediate access to iNOVBC, while WLC will receive access to the intervention approximately 3 months after the baseline measurement. WLC will undergo a second baseline assessment to reconfirm eligibility for iNOVBC prior the onset of the intervention and follow the same protocol measurements as experimental condition subjects.

### 3.6.6. Study intervention and assessments

After randomization, participants from both study arms will maintain access to the platform. While WLC will sustain the same access level obtained during the screening phase (e.g., study general information, baseline measures, etc.) and be informed about their intervention start date, participants assigned to Arm A will gain immediate access to the *Conversations* section at iTerapi, find a *Welcome Message* from the assigned therapist and a request at the *Notification Centre* to book an e-consultation (audio, video or chat). The purpose of this first e-consultation is discussing the structure of the program, reporting the baseline findings and tailoring the intervention according to participants' needs and preferences. Once therapists and participants reach an agreement, the selected optional modules should be prescribed along with the mandatory modules. Subsequently, access to the other sections at the platform and specifically to the first treatment module will be granted. The following treatment modules should be assigned in a weekly basis, with participants prompted to complete the modules in approximately one week. If the participants fail to complete the modules in the specified time frame, a reminder is automatically sent by e-mail/SMS. Within 24 h of module completion the therapists, based on the reported outcomes, should assess participants' progress and determine whether it is appropriate or not for the patients to proceed to the next module. If so, the participants should receive access to the following module. If not, therapists should instruct participants on what needs to be completed to be able to advance to the next module. A mid-test assessment (T1, approximately 1,5 months after treatment initiation), using Cancer AAQ, should be performed after the completion of at least 3 of the mandatory treatment modules, to assess treatment progress regarding psychological flexibility. After iNOVBC termination a post-test assessment (T2, approximately 2,5 to 3 months after treatment initiation) should be performed to assess the efficacy of the



intervention. At this point, WLC should be performing a second assessment to be compared with the results yielded by the experimental group and test the iNNOVBC efficacy. This assessment will be used to reassess the eligibility requirements of the WLC to cross-over to iNNOVBC intervention. The same treatment and assessment protocol should be implemented in the WLC for ethical reasons. This entails that there will be no control group to compare with after T3 (3 months after experimental group end of treatment).

### 3.6.7. Participant discontinuation from study intervention and/or study participation

Participants may withdraw from iNNOVBC and/or the study at any time and for any reason or be dropped from the study by the researcher if a severe aggravation of the baseline symptoms occurs. In this case, the participant should be referred to the respective Psychiatric/Psychoncology Department at the study sites. The main reason for discontinuing iNNOVBC and/or the study must be registered at iTerapi. Patients discontinuing prematurely iNNOVBC but willing to keep participating in the study, should perform the protocolled follow-up assessments. This information will be analysed to assess the feasibility and adequacy of the program. If it's the participant intent to completely withdraw from the study, the reason for withdrawal should be reported and a final assessment should be performed whenever the participant agrees with it. When contact is lost with a participant, the research team should contact the participant via telephone before acknowledging him/her as lost to follow-up.

### 3.6.8. Participants and sites replacement

Lost to follow-up participants may be replaced to ensure an acceptable number of evaluable participants in each study arm. However, the replacement should be performed by re-opening the recruitment period and it is not allowed to randomize a participating subject twice. Additional sites may be included in the study if the current enrolled sites fail to meet the established recruitment threshold. The research protocol must be approved by the new site's board and ethical committee prior to inclusion in the study. Participating sites may be replaced due to excessively slow recruitment or protocol violation/non-adherence.

### 3.6.9. Follow-up assessments

Long-term effects will be examined by performing three follow-up assessments in this study: T3 (3 months after end of treatment); T4 (6 months after end of treatment) and T5 (12 months after end of treatment).

### 3.6.10. End of study

The end of the study will be reached when all participants from both study arms have completed the final follow-up assessments.

### 3.6.11. Project timeline

Fig. 2 describes this project timeline.

### 3.6.12. Data handling and storage

All data will be collected via iTerapi. The study sites will be responsible for data entry concerning clinical and socio-demographic information. The remaining data will be entered by the participants. The research team will be responsible for the data management and quality control. Compliance with security requirements enforced by the laws and regulations described on Section 3.6.1 will be ensured. All sensitive data will be stored encrypted in the database. The key that produced the code that allows the indirect identification of the participants will be deleted five years after the end of the study, as instructed by *Deliberação n. ° 1704/2015 (Deliberação da Comissão Nacional de Protecção de Dados Aplicável aos tratamentos de dados pessoais efectuados no âmbito de Investigação Clínica)*.

## 3.7. Statistical and economic analysis

### 3.7.1. Power and sample size

Considering previous randomized-controlled trials (RCT), systematic reviews and meta-analysis assessing the effectiveness of internet-delivered treatments (Andersson and Cuijpers, 2009; Richards and Richardson, 2012; Barak et al., 2008), a moderate effect size (Cohen's  $d = 0.5$ ), should be expected. Therefore, to capture an effect size 0.5 as statistically significant in a two-tailed test at  $\alpha = 0.05$  and a power of  $(1 - \text{Beta}) = 0.80$ , a minimum of 64 participants per Arm will be required, as computed by G\*Power 3.0.10 (Faul et al., 2007).

### 3.7.2. Statistical analysis plan

IBM SPSS for Windows will be used for all analysis. The exact version of the software to be used will be reported in future publications.

Descriptive statistics will be calculated to characterize the study sample. Potential baseline differences between groups regarding clinical and socio-demographic variables and pre-treatment data will be examined using independent samples  $t$ -test for continuous variables and  $\chi^2$  test for categorical variables. Non-significant differences will confirm the success of randomization.

All data analysis will be performed according to the intention-to-treat principle, where all randomized participants are included in the analysis assuming missing data at random. A mixed models approach instead of analysis of variance will be used for this purpose, as suggested by Gueorguieva and Krystal (2004). This statistical approach is considered to present advantages over traditional data analytic approaches for the analysis of repeated-measures data such as, the ability to incorporate time-varying predictors, handle dependence among repeated observations in a flexible manner, and to provide accurate estimates with missing data under unrestrictive missing data assumptions (Hesser, 2015). The full information maximum likelihood estimation method will be implemented.

Effect sizes (Cohen's  $d$ ) and a 95% confidence interval will be calculated to measure the magnitude of the treatment effects for continuous outcomes, both within groups at post-intervention and follow-up assessments compared to baseline, and between-groups using the observed mean and pooled SD at post-treatment, and by the estimated means from the mixed-model. The following formula for converting standard error to standard deviation:  $SD = SE \times \sqrt{n}$  will be used for this purpose. According to Cohen (Cohen, 1992), effect sizes  $< 0.2$ , between 0.2 and 0.5 and  $> 0.8$  are considered small, moderate and large, respectively. A moderate effect size (Cohen's  $d = 0.5$ ) is expected to be captured in this research.

Clinical significance will be determined using Jacobson & Truax method (Jacobson and Truax, 1991). This method comprises two operations: the calculation of the Reliable Change Index (RCI) (the difference between a participant's pre-test and post-test scores, divided by the standard error of the difference) and the calculation of the Cut-off C value (a weighted midpoint between the means of the outcome at interest). These products are then combined to categorize individuals in one of the following categories: *recovered* (the participant has passed Cut-off C and the RCI in the positive direction); *improved* (the participant has passed the RCI in the positive direction but not the Cut-off C); *unchanged* (the participant did not pass either of the criterion); or *deteriorated* (the participant has passed the RCI in the negative direction) (Lappalainen et al., 2014).

An independent statistician who is blind to the allocation will test the research hypothesis.

### 3.7.3. Economic analysis plan

The economic analysis will be undertaken from a societal perspective, considering the intervention costs, direct costs (medical and non-medical) and indirect costs during the study period. The intervention costs refer to internet connection prices and time participants and therapists spend using the program and the training/salary of the

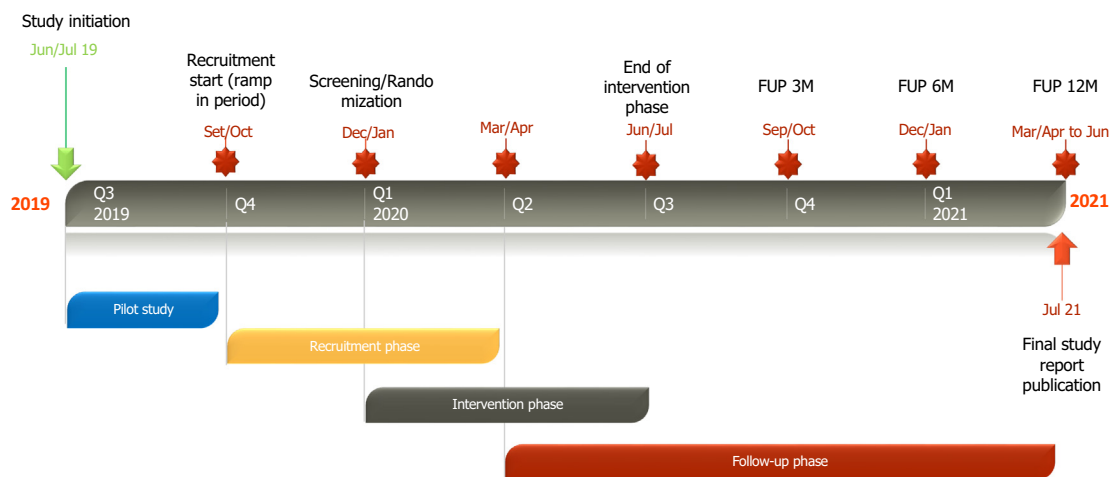


Fig. 2. Study timeline.

therapists. The costs related to software development and deployment costs (“sunk costs”) will not be assessed. Direct costs concern to all healthcare utilization (direct medical costs) and direct out-of-pocket expenses incurred by the participants (non-medical direct costs). Indirect costs are related to production losses namely, absenteeism (being absent from work because of illness) and presenteeism (being present at work while ill which may lead to reduced efficiency), both in paid labour and in the domestic setting. Health service uptake and production losses will be measured at T0, T2, T3, T4 and T5 based on TIC-P.

The source for intervention costs will be based on market prices. Economic costs due to direct medical costs will be obtained from *Portaria n.º 207/2017 de 11 de julho* issued by the Portuguese Ministry of Health and INFARMED prices; direct non-medical costs will be based on market prices; and indirect costs will be extracted from the monthly reports issued by *Direcção-Geral de Estudos, Estatística e Planeamento (DGEEP: <http://www.dgeep.mts.gov.pt>) and SISED - Sistema de Informação sobre Salários, Emprego e Duração do Trabalho* database from the Portuguese Ministry of Labour, Solidarity and Social Security. To estimate indirect costs the human capital method will be used. Considering that the timeframe of the present study is relatively short (12 months), costs will not be corrected for inflation nor discounted.

iNOVBC economic evaluation will encompass a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). For the CUA, QALYs will be calculated based on EuroQol EQ-5D-5L. Incremental cost-effectiveness and cost-utility ratios (ICERs) will be calculated by dividing the difference in total costs between conditions (experimental and WLC) by the difference in average outcomes between the two alternatives. Bootstrapping will be used to calculate 95% confidence intervals around the mean difference in total costs between the treatment conditions and to estimate the uncertainty related to the ICERs. ICERs will be depicted in cost-effectiveness planes and sensitivity analyses will be computed to determine the robustness of the results. ICER acceptability curves for a series of willingness-to-pay ceilings will also be produced. Since there is no universally accepted ICER threshold or a specific threshold adopted in Portugal, the most common cost-effectiveness threshold used in the United Kingdom (£20,000–30,000/QALY or LYQ) (Claxton et al., 2015) will be adopted to interpret the findings of this economic evaluation.

#### 4. Expected results

Results of this research will be published in accordance with CONSORT-EHEALTH (Eysenbach, 2011) guidelines. It is anticipated that iNOVBC will show to be an efficacious and cost-effective method to improve psychosocial outcomes such as anxiety, depression,

psychological flexibility, fatigue, insomnia and sexual dysfunction in breast cancer survivors as opposing to a WLC under TAU.

#### 5. Discussion

Providing access to comprehensive, cost-effective, patient-centred survivorship care is currently a challenge in many health care systems, and Portugal is no exception. Survival, in the breast cancer population, has increased steadily and significantly over the past years and delivering psychosocial care to the “significant minority” of survivors in need is imperative (Beckjord et al., 2016). Innovative healthcare delivery models, where self-management internet-delivered interventions are included, may prove crucial in overcoming organizational and financial barriers frequently associated to the traditional healthcare delivery model in the future, especially in countries where non-pharmacologic support is virtually absent in primary care, as is the case of Portugal (Kleiboer et al., 2016).

To the best of our knowledge, this is the first study assessing the efficacy and cost-effectiveness of internet-delivered interventions aiming at improving mild to moderate anxiety and depression in breast cancer survivors, in Portugal. Post and Flanagan (2016), in a recent integrative literature review identified 15 studies on the subject, of which only 6 included RCT designs. Additionally, most studies were conducted in the U.S, the Netherlands, Belgium, Canada and South Korea and targeted a wide variety of outcomes, including: self-efficacy, empowerment, working memory, fatigue, distress, depression, patient-provider communication, physical activity, symptom management, usability, acceptability and patient satisfaction.

iNOVBC aims at determining the acceptability, feasibility, efficacy and cost-effectiveness of a guided, internet-delivered individually-tailored ACT-influenced cognitive behavioural intervention designed to improve psychosocial outcomes such as, anxiety, depression, psychological flexibility, fatigue, insomnia, sexual dysfunction and HRQoL in breast cancer survivors when compared to TAU in a WLC. Consequently, an RCT design will be implemented to address the main limitation identified in previous studies. A *Pilot study* will anticipate the main study, to comply with user-centred development requirements and test the intervention's feasibility. An economic evaluation of iNOVBC will be undertaken from a societal perspective, considering intervention costs, direct medical costs, direct non-medical costs and indirect costs during the study period.

It is expected that iNOVBC will prove to be an efficacious and cost-effective method in improving psychosocial outcomes in breast cancer survivors, when compared to TAU in a WLC and that its conclusions will inform the implementation of internet-delivered programs, in the future. Additional strengths associated to this research are related to its

underlying theoretical frameworks, ACT and CBT, proved to be acceptable approaches in the oncology and internet-interventions fields (Andersson, 2016; Brown et al., 2016); its transdiagnostic, individually-tailored and guided characteristics; the fact that it will intervene in the sexual health of breast cancer survivors - a domain with high demand for interventions but limited resources - and report on longitudinal patient outcomes such as HRQoL.

This project may also encompass some limitations. The fact that, so far, no other study reported on the efficacy and cost-effectiveness of internet-delivered programs in the Portuguese population makes it impossible to estimate on the acceptability, feasibility and adherence of Portuguese breast cancer survivors to this type of programs. Therefore, it can be challenging to recruit the number of participants needed to conclude on the outcomes of this research and generalize the results to the Portuguese population of breast cancer survivors. In order to overcome this limitation, a multicentre study design was established and to guarantee optimal usage of the program, the study intervention was developed according to persuasive system development principles (responsiveness, simplicity, ease of access and use, reduction, tunneling, tailoring, personalization, reminders, suggestion and professional support) (Oinas-Kukkonen and Harjumaa, 2009). An additional limitation to be appointed to this study, is related to the fact that it only targets disease free BC survivors, not including participants with metastatic disease or another important group of survivors, the family and caregivers of breast cancer patients. The time frame available to implement this project and its feasibility, informed this decision.

## 6. Conclusions

This research will yield evidence-based information on the acceptability, feasibility, efficacy and cost-effectiveness of iNNOVBC in breast cancer survivors when compared to TAU in a WLC.

Its conclusions will contribute to understand the idiosyncrasies of designing and implementing internet-delivered interventions in breast cancer survivors.

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## Conflicts of interest

No conflicts of interest to disclose.

## References

- Abrahams, H.J.G., et al., 2016. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12,327 breast cancer survivors. *Ann. Oncol.* 27 (6), 965–974.
- Amidi, A., et al., 2018. Internet-delivered cognitive-behavioral therapy for insomnia in breast cancer survivors: a randomized controlled trial. *JNCI: Journal of the National Cancer Institute* 110 (8), 880–887.
- Andersson, G., 2014. *The Internet and CBT: A Clinical Guide*, 1 ed. CRC Press, Boca Raton, pp. 154.
- Andersson, G., 2016. Internet-delivered psychological treatments. *Annu. Rev. Clin. Psychol.* 12, 157–179.
- Andersson, G., Cuijpers, P., 2009. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cogn. Behav. Ther.* 38.
- Andersson, G., Titov, N., 2014. Advantages and limitations of internet-based interventions for common mental disorders. *World Psychiatry* 13 (1), 4–11.
- Andersson, G., et al., 2008. Development of a new approach to guided self-help via the internet: the Swedish experience. *J. Technol. Hum. Serv.* 26 (2–4), 161–181.
- Andersson, G., et al., 2013. Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. *J. Affect. Disord.* 151 (3), 986–994.
- Arch, J.J., Mitchell, J.L., 2016. An Acceptance and Commitment Therapy (ACT) group intervention for cancer survivors experiencing anxiety at re-entry. *Psychooncology* 25 (5), 610–615.
- Barak, A., et al., 2008. A comprehensive review and a meta-analysis of the effectiveness of internet-based psychotherapeutic interventions. *J. Technol. Hum. Serv.* 26 (2–4), 109–160.
- Bastien, C.H., Vallières, A., Morin, C.M., 2001. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2 (4), 297–307.
- Beckjord, E., G.J. van Londen, and R. Rechis, Chapter 9 - Survivorship, in *Oncology Informatics*. 2016, Academic Press: Boston. p. 159–179.
- Berg, S.W.V.D., et al., BREATH: web-based self-management for psychological adjustment after primary breast cancer—results of a multicenter randomized controlled trial. *Journal of Clinical Oncology*, 2015. 33(25): p. 2763–2771.
- Bock, M., et al., 2012. The impact of an electronic health questionnaire on symptom management and behavior reporting for breast cancer survivors. *Breast Cancer Res. Treat.* 134 (3), 1327–1335.
- Boquiren, V.M., et al., 2016. Sexual functioning in breast cancer survivors experiencing body image disturbance. *Psycho-Oncology* 25 (1), 66–76.
- Bouwman, C., et al., 2013. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Serv. Res.* 13 (1), 217.
- Bower, J.E., 2014. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat. Rev. Clin. Oncol.* 11 (10), 597–609.
- Boyes, A., Girgis, A., Lecathelinais, C., 2009. Brief assessment of adult cancer patients' perceived needs: development and validation of the 34-item Supportive Care Needs Survey (SCNS-SF34). *J. Eval. Clin. Pract.* 15 (4), 602–606.
- Bray, F., et al., 2018. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA, A Cancer Journal for Clinicians*.
- Brown, M., et al., 2016. Effectiveness of web-delivered acceptance and commitment therapy in relation to mental health and well-being: a systematic review and meta-analysis. *J. Med. Internet Res.* 18 (8), e221.
- Bruggeman Everts, F.Z., van der Lee, M.L., de Jager Meezenbroek, E., 2015. Web-based individual mindfulness-based cognitive therapy for cancer-related fatigue—a pilot study. *Internet Interv.* 2 (2), 200–213.
- Buhrman, M., et al., 2013. Guided internet-delivered acceptance and commitment therapy for chronic pain patients: a randomized controlled trial. *Behav. Res. Ther.* 51 (6), 307–315.
- Burgess, C., et al., 2005. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ: British Medical Journal* 330 (7493), 702.
- Carlbring, P., et al., 2011. Individually-tailored, internet-based treatment for anxiety disorders: a randomized controlled trial. *Behav. Res. Ther.* 49 (1), 18–24.
- Carpenter, J.S., et al., 2004. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. *Oncol. Nurs. Forum* 31 (3), 591–5598.
- Carpenter, K.M., et al., 2014. An online stress management workbook for breast cancer. *J. Behav. Med.* 37 (3), 458–468.
- Claxton, K., et al., 2015. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol. Assess.* 19 (14), 1–503 (v-vi).
- Cohen, J., 1992. A power primer. *Psychol. Bull.* 112 (1), 155–159.
- Damholdt, M.F., et al., 2016. Web-based cognitive training for breast cancer survivors with cognitive complaints—a randomized controlled trial. *Psycho-Oncology* 25 (11), 1293–1300.
- De Cocker, K., et al., 2015. Development and usability of a computer-tailored pedometer-based physical activity advice for breast cancer survivors. *European Journal of Cancer Care* 24 (5), 673–682.
- Ellegaard, M.-B.B., et al., 2017. Fear of cancer recurrence and unmet needs among breast cancer survivors in the first five years. A cross-sectional study. *Acta Oncol.* 56 (2), 314–320.
- Eysenbach, G., 2011. CONSORT-EHEALTH: improving and standardizing evaluation reports of web-based and Mobile health interventions. *J. Med. Internet Res.* 13 (4), e126.
- Fashler, S.R., et al., 2018. The use of acceptance and commitment therapy in oncology settings: a narrative review. *Psychol. Rep.* 121 (2), 229–252.
- Faul, F., et al., 2007. G\*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39 (2), 175–191.
- Ferreira, L.N., et al., 2016. Comparing Eq-5d-3l and Eq-5d-5l in a general population. *Value Health* 19 (7), A477.
- Goldstein, D., et al., 2012. Cancer-related fatigue in women with breast cancer: outcomes of a 5-year prospective cohort study. *J. Clin. Oncol.* 30 (15), 1805–1812.
- Gueorguieva, R., Krystal, J.H., 2004. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the archives of general psychiatry. *Arch. Gen. Psychiatry* 61.
- Haq, R., et al., 2013. Designing a multifaceted survivorship care plan to meet the information and communication needs of breast cancer patients and their family physicians: results of a qualitative pilot study. *BMC Medical Informatics And Decision Making* 13, 76.
- Hayes, S.C., Pistorello, J., Levin, M.E., 2012. Acceptance and commitment therapy as a unified model of behavior change. *Couns. Psychol.* 40 (7), 976–1002.
- Hesser, H., 2015. Modeling individual differences in randomized experiments using growth models: recommendations for design, statistical analysis and reporting of results of internet interventions. *Internet Interv.* 2 (2), 110–120.
- Hill-Kayser, C.E., et al., 2013. Impact of internet-based cancer survivorship care plans on health care and lifestyle behaviors. *Cancer* 119 (21), 3854–3860.
- Hodgkinson, K., et al., 2007. Breast cancer survivors' supportive care needs 2–10 years after diagnosis. *Support. Care Cancer* 15 (5), 515–523.
- Hulbert-Williams, N.J., Storey, L., Wilson, K.G., 2015. Psychological interventions for patients with cancer: psychological flexibility and the potential utility of Acceptance and Commitment Therapy. *Eur J Cancer Care (Engl)* 24 (1), 15–27.
- Hummel, S.B., et al., 2017. Efficacy of internet-based cognitive behavioral therapy in

- improving sexual functioning of breast cancer survivors: results of a randomized controlled trial. *J. Clin. Oncol.* 35 (12), 1328–1340.
- Jacobson, N.S., Truax, P., 1991. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J. Consult. Clin. Psychol.* 59 (1), 12–19.
- Jansen, F., et al., 2015. Cancer survivors' perceived need for supportive care and their attitude towards self-management and eHealth. *Support Care Cancer* 23 (6), 1679–1688.
- Jasper, K., et al., 2014. Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: a randomized controlled trial. *Psychother. Psychosom.* 83 (4), 234–246.
- Johnson-Turbes, A., et al., Evaluation of a web-based program for African American young breast cancer survivors. *American Journal of Preventive Medicine.* 49(6): p. S543-S549.
- Kim, S.H., et al., 2008. Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. *J. Pain Symptom Manag.* 35 (6), 644–655.
- Kleiboer, A., et al., 2016. European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED): study protocol for a randomized controlled, non-inferiority trial in eight European countries. *Trials* 17 (1), 387.
- Koch, L., et al., 2014. Fear of recurrence in long-term breast cancer survivors - still an issue. Results on prevalence, determinants, and the association with quality of life and depression from the Cancer Survivorship - a multi-regional population-based study. *Psycho-Oncology* 23 (5), 547–554.
- Köhle, N., et al., 2015. A web-based self-help intervention for partners of cancer patients based on Acceptance and Commitment Therapy: a protocol of a randomized controlled trial. *BMC Public Health* 15, 303.
- Köhle, N., et al., 2017. User-experiences with a web-based self-help intervention for partners of cancer patients based on acceptance and commitment therapy and self-compassion: a qualitative study. *BMC Public Health* 17 (1), 225.
- Lappalainen, P., et al., 2014. ACT internet-based vs face-to-face? A randomized controlled trial of two ways to deliver Acceptance and Commitment Therapy for depressive symptoms: an 18-month follow-up. *Behav. Res. Ther.* 61, 43–54.
- Lee, M.K., et al., 2014. A web-based self-management exercise and diet intervention for breast cancer survivors: pilot randomized controlled trial. *Int. J. Nurs. Stud.* 51 (12), 1557–1567.
- Lepore, S.J., et al., 2014. Comparing standard versus prosocial internet support groups for patients with breast cancer: a randomized controlled trial of the helper therapy principle. *J. Clin. Oncol.* 32 (36), 4081–4086.
- Low, J., et al., 2016. Acceptance and commitment therapy for adults with advanced cancer (CanACT): study protocol for a feasibility randomised controlled trial. *Trials* 17, 77.
- Lowery-Allison, A.E., et al., Sleep problems in breast cancer survivors 1–10 years post-treatment. *Palliative and Supportive Care*, 2017: p. 1–10.
- Maass, S.W.M.C., et al., 2015. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas* 82 (1), 100–108.
- McCarroll, M.L., et al., 2015. Feasibility of a lifestyle intervention for overweight/obese endometrial and breast cancer survivors using an interactive mobile application. *Gynecol. Oncol.* 137 (3), 508–515.
- Mendoza, T.R., et al., 1999. The rapid assessment of fatigue severity in cancer patients. *Cancer* 85 (5), 1186–1196.
- Mols, F., et al., 2005. Quality of life among long-term breast cancer survivors: a systematic review. *Eur. J. Cancer* 41 (17), 2613–2619.
- Mujcic, A., et al., 2018. Internet-based self-help smoking cessation and alcohol moderation interventions for cancer survivors: a study protocol of two RCTs. *BMC Cancer* 18 (1), 364.
- NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Survivorship. NCCN Guidelines® 2017a [cited 2017 25/7]; Available from: [https://www.nccn.org/professionals/physician\\_gls/pdf/survivorship.pdf](https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf).
- NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Cancer-related Fatigue. NCCN Guidelines® 2017b [cited 2017 26/7/2017]; Available from: [https://www.nccn.org/professionals/physician\\_gls/pdf/fatigue.pdf](https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf).
- NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for patients: Distress. NCCN Guidelines® 2017c [cited 2017 26/7/2017]; Available from: <https://www.nccn.org/patients/guidelines/distress/files/assets/basic-html/page-1.html#>.
- Oinas-Kukkonen, H., Harjumaa, M., 2009. Persuasive systems design: key issues, process model, and system features. *Commun. Assoc. Inf. Syst.* 24 (28).
- Olthuis, J.V., et al., 2016. Therapist-supported internet cognitive behavioural therapy for anxiety disorders in adults. *Cochrane Database Syst. Rev.* 3.
- Otte, J.L., et al., 2010. Prevalence, severity, and correlates of sleep-wake disturbances in long-term breast cancer survivors. *J. Pain Symptom Manag.* 39 (3), 535–547.
- Pais-Ribeiro, J., C. Pinto, and C. Santos, Validation study of the Portuguese version of the QLC-C30-V.3. *Psicologia, Saúde & Doenças*, 2008. 9: p. 89–102.
- Panjari, M., Bell, R.J., Davis, S.R., 2011. Sexual function after breast cancer. *J. Sex. Med.* 8 (1), 294–302.
- Paterson, C., et al., 2016. Body image in younger breast cancer survivors: a systematic review. *Cancer Nurs.* 39 (1), E39–E58.
- Pauwels, E., et al., 2013. Design and process evaluation of an informative website tailored to breast cancer survivors' and intimate partners' post-treatment care needs. *BMC Health Serv. Res.* 13 (1), 1–13.
- Paxling, B., et al., 2012. Therapist Behaviours in internet-delivered cognitive behaviour therapy: analyses of E-mail correspondence in the treatment of generalized anxiety disorder. *Behav. Cogn. Psychother.* 41 (3), 280–289.
- Pechorro, P., Diniz, A., Almeida, S., 2009. Validação portuguesa do índice de Funcionamento Sexual Feminino (FSFI). *Laboratório de Psicologia* 7 (1), 44.
- Post, K.E., Flanagan, J., 2016. Web based survivorship interventions for women with breast cancer: an integrative review. *Eur. J. Oncol. Nurs.* 25, 90–99.
- Raggio, G.A., et al., 2014. Prevalence and correlates of sexual morbidity in long-term breast cancer survivors. *Psychol. Health* 29 (6), 632–650.
- Reinertsen, K.V., et al., 2017. Fatigue during and after breast cancer therapy—a prospective study. *J. Pain Symptom Manag.* 53 (3), 551–560.
- Richards, D., Richardson, T., 2012. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin. Psychol. Rev.* 32 (4), 329–342.
- Rosen, C., et al., 2000. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *Journal of Sex & Marital Therapy* 26 (2), 191–208.
- Safarinejad, M.R., Shafiei, N., Safarinejad, S., 2013. Quality of life and sexual functioning in young women with early-stage breast cancer 1 year after lumpectomy. *Psycho-Oncology* 22 (6), 1242–1248.
- Schröder, J., et al., 2015. Development of a questionnaire measuring Attitudes towards Psychological Online Interventions—the APOI. *J. Affect. Disord.* 187, 136–141.
- Seav, S.M., et al., 2015. Management of sexual dysfunction in breast cancer survivors: a systematic review. *Women's Midlife Health* 1 (1), 9.
- Sheehan, D.V., et al., The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*, 1998. 59 Suppl 20: p. 22–33;quiz 34–57.
- Simard, S., et al., 2013. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *J. Cancer Surviv.* 7 (3), 300–322.
- Sousa, T.V., et al., 2015. Reliability and validity of the Portuguese version of the Generalized Anxiety Disorder (GAD-7) scale. *Health Qual. Life Outcomes* 13 (1), 50.
- Sprangers, M.A., Groenvold, M., Arraras, J.I., Franklin, J., te Velde, A., Muller, M., et al., 1996. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J. Clin. Oncol.* 14 (10), 2756–2768.
- Thewes, B., et al., 2012. Fear of cancer recurrence in young women with a history of early-stage breast cancer: a cross-sectional study of prevalence and association with health behaviours. *Support. Care Cancer* 20 (11), 2651–2659.
- Topooco, N., et al., 2017. Attitudes towards digital treatment for depression: a European stakeholder survey. *Internet Interv.* 8, 1–9.
- Torres, A., et al., Reliability and validity of the PHQ-9 in Portuguese women with breast cancer, in *icH&Hpsy 2016: 2nd International Conference on Health and Health Psychology*. 2016, Future Academy: Porto - Portugal. p. 411–423.
- Vlaescu, G., et al., 2016. Features and functionality of the Iterapi platform for internet-based psychological treatment. *Internet Interv.* 6, 107–114.
- Wen, K.-Y., et al., 2012. The development and preliminary testing of a multimedia patient-provider survivorship communication module for breast cancer survivors. *Patient Educ. Couns.* 88 (2), 344–349.
- Whelock, A.E., et al., 2015. SIS.NET: a randomized controlled trial evaluating a web-based system for symptom management after treatment of breast cancer. *Cancer* 121 (6), 893–899.
- Zainal, N.Z., et al., 2013. Prevalence of depression in breast cancer survivors: a systematic review of observational studies. *Asian Pac. J. Cancer Prev.* 14 (4), 2649–2656.
- Zhang, M., et al., 2017. Effects of cognitive behavioral therapy on quality of life and stress for breast cancer survivors: a meta-analysis. *Minerva Med.* 108 (1), 84–93.