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SUMMARY OF Ph.D. THESIS

DEVELOPING AND IMPLEMENTING ONCOVOX: A CONTEXTUAL BEHAVIORAL APPROACH TO AN ONLINE INTERVENTION FOR BREAST CANCER PATIENTS IN ACTIVE TREATMENT

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Abstract

Acceptance and Commitment Therapy (ACT) in an online delivery can be cost-effective and convenient for providing evidence-based treatment for breast cancer patients (BCP), but there are currently no such programs. The aim of this thesis was to develop, test and implement Oncovox, an iACT intervention for BCPs in active treatment.

Firstly, a systematic review of the literature was undertaken in Study 1. Its results informed the initial versions of the Oncovox prototype, that were tested and refined sequentialy on small groups of patients (n=15, Study 2.1. and n=50, Study 2.2). The final version of the intervention was tested in a two-arm, parallel, open label, waiting list randomised controlled trial (n=150, Study 4). The last two studies of the thesis were post-hoc analysis of the moderators for the intervention (Study 4) and the barriers and facilitators to adherence (Study 5). Finally, we collected data on the emotional impact of the Covid-19 pandemic on BCPs in active treatment (Study 6).

Oncovox strongly improves symptom interference, anxiety and depression symptoms and psychological flexibility, results further improving at 1- and 2- month follow-up timepoints. The intervention had also medium to large positive impact on QoL, behavioural activation and reward noticing, but only when analysing the imputed data. Oncovox is safe and useful for all BCPs in active treatment, but it is particularly efficient for patients that had gone through a more invasive type of surgery in reducing anxiety and depression symptoms and symptom interference. Barriers and facilitators to the adherence to the intervention are also explored, and the dropout phenomenon for this intervention is explained in detail. A particular group of participants that are affected by subjective cognitive impairment are especially likely to drop out of the intervention as they struggle with the content of the intervention.

Keywords: Acceptance and Commitment Therapy (ACT), Breast cancer patients, online interventions, e-mental health

CHAPTER 1: INTRODUCTION

1.1 Overview

Each year 12.000 women are diagnosed with BC in Romania. In 2020, 45.263 women had been living with BC for the past 5 years. This makes BS survivors the largest group of cancer survivors in the country, as it also is worldwide. Around 20%–30% of survivors of breast cancer experience sequelae of treatment, late side effects, and unmet supportive care needs, including poor physical, psychosocial, or practical functioning. These sequelae can occur in a period spanning from diagnosis to several years after primary treatment end and can cause clinically significant levels of distress (Beckjord et al., 2016; Arnaboldi et al., 2014). During treatment, patients` involvement in day-to-day activities is diminished due to them coming up against a multitude of physical symptoms and frequent required hospital attendance (Fernández-Rodríguez et al., 2021). Changes in functional status and interpersonal relationships have been linked to anxiety and depression, lower quality of life (QoL), tiredness, insomnia, and pain (González-Saenz de Tejada et al., 2016; Sibeoni et al., 2018; Hamer et al., 2017). These emotional difficulties appear to be related to behavioural inhibition, which narrows contact with rewarding and valuable stimuli and favours avoidance of unpleasant internal experiences associated with cancer (González-Fernández et al., 2018).

Given the complex coexisting psychosocial and physiological challenges faced by breast cancer patients (BCPs), early psychological support is essential for promoting psychosocial healthy adaptation (Han et al., 2019). It is suggested that interventions that are context-based, such as Acceptance and Commitment Therapy (ACT), may achieve better results since they are better adapted to the needs and worldviews of oncological patients (Hulbert-Williams, Storey & Wilson, 2014; Fashler et al., 2018). The theoretical basis of ACT suggests that outcomes of interest in intervention studies should not focus exclusively on symptoms or diagnoses, as has been done traditionally in the larger psychotherapy literature, but rather

measure the degree to which ACT interventions improve participants' functioning and well-being (Gloster et al., 2020). Several studies have demonstrated the feasibility and preliminary effect of ACT interventions on distress, QoL (Montesinos & Luciano, 2016; Johns et al.; 2020, Han et al., 2019; Trindade et al., 2020), symptom interference (Mosher et al., 2018; Hadlandsmyth et al., 2019; Arch et al., 2021), behavioural activation (Fernandez-Rodriguez et al., 2021) and healthy behaviours in cancer patients.

Most BCPs, especially those living in developing countries, are unable to timely access evidence-based care due to several barriers such as costs, distance and difficulty accessing adequately trained clinicians (Dear et al., 2022). Furthermore, 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 (Post & Flanagan, 2016).

Online psychological interventions are a promising solution to many of these barriers. The online delivery of a psychosocial intervention provides many advantages for oncology patients. Furthermore, this type of interventions has proved to be feasible, acceptable, and efficacious (Fridriksdottir et al., 2017; Leslie et al., 2022).

Connecting these two research avenues would benefit Romanian BCPs. Currently there are no web-based ACT interventions for women diagnosed with breast cancer. Building on previous research on ACT for BCPs in a face-to-face setting and on the high adherence and effectiveness of iACT interventions on different populations, developing an iACT intervention for BCPs seemed like a natural next step for the field. Also, the paucity of psychosocial interventions for Romanian BCPs and their openness and high digital literacy made this population a perfect candidate for this research venture. We are confident that developing such an intervention would benefit the Romanian cancer population.

1.2. The scarcity of psychological interventions for BCPs in Romania

The treatment gap for mental health problems among cancer patients is not by any means specific to Romania. A study reported that in 2013 47,5% of Romanian cancer patients were clinically depressed and 46,7% experienced anxiety disorders (Faludi & Degi, 2017).

As a BCPs looking for psycho-social support, it can be daunting and confusing – how do you know you or your family need to see a specialist? Where to find a psycho-oncologist? Who is a properly trained psycho-oncologist? Who decides for how long and when during your treatment you should see such a specialist? And who will pay for these services?

Psycho-oncology is deprioritized by most multidisciplinary oncology teams and cancer centres. The overwhelming majority of BCPs in Romania will go through their cancer treatment without knowing if there is a mental health specialist available to see them. They will probably not get an appointment even if they would like to, as even where available, this service is overbooked. Little to no counselling if ever offered to caregivers, partners, or families, not even in the palliative setting. But one could argue that there is also a paucity of psycho-oncologists in Romania, as there are few and far between programmes that train specialists in this field, and most are poorly designed and unsuccessfully advertised. There is also process of accreditation in Romania for a psycho-oncologist, apart from self-proclamation.

More recently CASMB started subsidising psychotherapy sessions for cancer patients upon referral by their oncologists. But these medical specialists are neither trained to assess patients` mental health, nor mandated to do so, nor given a national protocol to abide by.

The paucity of training, education, information, and availability of evidence-based psychological interventions affects all areas of mental health in Romania. BCPs are just a small part of those impacted. There is an acute need to redesign of such services for them to reach those in need while controlling the costs of healthcare provision without diminishing the quality of service. Online psychological interventions are a promising solution.

CHAPTER 2: ORIGINAL RESEARCH CONTRIBUTIONS

2.1. Aim of the thesis

The overarching aim of this thesis was to develop Oncovox – a guided, internet delivered ACT intervention designed to enhance QOL and improve psychosocial outcomes related to living a richer and a more meaningful life for BCPs in active treatment, using an UCD approach (Lyon & Koerner, 2016). Doing so, the first iACT intervention for BCPs would be developed, testing this model`s feasibility, usefulness, and efficiency for this population, with this delivery mode.

To achieve this, the following aims were identified.

a) Develop a better understanding of the existing web-based psychological interventions for cancer patients, their components, persuasive technology elements as well as their strengths and weaknesses.
b) Develop Oncovox – a guided iACT intervention tailored for non-metastatic breast cancer patients diagnosed in the past 24 months – define aims, structure, content, site development and initial testing.
c) Test Oncovox`s feasibility of recruitment, acceptability, usability, and efficiency.
d) Identify moderators of the intervention to better inform Oncovox`s implementation.
e) Understand adherence and attrition for Oncovox.
f) Understand the challenges cancer patients faced during the COVID-19 pandemic and their subsequent emotional responses.

To this end qualitative and quantitative methods were combined in six empirical studies.

First, we developed a better understanding of the existing web-based psychological interventions for CPs their components, persuasive technology elements as well as their strengths and weaknesses (Study 1). We then began prototyping and developing Oncovox – defining its aims, structure, content, and format, developing the website and did some initial

testing (Study 2.1). After that, Oncovox`s acceptability, usefulness, usability, feasibility, and efficiency were tested. First in two pilot studies, on smaller samples of participants, to enable us to go back to the original design and tweak it (Study 2.2) and then on a larger sample (Study 3). Lastly, planning for nation-wide dissemination we investigated moderators for the intervention (Study 4) and barriers and facilitators for adherence (Study 5). Study 6 explored the emotional impact of the Covid-19 pandemic on BCPs in active treatment.

The research activities were approved by the ethics review board of Babeș-Bolyai University, Cluj-Napoca, Romania (approval number: 13.610/ 26.10.2021). The development and the empirical findings supporting the development processes of Oncovox are further described below.

2.2. Study 1: A Systematic Review of the Effects of Internet-based Psychosocial Interventions on Emotional Distress and Quality of Life in Adult Cancer Patients[1]

2.2.1 Aims

The first phase of development of Oncovox was based on the current literature. We aimed to identify the characteristics of effective online interventions for cancer patients, for what type of participants and the required components of the interventions. The purpose of this study was to update the existing evidence by (a) identifying web-based psychological interventions evaluated via RCT that aimed to improve patient-reported psychological distress and/or QOL among oncology patients, (b) evaluate the quality of the intervention studies and (c) evaluate if developed interventions have been efficient in improving psychological distress and/or QOL, as compared with control conditions in RCTs. These findings guided Oncovox's development.

[1] *This study was published as Goliță, S., & Băban, A. (2019). A systematic review of the effects of internet-based psychological interventions on emotional distress and quality of life in adult Cancer patients. Journal of Evidence-Based Psychotherapies, 19(2), 47-78.* https://doi.org/10.24193/jebp.2019.2.13

2.2.2. Methods

Due to substantial heterogeneity in study design, population, type of intervention and outcome, a systematic review was the best way to address these issues. To our knowledge, this was the first systematic review to specifically focus on psychological distress and QOL outcomes of web-based psychotherapy interventions.

We conducted this review using preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, searching five databases for RCT of web-based interventions for oncology patients that included a patient-reported psychological distress and/or QOL outcome. We assessed the quality of the included studies using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies. We used a narrative synthesis to summarize the results.

2.2.3. Results

Our search identified nineteen RCTs involving 4084 patients diagnosed with primary cancer investigating web-based psychological interventions. Twelve of the studies targeted cancer survivorship, five studies aimed at the first 18 months after diagnosis and the three other studies recruited irrespective of the treatment stage of the participants. Quality-wise, six studies received a “strong” rating, eight received a “moderate” rating and five of the studies received a “weak” rating.

Nine interventions (56%) were associated with significant improvements in psychological distress relative to control conditions, and five interventions (33%) with the same improvements in QOL. Thus, there is mixed support for the evidence that web-based psychotherapeutic interventions can improve psychological distress and QOL in cancer patients’ samples, slightly in favour for improving psychological distress. Interventions aimed at improving psychological distress appear to be comparably positive between conditions, with no clear conclusion as to what is the best stage of treatment to target distress, or for which

population. Less interventions focused on increasing QOL than on reducing distress, and the ones that did seem to have a harder time reaching a statistical and clinical significance, even though most prove small to medium effect sizes. Interventions aimed at a heterogenic diagnosis seem to have had better effects, but our sample is too small for a definitive conclusion.

All the interventions were positively assessed in terms of satisfaction with the web-based intervention, it`s utility, the perceived ease of use and it`s feasibility. Attrition, defined as non-use rates (Eysenbach, 2011), ranged from 3% to 45%, which is expected for online interventions (Kelders et al., 2012). Interventions that aimed at a specific diagnosis, at a specific issue (insomnia or fatigue) or at survivorship in general had better attrition rates irrespective of the length, components of the intervention or of the support given by the psychotherapists, when available. Tailorable interventions also had overall better attrition rates than the ones that could not be customized. Therapist involvement varies considerably across all studies. Interventions have generated statistical and clinically significant improvement with good compliance when offering strong therapist involvement (Abrahams et al., 2017; Zernicke et al., 2014, Hummel et al., 2017) and when no therapeutic support was available (Wootten et al., 2015).

2.2.4 Discussion

In the present review has found mixed support for web-best psychological intervention to improve psychological distress and QOL in cancer patients' samples. Interventions aimed at alleviating distress were more efficient across investigated cancer types and treatment stages. The interventions aimed at enhancing QOL were less efficient, even though most of them were efficient in decreasing distress. It is our opinion that most of the interventions employed were CBT-based, and that their inherent focus might have been predominantly on symptom control and thus distress decrease. Including an analysis of mechanisms of change in future studies could provide answers to some of these questions. Despite the marked

variability of the interventions reviewed, some were efficient and received good attrition and compliance.

It is important that the content and the timing of interventions are appropriate to the idiosyncratic needs of the patients. Additional exploration is necessary to (1) further understand how to better design interventions matched to users' capabilities and avoid inadvertent negative consequences (2) to successfully recruit a heterogenous population of cancer patients. User involvement in the development phase and early feedback may are recommended for future web-based interventions.

2.2.5. Conclusion

Web-based delivery format show potential in effective management of psychological distress and QOL in cancer patients. Still, due to heterogeneity in interventions tested and targeted populations, additional high-quality studies and further clarifications are needed for these treatments to be considered empirically supported treatments.

2.3. Study 2: Pilot Study of a Web-Based Acceptance and Commitment Therapy Intervention for Breast Cancer Patients[2]

Our aim was to develop an online intervention that is both effective and acceptable for BCPs in active treatment. Using a mixed approach between qualitative and quantitative analysis we prototyped the intervention and then tested in two stages (Study 2.1 and Study 2.2). Participants` feedback informed modifications to the protocol and to the delivery of the intervention.

[2] This study was published as Goliță, S., Băban A.S. (2020). Acceptability and User-Experience of a Web-Based Acceptance and Commitment Therapy Intervention for Breast Cancer Patients in D. Cozman & A. Paziuc (Eds.), Proceedings of 23rd World Congress of Social Psychiatry 2019 (pp.87-93), Bologna, Filodiritto Editore. ***DOI: 10.26352/DX25-PSYCHIATRY2019***

2.3.1. Study 2.1: Acceptability and Usability of a Web-Based Acceptance and Commitment Therapy Intervention for Breast Cancer Patients

2.3.1.1 Aims

We developed a protoype of Oncovox and tested it regarding (1) the acceptability of the online delivery modality of the psychological therapy; (2) whether participants would consider using the program in their current treatment stage, (3) adherence to the content and (4) to gather feedback on content, format, and flow of the program.

2.3.1.2 Methods

Design, sampling, and recruitment

A convenience sample of fifteen women (mean age=48,1 year, range=35-61 years) diagnosed within non-metastatic breast cancer were offered the first two modules of the intervention and were subsequently interviewed. A thematic analysis directed by specific guiding questions was performed on interview transcripts. Participants had been diagnosed in the past 18 months (mean=7,8months), and were undergoing either chemotherapy (25%), radiotherapy (52%) or hormonal therapy (22%). All participants gave their informed consent.

Intervention description

Oncovox is an 8-modules guided web-based ACT intervention delivered via a website build for this purpose. Its structure and content are built on prior research interventions developed for breast cancer patients (Rost et al., 2012; Feros et al., 2011; Fashler et al., 2017; Johns et al., 2020) that have been considered effective for various outcomes in this specific population. The intervention has a transdiagnostic structure, featuring treatment strategies and topics considered relevant for this population by the literature. Through experiential exercises, metaphors and homework assignments, the intervention aims at reducing patients' resistance towards their symptoms and increasing psychological flexibility. Each module consists of short texts, images, videos, downloadable audio-files, quizzes, ACT-based exercises, and homework

assignments and takes approximately 90-120 minutes to complete. Participants were recommended to complete one module per week, in a sequential order. Support was offered to participants in an integrated chat in the form of weekly feedback, prompts and reminders by me. I am a certified psychotherapist, working with ACT for more than 10 years. Participants were also sent automatic e-mails throughout the intervention, which served to inform them about the new available module and promote engagement with the course.

Interview guide

We designed a semi-structured interview guide to collect participant`s overall impressions of the program, their opinion on the length, duration, style and content of the course, their feedback on their psychotherapist, their likes/dislikes of the program and how they worked through the program materials.

Data analysis

Transcriptions and analysis were conducted using thematic analysis following the steps recommended by Braun & Clark (2006). Analysis was inductive, as no previous hypothesis about possible themes existed.

2.3.1.3 Results

Overall, the Oncovox program and the ACT approach were regarded as positive and useful. Table 1 displays six emerging themes and their subthemes.

Table 1: Themes and subthemes of participants` views

Acceptability	Main resource Restricted audience
Benefits	Tool post-treatment Anonymity Flexibility
Concerns	Women`s state of mind Module`s difficulty Accessibility
Importance of support	Benefits of support
Implementation	Modes of implementation Ways of timing and promotion
Oncovox	

2.3.1.4. Discussion

Fifteen women diagnosed with breast cancer used the first two modules of Oncovox. Our primary aims were to establish whether they would find the program acceptable overall, how to best present its content and flow for various cancer stages and treatment timing and to collect suggestions for improving the program. Based on our findings, iACT is a useful, and appropriate psychotherapeutic approach for women diagnosed with breast cancer. Overall, the acceptability of the mode of treatment delivery as well as the content and design were high. Small but useful modifications were made based on participant feedback, such as (a) shortening the module length, (b) the exclusion of some of the exercises that were not popular or were hard to understand, (c) adding a degree of flexibility to the schedule of the intervention, (d) providing significant support and more encouragement to take breaks to have more time to process the new information and (e) take more time to practice the new abilities. Also, based on their popularity, we will introduce more videos than originally planned. At the same time, some changes were made in the user-interface for it to be more intuitive and easier to use.

Nonetheless, more research is needed to develop successful engagement strategies for a longer intervention, as this study investigated just the first two modules of the intervention.

2.3.1.5 Conclusion

This was the first specific iACT intervention for BCPs dealing with high distress and low QOL and we have obtained valuable feedback by engaging our users in the development phase. We hope this will lead to better outcomes and engagement for future users. The first two modules of Oncovox had been well received and the feedback the users had given us was enough for us to adapt the existing modules and continue developing six more modules.

2.3.2. Study 2.2: Testing and Initial Implementation of a Web-based ACT Intervention for Breast Cancer Patients

2.3.2.1. Aims

Following the previous study that tested a prototype of Oncovox, an 8-module intervention was developed. The aim of this study was to assess the acceptability, usability, implementation, and efficacy of the entire intervention and to improve its outcomes further rapidly.

2.3.2.2. Methods

Design

We used a double one-arm design. Psychosocial assessments were administered online at baseline, after module 3, after module 5 and post-treatment. Demographic and clinical data were collected at baseline. We performed a within-group analysis and a post-treatment interview and an exploratory qualitative analysis of participants` views. A thematic analysis directed by specific guiding questions was performed on the interview. We refined the intervention`s content and flow across two consecutive cohorts, implementing the first cohort`s feedback for the second one.

Recruitment

Recruitment was done exclusively online, using Facebook cancer patient groups. Screening consisted of an online assessment tool of demographic and medical information, questionnaires assessing inclusion, exclusion criteria as well as a baseline assessment for the study`s outcomes.

Participants

Participants (n = 52) were required to (1) read and write in Romanian, (2) have internet access as well as basic computer skills, (3) have a curative breast cancer diagnosis as main

diagnosis in the past 18 months, (4) be willing to dedicate 2-3 hours/week to the intervention. Exclusion criteria: (1) suicidal ideation, maniacal episode, psychotic symptoms, learning disabilities, cognitive severe disabilities, (2) already undergoing psychotherapy, (3) major changes in psychiatric medication doses during the intervention, (4) receiving palliative care or (5) cancer relapse.

Intervention description

The prototype described in the previous study was extended to 8 weekly sequential modules that took approximately 75-90 minutes to complete.

Outcome variables and outcome measures

Participants characteristics

The following socio-demographic and medical variables were collected: age, date of diagnosis, cancer stage, treatment received.

Symptom Interference (SI)

Symptom Interference with cognition, mood, and activities was assessed with the 6-item global symptom interference subscale of the MD Anderson Symptom Inventory (MDASI, Cleeland et al., 2000).

Behavioral Activation (BA)

Behavioral Activation for Depression Scale (BADS; Kanter et al., 2006) consists of 25 items measuring four dimensions: Activation, Avoidance/Rumination, Work/School Impairment and Social Impairment. A 7-point Likert scale is used.

Reward Noticing (RN)

We used the Environmental Reward Observation Scale (EROS; Armento & Hopko, 2007), which informs us on the quantity and availability of reinforcement received from the patient's environment. It consists of 10 items, answered using a 4-point Likert scale.

Secondary outcome measures

Cancer-specific Quality of Life (QoL)

The Functional Assessment of Cancer Therapy-Breast (FACT-B; Cella et al., 1993) version 4 was used to evaluate the participants' QoL. FACT-B is a 36-item questionnaire that uses a five-point Likert scale.

Anxiety and depression symptoms

The Hospital Anxiety and Depression Scale (HADS), (Zigmond & Snaith, 1983) is a 14-item scale with 2 subscales, Anxiety and Depression. In depression and anxiety subscales, 8-10 indicate probable non-clinical cases, and scores over 11 indicate clinical cases.

Process outcome

Psychological Flexibility (PF)

The 15-item Acceptance and Action Cancer Questionnaire measured change in ACT processes adapted from the AAQ-II for cancer patients (Arch & Mitchell, 2016).

Feasibility and acceptability

The number of patients that started the intervention is defined as the intervention's uptake. The drop-out rate relates to attrition. The number of completed modules, participants' engagement with assignments and their psychotherapists will be reported as adherence to treatment.

Data collection

We conducted 24 individual post-treatment recorded video-conference interviews between September and November 2021, and then transcribed them verbatim. Data collection ended when saturation was met, and no new themes were revealed.

Data analysis

Repeated measures ANOVAs were employed to assess the significance of the main effect of time for all outcome and process variables. As we expected significant improvements in between timepoints, significance levels were assessed using one-tailed tests and were

interpreted based on the $p < .05$ criterion. Transcriptions and analysis were conducted using an exploratory analysis. Analysis was inductive, as no previous hypothesis about possible themes existed. Transcripts were read thoroughly for the identification of features that were meaningful and relevant to the research topic.

2.3.2.3 Results

Initially 35 new users registered on http://oncovox.ro. Only 27 (77%) completed the screening assessment and were assessed for eligibility via phone call. After the assessment interview, 25 (92%) participants were included in the study. Post-intervention 7 participants (28%) responded to the questionnaire. On the second iteration 30 new users registered on the website, 25 participants (83%) completed the screening assessment and were assessed via phone. All 25 (100%) patients were included in the study. Post-intervention 17 participants (68%) responded to the questionnaire. Drop-out analysis revealed no significant differences between dropouts and completers on any outcome variable at baseline or as time or group interaction between the pre- and post-measure. The average age of the 50 participants was 47,3 years (SD=9,5). All of them were Romanian. The mean disease duration was 9,4 months (SD=6,4). Most participants had stage II breast cancer (64%) and had had surgery (70%). Most participants were currently on hormonal treatment (40%).

Intervention outcomes

Quality of Life

For the first sample, the multivariate test indicated nonsignificant Time differences in terms of quality of life scores ($F(3, 21) = 1.22$, $p = .327$, *partial* $\eta^2 = .04$). For the second sample, the multivariate test indicated nonsignificant Time differences ($F(3, 21) = 1.03$, $p = .399$, *partial* $\eta^2 = .04$).

Symptom interference

For the first sample, the multivariate test indicated significant Time differences in terms of symptom interference scores ($F(3, 21) = 3.26$, $p = .042$, *partial* $\eta^2 = .13$). Post hoc tests (Figure indicated significant decreases from the first timepoint to the third (*Mean difference* = 9.88, *SE* = 3.49, $p = .021$, Cohen's $d = .66$) and forth timepoints (*Mean difference* = 13.26, *SE* = 3.51, $p = .008$, Cohen's $d = .90$). For the second sample, the multivariate test indicated significant Time differences ($F(3, 21) = 3.07$, $p = .050$, *partial* $\eta^2 = .12$). Post hoc tests indicated significant decreases between the beginning of the study and the end (*Mean difference* = 11.81, *SE* = 3.56, $p = .012$, Cohen's $d = .78$).

Behavioural activation

For the first sample, the multivariate test indicated nonsignificant Time differences in terms of behavioural activation ($F(3, 21) = 0.73$ $p = .544$, *partial* $\eta^2 = .02$). For the second sample, the multivariate test indicated nonsignificant Time differences ($F(3, 21) = .60$, $p = .621$, *partial* $\eta^2 = .02$) .

Reward noticing

For the first sample, the multivariate test indicated significant Time differences in terms of reward noticing scores ($F(3, 21) = 3.21$, $p = .044$, *partial* $\eta^2 = .13$). Post hoc tests indicated significant increases from the beginning of the study to the final timepoint (*Mean difference* = 4.65, *SE* = .99, $p = .003$, Cohen's $d = 1.10$). For the second sample, the multivariate test indicated nonsignificant Time differences ($F(3, 21) = .31$, $p = .821$, *partial* $\eta^2 = .01$).

Anxiety and Depression

For the first sample, the multivariate test indicated nonsignificant Time differences in terms of anxiety and depression ($F(3, 21) = 2.71$ $p = .071$, *partial* $\eta^2 = .10$). For the second sample, the multivariate test indicated nonsignificant Time differences ($F(3, 21) = 2.49$, $p = .088$, *partial* $\eta^2 = .09$)

Psychological flexibility

For the first sample, the multivariate test indicated significant Time differences in terms of psychological flexibility scores ($F(3, 21) = 3.39$, $p = .041$, *partial* $\eta^2 = .13$). Post hoc tests indicated significant increases from the beginning of the study to the final timepoint (*Mean difference* = 18.82, *SE* = 5.51, $p = .011$, Cohen's $d = .80$). For the second sample, the multivariate test indicated nonsignificant Time differences ($F(3, 21) = .93$, $p = .441$, *partial* $\eta^2 = .04$).

Intervention acceptability, usability

A few themes emerged clearly from the first`s cohort feedback, and as such we proceeded on adapting the intervention accordingly. This led to an increase in treatment adherence and usage for the second cohort. Overall, Oncovox and the ACT approach were regarded as useful and interesting. Table 2 displays the emerging themes that informed changes in the intervention and protocol.

Table 2

Participants` views on the intervention and protocol

"I would like to see more of…"	• Contact with psychotherapist. • Time per module • Audio recordings • Actionable content • Personalization • Standardization of clinician support
"I would like to see less of…"	• Content • Written exercises. • Academic language • Too many tests
Difficulties	• With longer mindfulness exercises and imagery exercises • With website • Finding time – would need more prompts reminders
Other suggestions	• Adding a forum • Adding a video session with the assigned clinician • Easier navigation of website • Extend inclusion criteria

After the second cohort`s feedback and improved adherence rates we decided that the Oncovox was ready to be tested in a randomised controlled trial.

2.3.2.4. Discussion

This pilot study was the first to our knowledge to evaluate the effectiveness, acceptability, and usability of an iACT intervention on QoL, symptom interference, behavioural activation and reward noticing for breast cancer patients. The data showed significant improvements with a large effect size for symptom interference in both cohorts. QOL, behavioural activation and anxiety and depression symptoms saw no improvements in either cohort, and the intervention effect was consistently small for behavioural activation, small to medium for QOL and medium to large for anxiety and depression. The first version of the intervention significantly improved participants` reward noticing and psychological flexibility with a large effect size, whereas these changes were non-observable for the second version of the intervention, with effect sizes dropping to small. Overall, both versions of the intervention elicited good participants` feedback, good satisfaction, and an increase in adherence after implementing suggested feedback. Most importantly, applying an iterative process to refine Oncovox across two sequential cohorts was useful in significantly increasing adherence.

Taking in account participants` feedback we have adjusted the length of the intervention, increased the support available, introduced more prompts and reminders and switched written exercises for audio recordings and more actionable content and lessened the therapeutic jargon. While the modifications implemented improved adherence to the intervention, effectiveness dropped in terms of reward noticing and psychological flexibility, the only improved outcomes consistently persisting being symptom interference. Cutting out some of the exercises and shortening the modules to increase adherence could have caused a reduction in treatment dose, and thus the second version of the intervention could have a too low intensity to continue to impact reward noticing and psychological flexibility.

We emphasize that these results need to be interpreted with caution because of the small sample size, the absence of a control group and the limited follow-up. However, the results were sufficiently promising to justify conducting a RCT to determine whether it outperforms a control condition (i.e., usual care).

2.3.2.5. Conclusion

Study 2.2 has built on Study 2.1`s conclusions and recommendations and the intervention has come a long way since its prototype. Adjusting and fine tuning the content, the exercises, the mode of delivery and the support provided has consistently provided better participant satisfaction, feedback and has increased adherence. Employing an iterative testing process has also enabled us to test previous users` feedback as to ensure we were not biasing the intervention`s development based on a small group of participants.

2.4. Study 3: Oncovox: A Randomised Controlled Trial of a Web-Based Acceptance and Commitment Therapy for Breast Cancer Patients[3]

2.4.1. Aims

The present study aimed to examine the efficacy and acceptability of an 8-week guided iACT intervention designed to improve BCPs` QoL, symptom interference, behavioral activation, and reward noticing compared to treatment as usual. We also aimed to assess the efficacy of the intervention on anxiety and depression symptoms and psychological flexibility and whether psychological flexibility mediates other outcomes

[3] Nicolescu, S., Secară, E., Jiboc N.M, Băban, A. (2023). Effectiveness of a web-based Acceptance and Commitment Therapy intervention for Breast cancer patients: Results of the Oncovox Randomised Controlled Trial (submitted, currently under revision with JCBS)

2.4.2. Methods

Recruitment

A Facebook Ads campaign for the study ran for four weeks. The campaign reached 119.000 people; 7620 visited the website and 363 created accounts. Once on the website, participants consented to participate and completed an online screening. Following this, they were phoned by a psychotherapist that would finalize the screening and confirm enrolment. Inclusion and exclusion criteria are described in Table 3.

Table 3: Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Good Romanian literacy 2. Good digital literacy 3. Access to internet 4. Curative breast cancer diagnosis within the past 24 months. 5. A score ≥ 5 on the Distress Thermometer (DT) and/or ≥ 11 on the Hospital Anxiety and Depression Scale (HADS)	1. Suicidal ideation, manic episode, psychotic symptoms, learning disabilities, severe cognitive impairment. 2. Already doing psychotherapy 3. Major changes in psychiatric medication doses during the intervention 4. In palliative care 5. Recurrence of cancer

Design

A two-arm, open-label parallel RCT with a waiting-list control group (WLCG). Eligible participants were randomly assigned at a ratio of 1:1 using block randomization with randomly selected block sizes to the iACT group or the WLCG. Patients were stratified according to time since diagnosis, and baseline distress was measured with the 10-point Distress Thermometer Scale. Socio-demographic, medical and clinical data were collected at baseline. The iACT group rated satisfaction with intervention at post-intervention. The study ran from November 2021 to March 2022.

Study intervention

The intervention described in the previous study was modified into 1-hour long modules (Table 4). Seven PhD students and certified psychotherapists with prior ACT experience guided each participant, gave feedback on exercises and assignments or prompts and reminders, as necessary. The WLCG's assessment mirrored the iACT group. Using a crossover design, the control group started the intervention approximately 3 months from baseline.

The same outcome variables and outcome measures were assessed as in the previous study (Study 2.2).

Participant satisfaction

Post-intervention participants were assessed with an author-generated questionnaire of 8 items with a four-point Likert scale (from 0 =" completely disagree" to 3 =" strongly agree"). The questionnaire evaluated clarity of objectives, ease of understanding, interest in the intervention, usefulness, needs met, and willingness to recommend to others. We also assessed Intervention Usability and Team Satisfaction using the same type of questionnaire. For Intervention Usability, the items rated website ease of navigation, understanding the content, and communication with the psychotherapist. The Team Satisfaction Questionnaire assessed the quality of support, communication, and frequency of communication with the online psychotherapist.

Table 4. List of modules, content, and timeframe

	ACT process	Topic	Examples of exercises, metaphors.	Assessment
				T1 – baseline intervention & control group
Module 1	Contact with the present moment	Sleeping difficulties	Attending to breathing (Walser & Westrup, 2007) Tug-of-war with a monster (Hayes et al., 1999) Jump (Hayes et al., 1999) Your mind is not your friend (Hayes et al., 1999)	
Module 2	Values	Nausea and fatigue	Bull`s eye exercise (Lundgren et al., 2012), Body scan (Walser & Westrup, 2007)	

Module 3	Defusion	Anxiety & sticky thoughts	Hands as thoughts (Harris, 2014); Pushing away paper exercise (Harris, 2015); Floating leaves on a moving stream (Hayes, 2005)	
Module 4	Values and committed action	Close relationships	Matrix (Polk & Schoendorff, 2014); Mindfulness exercise.	T2 - intervention & control group
Module 5	Acceptance	Body image concerns	Passengers on a bus (Hayes et al., 1999); Chocolate Cake (Hayes et al., 1999); Hand on heart	
Module 6	Self-compassion	Self-compassion	Compassion Mindfulness (Walser & Westrup, 2007)	T3 - intervention & control group
Module 7	Self as context	Sexuality, sexual functioning	Observer Exercise (Hayes et al., 1999)	
Module 8	Recap & committed action	Recap	Expanding circle & Basketball game (Luoma et al., 2007)	T4 – post-intervention & control group
Follow-up 1 + 4 weeks	Intervention group			
Follow-up 2 + 4 weeks	Intervention group			

Statistical analysis plan

Multiple imputations were performed to account for missing data. Five imputed datasets were generated using pretest data as predictors and available data from other time points. A 95% Confidence Interval (CI) was used for the statistical analysis. In our analysis, we report complete case results ($N_{treatment} = 33$ and $N_{control} = 34$) and compare them to the pooled imputed results ($N_{treatment} = 75$ and $N_{control} = 75$ (Appendix 1)

Mixed ANOVA was used to assess the significance of Time x Group interactions for all outcome and process variables. As we expected significant improvements in the experimental group, significance levels were evaluated using one-tailed tests and were interpreted based on the $p < .05$ criterion.

Mediation analyses were performed using the structural equation modelling technique (SEM, Kline, 2011). Based on the recommendations of Goldsmith et al. (2018), we employed a simplex model with lagged b path effects which accounted for contemporaneous covariance paths. This model analyses the effect of the mediator (i.e., psychological flexibility) on the outcome (i.e., QOL, SI, BA, RN, anxiety, and depression) at a later date, while accounting for the simultaneous measurements of variables and therefore can be affected by occasion-specific

errors. Following the guidelines of Hu & Bentler (1999), a model was considered to adequately fit the data if the CFT and TLI presented values close to .95, SRMR presented values close to .08 and RMSEA presented values close to .06. Analyses were run in MPlus, using the Full Information Maximum Likelihood estimator (FIML). Indirect effects were estimated through the bootstrapping procedure with 1000 samples.

2.4.3. Results

The participants` selection process is described in Figure 1. Drop-out analysis revealed no significant differences in outcome variables at baseline or Time x Group between measurements.

Intervention feasibility, usage, and satisfaction

The median duration of completion of the intervention was 9,8 weeks.

Clinicians spent a median time of 245 minutes (IQR, 180 – 480 minutes) guiding participants, dedicating 23,3 minutes/participant/week (IQR 10 – 30 minutes). The program's usability was high (SUS mean score = 95; IQR 87,5 – 100), the therapeutic alliance was rated favorably (TSS mean score = 13,5; IQR 12,4 – 16) as was the participants' satisfaction with the intervention with a mean of 14,2 (IQR 11,3 – 16).

Intervention outcomes

QOL

The multivariate test indicated non-significant Time x Group differences between the experimental and control group in terms of QoL scores ($F (3, 61) = 2.25$, $p = .092$, partial $\eta^2 = .10$). However, when analyzing the imputed data, the multivariate test indicated significant differences for each of the five iterations (F's $(3, 143) > 4.74$, p's $< .003$, partial η^2 between .09 and .14). The within-subject effect of Time x Group was significant in all iterations (F's > 8.00, p's $\leq .001$, partial η^2 between .52 and .64). Pairwise comparisons of the pooled data indicated that the ACT group displayed better QoL at T3 ($Md = 15.56$, $S.E. = 4.14$, $p < .001$, $CI = [8.76, 22.36]$, $d = .61$) and T4 ($Md = 6.67$, $(S.E.) = 2.97$, $p = .041$, $CI = [1.79, 11.55]$, $d = .37$). At follow-up, significant differences across time points in the original data ($F (3, 18) = 3.90$, $p = .026$, partial $\eta^2 = .39$) and all five imputations were detected. Pairwise comparisons indicated a significant increase in QoL from the study endpoint to the first follow-up

assessment (Md = 8.38, S.E. = 2.63, p = .028, 95%CI [.69, 16.07], d = .57). The imputed data supported this result and suggested significant additional increases between T1 and T5 (Md = 8.04, S.E. = 1.53, p < .001, CI = [5.51, 10.54], d = .74) and T6 (Md = 5.84, S.E. = 1.59, p < .001, CI = [3.11, 8.46], d = .55), and a significant decrease from the T5 to T6 (Md = 2.20, S.E. =.94, p = .024, CI = [.65, 3.74], d = .23).

Symptom Interference (SI)

The multivariate test indicated a significant Time x Group difference between the two groups for SI (F (3, 61) = 4.00, p = .012, partial η^2 = .16). Pairwise comparisons revealed significant differences between groups only at the T4 (Md = 10.51, S.E. = 3.47, p = .004, CI = [3.58, 17.50], d = .58). The imputed datasets concurred (Md = 7.88, S.E. = 2.71, p = .008, CI = [3.43, 12.34], d = .48). Both analyses suggest the ACT group experienced significantly lower SI than the WLCG at intervention endpoint. Within-subject pairwise comparisons indicated no significant differences across time points for the WLCG. Significant differences were observed between the final scores and those registered at previous time points for the experimental group (T1-T4: Md = 11.16, S.E. = 2.16, p < .001, CI = [5.29, 17.02], d = .78, T2-T4: Md = 6.78, S.E. = 2.45, p = .044, CI = [.12, 13.44], d = .45, T3-T4: Md = 5.13, S.E. = 1.87, p = .048, CI = [.03, 10.22], d = .38). In the imputed dataset, significant differences were observed in the WLCG between T1 and T3 (Md = -5.34, S.E. = 2.04, p = .018, CI = [-8.69, -1.98], d = .35), between T3 and T4 (Md = -4.58, S.E. = 2.01, p = .031, CI = [-7.88, -1.28], d = .27) and in the experimental group between all-time points, except for T2-T3.

For the follow-up analysis, the multivariate test indicated significant differences across time points in the original data (F (3, 17) = 7.38, p = .002, partial η^2 = .57) and all five imputations. Pairwise comparisons indicated a significant decrease in SI between baseline and both follow-ups (Md = 11.50, S.E. = 2.74, p = .003, CI = [3.47, 19.53], d = .80 and respectively Md = 12.15, S.E. = 2.47, p = .001, CI = [4.91, 19.40], d = .75). The analysis of the imputed data supported this result and suggested a significant decrease between the study endpoint and the two follow-up assessments (Md = 5.33, S.E. = 2.31, p = .042, CI = [1.52, 9.13], d = .28 and respectively Md = 6.24, S.E. = 2.43, p = .024, CI = [2.24, 10.24], d = .37).

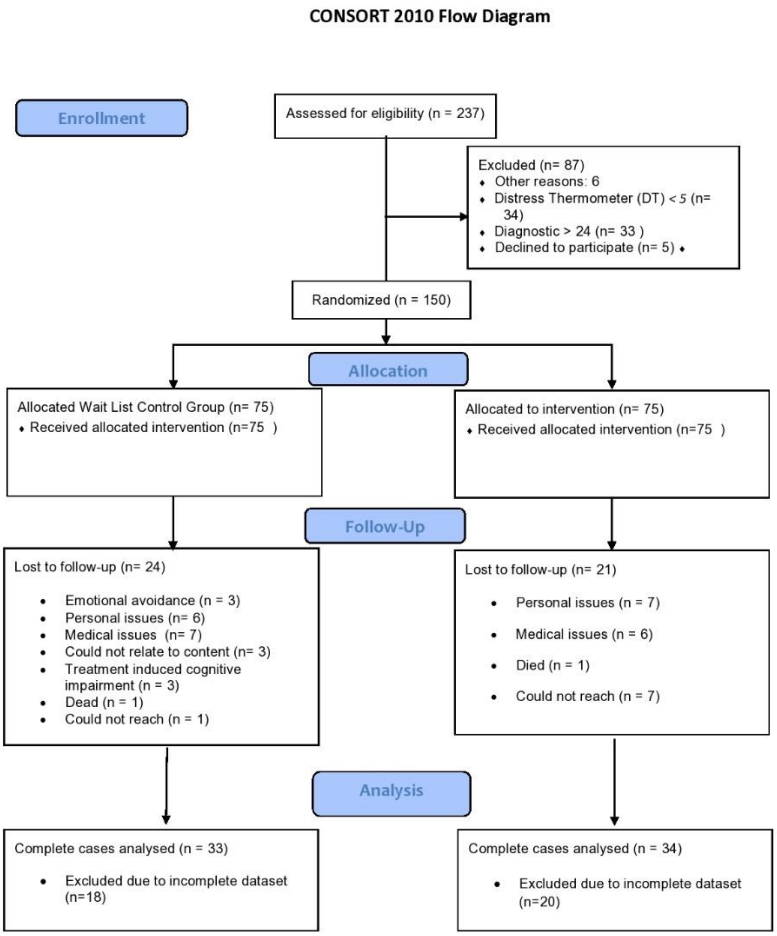

Figure 1

Behavioral Activation (BA)

The multivariate test indicated non-significant Time x Group differences between the experimental and WLCG for BA (F (3, 60) = 1.65, p = .187, partial η^2 = .08). However, when analyzing the imputed data, the multivariate test indicated significant differences for all five imputations (F's (3, 143) > 3.134, p's < .028, partial η^2 between .06 and .14). Pairwise comparisons of the pooled data indicated that the ACT group displayed more BA at T3 (Md = 13.36, S.E. =6.51, p = .039, CI = [2.65, 24.07], d = .35). In the experimental group, significant decreases in BA were seen between T1 and T2 (Md = 5.34, S.E. = 2.12, p = .009, CI = [1.85, 8.83], d = .28), and between T1 and T4 (Md = 7.88, S.E. = 3.12, p = .014, CI = [2.75, 13.01], d = .33). In the WLCG, significant decreases in BA were observed between T3 and all other time points (T3-T1: Md = -14.27, S.E. = 3.95, p = .002, CI = [-20.77, -7.77], d = .52; T3-T2:

Md = -10.91, S.E. = 4.77, p = .047, CI = [-18.76, -3.06], d = .29 and T3-T4: (Md = -11.79, S.E. = 4.91, p = .038, CI = [-19.86, -3.72], d = .30). At follow-up, significant differences were displayed across time points in the original data (F (3, 11) = 4.71, p = .024, partial η^2 = .56) and all imputations. Pairwise comparisons indicated a significant increase in BA from baseline to the T6 (Md = 13.86, S.E. = 4.01, p = .029, CI = [1.16, 26.56], d = .82). Analysis of the imputed data concurred with further significant increases between baseline and the T1 (Md = 14.25, S.E. = 1.77, p < .001, CI = [11.33, 17.16], d = 1.02) and between T4 and both follow-up assessments (Md = 7.56, S.E. = 3.26, p = .035, CI = [2.20, 12.92], d = .31; Md = 8.59, S.E. = 3.38, p = .024, CI = [3.02, 14.15], d = .35).

Reward Noticing (RN)

Non-significant Time x Group differences were observed between the experimental and WLCG for RN (F (3, 63) = 1.73, p = .171, partial η^2 = .08). However, when analyzing the imputed data, significant differences for each of the five imputations (F's (3, 143) > 3.76, p's < .028, partial η^2 between .06 and .14) were detected. Pairwise comparisons of the pooled data indicated that the ACT group displayed more RN at T2 (Md = 1.88, S.E. =.89, p = .037, CI = [.42, 3.34], d = .35) and T3 (Md = 6.01, S.E. = 1.62, p = .001, CI = [3.34, 8.67], d = .61). No significant changes in RN were observed when analyzing the pooled data of the experimental group. However, in the case of the control group, RN was significantly lower at T3 as compared to all other time points (T3-T1: Md = -5.10, S.E. = 1.01, p < .001, CI = [-6.77, -3.44], d = .56; T3-T2: Md = -3.67, S.E. =.95, p = .001, CI = [-5.23, -2.11], d = .35 and T3-T4: (Md = -4.57, S.E. = 1.59, p = .020, CI = [-7.18, -1.96], d = .41).

For the follow-up analysis, the multivariate test indicated non-significant differences across time points in the original data (F (3, 16) = 1.80, p = .188, partial η^2 = .25) and a significant difference in one of the five imputations (F (3, 72) = 4.32, p = .007, partial η^2 = .15). The within-subject effect of time was non-significant in all data sets.

Secondary outcomes

Anxiety and Depression

The multivariate test indicated significant Time x Group differences between the experimental and WLCG for anxiety and depression scores (F (3, 63) = 6.97, p < .001, partial η^2 = .25). The results did not differ between the five imputed data sets. Pairwise comparisons indicated that the groups did not differ at pretest (Md = 2.67, S.E. = 1.53, p = .085, CI = [-.38, 5.72], d = .43).

The only significant difference observed was at T4, the ACT group displaying significantly lower anxiety and depression scores than the control group (Md = 4.25, S.E. = 1.96, p = .034, CI = [.33, 8.17], d = .53). The difference at T4 was significant in four of the five imputed datasets, being the only significant between-group difference across all time points (Md_{pooled} = 3.49, $S.E._{pooled}$ = 1.66, CI = [.75, 6.22], p = .047, d = .35). For the treatment group, significant decreases in depression and anxiety were observed between the T1, T2 (Md = 4.85, S.E. = .88, p < .001, CI = [2.46, 7.24], d = .49), T3 (Md = 4.97, S.E. = .99, p < .001, CI = [2.29, 7.65], d = .43) and T4 (Md = 7.39, S.E. = 1.07, p < .001, CI = [4.49, 10.30], d = .62) and between T2 and T4 (Md = 2.25, S.E. = .87, p = .008, CI = [.18, 4.91], d = .20). The imputed datasets confirmed these differences, suggesting significant differences not only between the first time point and all the others (T1-T2: Md = 3.22, S.E. = .92, p < .001, CI = [1.70, 4.47], d = .41; T1-T3: Md = 3.20, S.E. = .96, p < .001, CI = [1.62, 4.77], d = .43, T1-T4: Md = 5.16, S.E. = 1.12, p < .001, CI = [3.31, 7.00], d = .51) but also between the T4 and T2 (T4-T2: Md = -1.94, S.E. = .96, p = .044, CI = [-3.51, -.36]). The WLCG did not show significant differences in depression and anxiety across time points (all p's > .810). Imputed data suggests significant differences between T1, T2 (Md = 3.27, S.E. = .89, p = .001, CI = [1.81, 4.73], d = .46), and T3 (Md = 4.03, S.E. = 1.04, p < .001, CI = [2.31, 5. 47], d = .50) and between T4, T2 (Md = 2.49, S.E. = .97, p = .020, CI = [.89, 4.07], d = .27), and T3 (Md = 3.23, S.E. = 1.43, p = .050, CI = [.89, 5.58], d = .25). For the follow-up analysis, the multivariate test indicated significant differences across time points in the original data (F (3, 18) = 6.98, p = .003, partial η^2 = .54) and all imputations. Pairwise comparisons indicated a significant decrease in anxiety and depression from baseline to T5 and T6 (Md = 7.38, S.E. = 1.63, p = .001, CI = [2.63, 12.14], d = .83 and Md = 7.24, S.E. = 1.76, p = .003, CI = [2.10, 12.38], d = 1.00). Analysis of the imputed data supported this result and indicated no other significant changes.

Psychological Flexibility (PF)

The multivariate test indicated significant Time x Group differences between the experimental and WLCG for PF (F (3, 63) = 7.97, p < .001, partial η^2 = .25). Similar results were obtained for all but one of the five imputed data sets (p = .055, partial η^2 = .02 while other p's < .048, partial η^2 between .02 and .06). The experimental group displayed more PF at T3 (Md = 12.44, S.E. = 4.85, p = .013, CI = [2.75, 22.13], d = .16) and T4 (Md = 14.41, S.E. = 5.20, p = .007, CI = [4.03, 24.79], d = .58). Two of the imputed datasets did not indicate any significant differences, another two revealed significant differences only at T4, and one dataset indicated significant differences at the T2 and T3. The WLCG showed no significant modification of PF

across time points (all p's > .207). When analyzing the pooled results from imputed data, significant differences were observed between the baseline values and those at T3 (Md = 12.98, S.E. = 3.70, p = 002, CI = [6.89, 19.05], d = .44). The experimental group showed increases in PF between baseline, T3 (Md = 12.94, S.E. = 2.46, p < .001, CI = [6.26, 19.61], d = .63) and T4 (Md = 15.94, S.E. = 3.07, p < .001, CI = [7.60, 24.28], d = .81), T2, T3 (Md = 6.91, S.E. = 1.96, p = .005, CI = [1.60, 12.22], d = .37) and T4 (Md = 9.91, S.E. = 2.43, p = .001, CI = [3.32, 16.50], d = .51). Analysis of the pooled imputed data indicated significant increases in PF between all-time points. For the follow-up analysis, the multivariate test indicated significant differences across time points in the original data (F (3, 17) = 6.78, p = .003, partial η^2 = .55) and all five imputations. Pairwise comparisons indicated a significant increase in PF from baseline to T5 (Md = 19.30, S.E. = 4.17, p = .001, CI = [7.06, 31.54], d = .91). The imputed data supported this result and indicated significant increases between baseline and T6 (Md = 19.39, S.E. = 2.49, p < .001, CI = [15.30, 23.49], d = 1.13) and between T4 and T5 (Md = 9.03, S.E. = 3.31, p = .015, CI = [3.59, 14.47], d = .31).

Mediation analysis

To analyze the role of PF as a mechanism of change, it was introduced in models with the previously mentioned outcomes as criteria at the four time points and the group as a predictor. None of the tested models presented an acceptable fit: $\chi^2(20) = 114.88$, p < .001, RMSEA = .18 90%CI[.15, .21], CFI = .76, TLI = .57, SRMR = .24 for QoL; $\chi^2(20) = 76.83$, p < .001, RMSEA = .14 90%CI[.11, .17], CFI = .87, TLI = .77, SRMR = .16 for SI, $\chi^2(20) = 117.43$, p < .001, RMSEA = .18 90%CI[.15, .22], CFI = .82, TLI = .67, SRMR = .17 for BA, $\chi^2(20) = 82.35$, p < .001, RMSEA = .15 90%CI[.11, .18], CFI = .89, TLI = .80, SRMR = .09 for anxiety and depression, and RN the model did not converge. Alternative models (e.g., contemporary paths or latent growth models) did not adequately fit the data.

2.4.4. Discussion

To our knowledge, this is the first RCT to evaluate the effects of an iACT intervention on psychosocial outcomes for BCPs. The online delivery of an ACT intervention was feasible and acceptable in the present sample of BCPs, with high uptake, adherence, participant satisfaction and low attrition. The original data showed significant improvements with a large effect size within for the ACT group for SI, anxiety and depression symptoms and PF, with

results further improving to 1- and 2- month follow-up time points with the same large effect size. This effect was also observed in the imputed data, which adds to its robustness. The intervention also had a medium to a large positive impact on QoL, BA and RN, but only when analysing the imputed data. Both groups saw an increase in QoL and RN throughout the time points, whereas BA improvement had a zig-zag pattern. The changes were maintained at follow-up, in both data sets, with large effects, except for RN, where no increase was observed past the intervention's end.

PF was explored as a mediator, as suggested by previous empirical studies (Hayes et al., 2022). The results did not support our hypothesis regarding the mediating role of PF. In the face of overwhelming opposite findings in the literature, we assume that either the study was underpowered, having a sample size too small to detect a small mediation effect or that the applied instrument lacked validity. Arch et al., (2022) reviewed the literature and concluded that the AAQ-II performs more as a measure of distress/neuroticism than of experiential avoidance, and therefore it more likely measures outcomes and symptoms rather than ACT processes. Regrettably, we had chosen it nonetheless because it was context-specific, assuming that it would perform better in our population as recommended by Ong et al., (2019). Therefore, we cannot clearly state that Oncovox positively influences PF, even if both datasets support this claim. We tentatively postulate that Oncovox strongly improves distress and experiential avoidance, a claim supported by participants' feedback.

Though originally well-powered, the drop-out rate rendered it underpowered, requiring a robust intention-to-treat analysis. Imputed data analysis should be interpreted cautiously, as it might be subject to bias and reduced observed efficiency (Manly & Wells, 2014). Second, while the study aimed to recruit a diverse group of breast cancer patients, married, younger, highly educated with high incomes patients were overrepresented. Thirdly, as the WLCG was provided with the treatment after the intervention period, it cannot be determined whether

follow-up improvements result from the intervention. Also, we used an inactive WLCG, leaving important non-specific treatment ingredients (i.e., expectation) uncontrolled (Leslie et al., 2022).

2.4.5. Conclusion

Oncovox as an iACT is acceptable and feasible, with good participant satisfaction. It can strongly improve symptom interference, anxiety and depression symptoms and psychological flexibility, with results further improving to 1- and 2- month follow-up time points with the same large effect size. The intervention also had a medium to a large positive impact on QoL, behavioural activation and reward noticing compared to the control group, but only when analysing the imputed data. These results add new insight to the scarce evidence of the effectiveness and acceptability of iACT interventions for BCPs.

Oncovox has the potential to reach a large group of BCPs and could adequately serve as an appropriate intervention into stepped care for the Romanian population of BCPs, assisting them in living a richer, more meaningful life during their cancer journey.

2.5. Study 4: Type of Surgery Moderates the Effects of a Web-based Acceptance and Commitment Therapy Intervention on Symptom Interference and Anxiety and Depression Symptoms for Breast Cancer Patients

2.5.1. Aims

Building on the discussion from the previous study, this study aims to explore which moderators may influence these outcomes to inform future allocation of the intervention.

2.5.2. Methods

The data analysed in this study were collected as part of the previously described RCT (Study 3). Demographic variables that were assessed as possible moderators were age, maternity status, educational level, employment status, income level. Disease-related

information – the information assessed as possible moderators were time since diagnosis, type of surgery, cancer stage, current treatment, menopausal issues, fertility issues, presence/absence of comorbidities.

Mixed ANOVA was used to assess the significance of Time x Group interactions for all outcome and process variables. As we expected significant improvements in the experimental group, significance levels were evaluated using one-tailed tests and were interpreted based on the $p < .05$ criterion.

2.5.3. Results

The only interaction effect observed was Type of surgery.

Symptom interference

The multivariate test indicated significant Time x Group x Surgery type differences between the experimental and control group in terms of symptom interference ($F(12, 137.87) = 2.14$, $p = .018$, *partial* $\eta^2 = .14$). The within subject effect of Time x Group x Surgery Type was significant ($F(12, 162) = 2.27$, $p = .011$, *partial* $\eta^2 = .14$). Significant differences were obtained on two of the five imputed datasets. The only significant difference observed was at the endpoint of the study, the ACT group displaying significantly lower symptom interference than the control group in the case of patients who did not undergo surgery (*Mean difference* = 30.70, *S.E.* = 11.89, $p = .013$, 95%CI[6.87, 54.53]). This difference was significant in both imputed datasets. In these datasets, the experimental group displayed significantly lower scores than the control group at the study endpoint in the case of patients which underwent unilateral mastectomy without reconstruction (*Mean difference* = 11.09, *S.E.* = 3.72, $p = .003$, 95%CI[3.73, 18.44]), and in the case of patients which underwent bilateral mastectomy without reconstruction (*Mean difference* = 18.59, *S.E.* = 8.08, $p = .023$, 95%CI[2.61, 34.57]).

Anxiety and depression

The multivariate test indicated significant Time x Group x Surgery type differences between the experimental and control group in terms of anxiety and depression scores (F(12, 143.16) = 3.06, p = .001, *partial* η^2 = .18). The within subject effect of Time x Group x Surgery Type was significant (F(10.16, 142.24) = 2.91, p = .002, *partial* η^2 = .17). Significant differences were obtained on two of the five imputed datasets. The only significant difference observed was at the endpoint of the study, the ACT group displaying significantly lower anxiety and depression scores than the control group in the case of patients who did not undergo surgery (*Mean difference* = 19.30, *S.E.* = 6.62, p = .005, 95%CI[6.05, 32.55]). This difference was significant in both imputed datasets. In these datasets, the experimental group displayed significantly lower scores than the control group at the study endpoint in the case of patients which underwent unilateral mastectomy without reconstruction (*Mean difference* = 7.56, *S.E.* = 2.33, p = .001, 95%CI[2.96, 12.17]), and in the case of patients which underwent bilateral mastectomy without reconstruction (*Mean difference* = 11.45, *S.E.* = 4.71, p = .016, 95%CI[2.14, 20.76]).

Psychological flexibility

The multivariate test indicated nonsignificant Time x Group x Surgery type in terms of psychological flexibility (F(12, 143.16) = 1.80, p = .054, *partial* η^2 = .12). This was consistent across imputed datasets.

2.5.4. Discussion

Our exploratory, post-hoc analyses revealed that compared to control condition, neither demographic nor disease related factors functioned as moderators of symptom interference, anxiety and depression symptoms, and psychological flexibility respectively over the course of the intervention, apart from type of surgery. Type of surgery is the only moderator that was shown to be relevant in improving symptom interference, anxiety, and depression symptoms, but not psychological flexibility. These findings were maintained in the follow-up analysis and

indicate on the one hand that there are no restrictions on the allocation of the iACT intervention and that it is beneficial to all the subgroups of our population and that on the other hand Oncovox would be especially beneficial to BCPs that underwent a more invasive type of surgery (unilateral or bilateral mastectomy without reconstruction). The moderator analysis was exploratory; therefore, the results need to be interpreted with caution.

2.5.5. Conclusion

Our results show that Oncovox is recommended to any BCP in active treatment withing 24 months of diagnosis, regardless of their sociodemographic and clinical characteristics. This resulted in relevant insights about the future allocation of Oncovox towards BCPs in an institutional setting and highlighted specific patient subgroup for which this intervention could be especially beneficial.

2.6. Study 5: A Qualitative Exploration of Barriers and Facilitators to Adherence to a Web-based Acceptance and Commitment Therapy Intervention for Breast Cancer Patients

2.6.1. Aims

The aim of this study was to perform a qualitative analysis of patients` experience with Oncovox to achieve a deeper insight into the phenomenon of adherence and drop-out.

2.6.2. Methods

We interviewed by phone the 75 participants assigned to the intervention group in Study 3. We defined completers as the participants that finalized at least six modules of the intervention and non-completers as participants that dropped out of the study before completing six modules.

Data analysis

We used conventional qualitative content analysis to analyse the data. Qualitative data was collected through semi-structured interviews consisting of open-ended questions, in which the participants would evaluate (1) their overall experience and interaction of the treatment and their assigned clinician and (2) potential difficulties they encountered with either the content, the site or their assigned clinician, (3) feedback related to the timing of the intervention, (4) adherence and usage patterns, (5) relevance and the observed impact of the intervention. For non-completers the interview especially focused on reasons for dropping out.

Table 5. Adherence to intervention

	Participants in iACT (%)
Module 1	73 (97%)
Module 2	71 (95%)
Module 4	58 (77%)
Module 6	51 (68%)
Module 8	51 (68%)
Follow-up 1	45 (60%)
Follow-up 2	37 (49%)

2.6.3. Results

Characterization of sample

We were able to interview only 67 (89%) participants assigned to the first arm of the treatment. The identified themes of both completers and non-completers are presented below (Table 6 and 7).

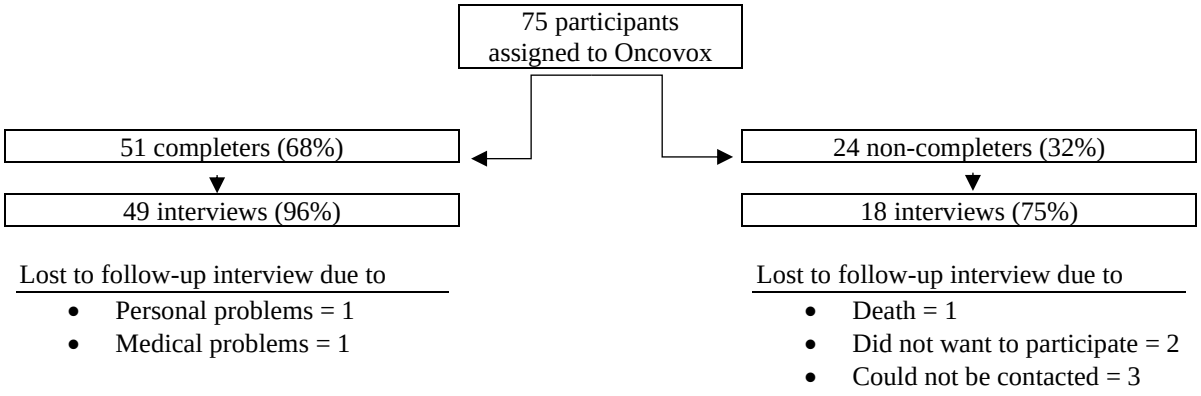

Table 6: Themes and subthemes of completers

Facilitators	Connection	• Feeling seen and understood • Being part of a community
	Experiencing change	• Perspective change on internal experiences • Acceptance of difficult thoughts and feelings • Experiencing reliable change
	Intervention characteristics	• Treatment timing • Online delivery • Flexibility of delivery
Barriers		• Awareness of emotions • Courage in the face of difficult emotions • Cultivating patience in imagery/mindfulness exercises

Table 7: Themes and subthemes of non-completers

Facilitators	• Online delivery • Flexibility of delivery • Symptom improvement	
Barriers	Practical barriers	• Illness related barriers. • Computer/technology barriers • Schedule conflicts
	Emotional barriers	• Uncomfortable emotional experiences - Triggering content • Mismatched with current cognitive resources. • Not enough support from therapist to current needs • Irrelevant to current experience

2.6.4. Discussion

The emerging themes were quite different for completers compared to non-completers, and a valuable finding is the division amongst non-completers between participants that valued the intervention, drew some minimal benefit from it but dropped out due to practical reasons and non-completers for which the intervention was ill-matched. Patients affected by treatment induced cognitive impairment (or "chemo brain") are a small but relevant subgroup for which the intervention was not useful or valuable. Fortunately, the intervention was not reported to have been harmful by any of the participants. In line with previous findings in the literature (Beatty et al., 2017) completers in our study reported a series of facilitating factors for their adherence to the intervention: sense of connection to the other participants and to the research team, feeling seen and understood, experiencing change. The barriers that completers reported

were related mainly to emotional avoidance and lack of mindfulness skills related to specific practices. A series of barriers were also reported by the non-completers: illness related barriers (n=6), personal barriers (n=6), emotional barriers (n=6) and computer related barriers (n=2), with some overlap between them. This study shone light on a subgroup of participants of 8% of the general sample for which Oncovox was unsuitable. The intervention was too emotionally triggering or exceeding their current cognitive resources and as a result they chose to drop-out. This study is limited by the retrospective nature of the interview.

2.6.5. Conclusion

This is the first study to qualitatively explore facilitators and barriers of an iACT for BCP in active treatment for both completers and non-completers. The interviews with completers highlighted a series of facilitating factor for adherence: sense of connection to the other participants and to the research team, feeling seen and understood, experiencing change. Barriers for this group were difficulty in being aware and contacting their own emotions and cultivating patience during mindfulness and imagery exercises. This study also establishes that when we conceptualise dropout in terms of the number of sessions completed there are two distinct groups of participants: drop out due to due to practical barriers, where the intervention was deprioritised and drop-out due to intervention content.

2.7. Study 6: Pandemic and resilience: A Qualitative Analysis of the Emotional Impact of the COVID-19 Pandemic on Breast Cancer Patients in Active Treatment [4]

2.7.1. Aims

The COVID-19 pandemic has had an unequivocal disruptive impact on all walks of life. Cancer care and the patients involved have been especially affected due to disruptions in

[4] This study was published as Nicolescu, S., & Băban, A. (2021). Pandemic and resilience: A qualitative analysis of the emotional impact of the COVID-19 pandemic on breast cancer patients in active treatment. Cognition, Brain, Behavior, 25(3), 243-259. DOI:10.24193/cbb.2021.25.13

treatment scheduling and enhanced vulnerability to COVID-19 infection. The present study undertook an exploratory qualitative analysis to investigate the emotional impact the COVID-19 pandemic has had on breast cancer patients undergoing active treatment.

2.7.2. Methods

Ten breast cancer patients were interviewed concerning their illness and pandemic perception. The patients were all women diagnosed with breast cancer in the past 36 months (Mean=12,3 months, SD = 28,25; with a mean age of 44 years (range 40 – 49, SD = 9,6), all in active treatment. To supplement their perspective, we also interviewed six psycho-oncologists on the emotional impact the pandemic has had on the patients they provide care to. The data collected during the interviews was inductively analysed using thematic analysis.

2.7.3. Results

The perceived emotional impact of the Covid-19 pandemic was regarded as being complex. Table 26 and 27 display the emerging themes and their subthemes of patients` experience and psycho-oncologists` observation of patients` experience.

Table 8: Themes and subthemes of participants' experience

Emotional changes	• Increased anxiety about delayed treatment and communication difficulties with the medical team • Enhanced uncertainty over illness progression • Loneliness due to social isolation • Perceived enhanced health vulnerability in the case of Covid-19 infection
Adapting	• Prioritizing cancer treatment • Constant readjustment to changing emotions. • Flexibility and resilience
Resulting behavioural changes	• Enhanced health precautions • Appling more problem-solving skills • Social support • Developing new habits

Table 9: Themes and subthemes of psycho-oncologists' experience

Increased anxiety	Related to changes and delays in treatment. Uncertainty over illness progression Perceived enhanced health vulnerability in the case Covid-19 infection
Enhanced vulnerability	Newly diagnosed patients

	Patients that lack social support
Resilience retention	Flexibility with difficult situations Acceptance of distress and uncertainty Focusing on concrete actions
Social support	

2.7.4. Discussion

Cancer patients have experienced increased emotional distress symptoms during the COVID-19 pandemic, while prioritising the cancer treatment over the threat of infection. Those that had developed emotional regulation skills prior to the pandemic made good use of them, providing proofs of emotional resilience. More vulnerable were establised, such as newly diagnosed cancer patients and those lacking social support.

2.7.5. Conclusion

Our study provides a useful insight into the emotional experience of the assessed oncology patients during the Covid-19 pandemic, and useful insight into the mechanisms that build resilience and flexibility for this population.

CHAPTER 3: GENERAL DISCUSSSION AND CONCLUSION

3.1. Main findings

Study 1 indicates mixed support for online interventions to improve psychological distress and QOL in cancer patients' samples. Specific persuasive technology elements such as proving support, reminders, integrated chat system, and tailoring the content for specific subgroups promote adherence, usability and ultimately efficacy.

Participants (n=15) that tested the prototype of Oncovox in Study 2.1 reported high acceptability of the internet delivery format, good engagement with the intervention, and user-friendly content. In Study 2.2 where we developed the full 8 module intervention, the data showed significant improvements with for symptom interference in both cohorts (2 x n=25). QOL, behavioural activation and anxiety and depression symptoms saw no improvements in either cohort, and the intervention effect was consistently small for behavioural activation, small to medium for QOL and medium to large for anxiety and depression. Overall, both versions of the intervention elicited good participants` feedback, good satisfaction, and an increase in adherence after implementing suggested feedback.

Study 3 examined the efficacy of Oncovox. To our knowledge, this is the first RCT to successfully evaluate the effects of an iACT intervention on psychosocial outcomes for BCPs. The online delivery of an ACT intervention was feasible and acceptable in the present sample of BCPs, with high uptake, adherence, participant satisfaction. The original data showed significant improvements with a large effect size for the ACT group for symptom interference, anxiety and depression symptoms and psychological flexibility, with results further improving to 1- and 2- month follow-up time points. This effect was also observed in the imputed data, which adds to its robustness. The intervention also had a medium to a large positive impact on QoL, behavioural activation and reward noticing, but only when analysing the imputed data.

Study 4 provided insight into intervention moderators. Type of surgery is the only moderator that was shown to be relevant in improving symptom interference, anxiety, and depression symptoms, but not psychological flexibility. These findings were maintained in the follow-up analysis and indicate that there are no restrictions on the allocation of the iACT intervention and that it is beneficial to all the subgroups of our population, especially to those that had underwent a more invasive type of surgery.

Study 5 showed that the completers experiences is quite different than of non-completers. A valuable finding is the division of non-completers between those that valued the intervention, drew some minimal benefit from it but dropped out due to practical reasons and non-completers for which the intervention was ill-matched. Patients affected by treatment induced cognitive impairment (or "chemo brain") are a small but relevant subgroup for which the intervention was not useful or valuable. Fortunately, the intervention was not reported to have been harmful by any of the participants.

Our analysis in study 6 provided a useful insight into the emotional experience of the assessed oncology patients during the Covid-19 pandemic, and useful insight into the mechanisms that build resilience and flexibility for this population.

3.2. Implications for design of iACT interventions for BCPs

The literature comprises of substantial heterogeneity of research design, analytic strategy, comparator groups, methodological quality, sample sizes and outcome measures utilized, and thus it is truly challenging to evaluate efficacy and formulate specific recommendations. Multicomponent interventions are advised, such as combining content with a chat. A range of web-based components may be necessary to meet individual needs including the direct interactivity with health-care professionals (Fridriksdottir, 2018). On the other hand, including too many components bears the risk of diluting the intervention or over-burdening participants. Their time, energy and willingness are limited, and must be used sparingly.

Our studies confirm the importance of aligning the provided interventions to patients' specific health and emotional status. The development of online psychotherapy interventions should be tailored to the stage of the cancer trajectory the participant is in as it enables addressing specific needs (Corbett et al., 2018; Atema et al., 2017). As previously reported in the literature (Leslie et al., 2022), it has also been our experience that tailoring the content to a specific group, having a multi-component intervention, and offering guidance of the intervention`s content as well as personalized support, feedback and e-messages led to participants` better engagement with the intervention. These intervention features are trans-paradigmatic, transdiagnostic and foster the implementation of an evidence-based intervention such as iACT. We advise that any novel online intervention be thoroughly and repeatedly tested in several versions on small groups of participants. The advantage of the online medium is that most interventions are easily tweaked and modified, and that rapid testing is more convenient than with face-to-face protocols.

3.3. Implementation of web-based interventions in the cancer setting and future dissemination

Oncovox has the potential to reach a large group of BCPs and we believe that it would adequately serve as a relevant step in stepped care for Romanian BCPs in any in- or out-patient cancer centres in Romania. Patients could then be allocated to the intervention, or they could be referred to a psycho-oncologist. Psycho-oncologists could also use Oncovox as an aid in their treatment, especially with patients that they do not see regularly. Oncovox does not substitute a clinical evaluation or a psychiatric consultation but could provide low tier support and aid. It is now our aim to further disseminate Oncovox nationally, to as many BCPs in active treatment. Starting summer 2023, the intervention will be available via an NGO to all those interested. The results of these studies have provided sufficient evidence for this next step and for private companies and individuals to sponsor this project.

3.4. Future research directions

Future research is still needed to understand the participants and treatment-related factors associated with treatment efficacy to support the generalisability of the findings and guide efforts to further improve treatment outcomes. Such research could compare this intervention to more robust and active control groups and disorder-specific interventions and could examine the generalisability of findings to different settings and broader groups of people with different chronic health conditions. Another interesting avenue would be adapting the existing intervention for cancer survivors no longer in active treatment or for patients diagnosed with other types of cancer and for partners and family members of CPs. Another future development for Oncovox could be offering participants the opportunity to customise the intervention to better meet their needs. This is a technical feature also recommended in the literature that can be easily built into the intervention platform and thus represents a simple, cost-effective way to maybe increase the intervention engagement (Leslie et al., 2022).

As we previously stressed, it paramount that the content and the timing of interventions are appropriate to the idiosyncratic needs of the patients and that we submit our results to idiographic research – the intensive study of the individual organism. Notwithstanding the value of group-based studies and RCT's, it is believed that group studies should be supplemented with a detailed focus on the individual, to contribute more knowledge, and to contribute different knowledge (Trompetter, 2014). An important goal for psychosocial research in the cancer setting should be to bridge the gap from average scientific outcomes to more adequate treatment of individual CPs who need help in clinical practice. Idiographic methods need special contemporary emphasis, because traditional methodological and statistical approaches to processes of change are based on mathematical assumptions that cannot be met and thus limit progress in this area (Hayes et al., 2022).

3.5. Conclusion

This thesis describes the first adaptation of ACT intervention for BCPs to a web-based format. In this presentation, iACT is an acceptable and feasible intervention for BCPs in active treatment diagnosed within the past 24 months. Moreover, Oncovox, can strongly improve symptom interference, anxiety and depression symptoms and psychological flexibility. The intervention also improves QoL, behavioural activation and reward noticing. Oncovox is safe to use and can be recommended to any BCP in active treatment, regardless of their sociodemographic and clinical characteristics, especially if they have had a more aggressive type of surgery.

Dropout is a nuanced experience. Participants either valued the intervention, drew some minimal benefit from it but dropped out due to practical reasons or they were not satisfied with the intervention. Patients affected by treatment induced cognitive impairment (or "chemo brain") are a small but relevant subgroup for which the intervention was not useful or valuable. Fortunately, the intervention was not reported to have been harmful by any of the participants.

During the development of Oncovox, we have learned valuable lessons that apply to the process of developing an online intervention, such as carefully tailoring the intervention for the intended participants, and not overreaching in that goal. We advise that any novel online intervention be thoroughly and repeatedly tested in several versions on small groups of participants, to confirm that it`s content and scope fits the patients` needs and expectations.

These results add new insight to the scarce evidence of the effectiveness and acceptability of an iACT interventions for breast cancer patients. Oncovox has the potential to reach a large group of breast cancer patients and it is believed that it could adequately serve as a relevant step in stepped care for the Romanian population of breast cancer patients, assisting them in living a richer, more meaningful life in the mist of their cancer journey.

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