Design and evaluation of a digital health intervention with proactive follow-up by nurses to improve healthcare and outcomes for patients with breast cancer in Mexico: protocol for a randomised clinical trial

Saúl Eduardo Contreras Sánchez,1 Svetlana V Doubova1, Rocio Grajales Álvarez,2 Abdel Krim Dip Borunda,2 Wendy Jazmin Martinez Pineda,3 Jose Gustavo Nuñez Cerrillo,4 Fernando Silva Bravo,4 Rita Zalapa Velázquez,4 Marcos Gutiérrez de la Barrera,5 Hannah H Leslie6

ABSTRACT

Introduction Nearly 30 000 Mexican women develop breast cancer annually, frequently presenting unmet supportive care needs. In high-income countries, incorporating electronic patient-reported outcomes (ePROs) into cancer care has demonstrated potential for increasing patient-centred care and reducing unmet needs. No such ePRO interventions have been implemented in Mexico. This paper presents the study protocol for designing and evaluating an ePRO digital health application combined with proactive follow-up by nurses.

Methods and analysis We designed a two-component intervention for women receiving breast cancer treatment: a responsive web application for monitoring ePRos and clinical algorithms guiding proactive follow-up by nurses. We will conduct a pilot test of the intervention with 50 patients with breast cancer for 6 months, followed by a parallel arm randomised controlled trial assigning 205 patients each to intervention and control in one of Mexico’s largest public oncology hospitals. The intervention will be provided for 6 months, with additional 3 months of post-intervention observation. The control group will receive usual healthcare and a list of breast cancer information sources. Women diagnosed with stages I, II or III breast cancer who initiate chemotherapy and/or radiotherapy will be invited to participate. The primary study outcome will be supportive care needs; secondary outcomes include global quality of life and breast symptoms. Information on the outcomes will be obtained through web-based self-administered questionnaires collected at baseline, 1, 3, 6 and 9 months.

Ethics and dissemination The National Research and Ethics Committees of the Mexican Institute of Social Security approved the study (R-2021-785-059). Participants will sign an informed consent form prior to their inclusion. Findings will be disseminated through a policy brief to the local authorities, a webinar for patients, publications in peer-reviewed journals and presentations at national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The intervention focuses on early chemotherapy and radiotherapy, a critical window in which patients with breast cancer face the most important supportive care needs.
⇒ The electronic patient-reported outcome (ePRO) intervention and proactive care model were developed through a multistage design and validation process with patient input and an expert group of advisors; the pilot test will enable the assessment of usability of the web-based ePRO application and inform necessary adjustments.
⇒ The limited working hours of the study nurses could affect ePRO application use by patients and therefore the effectiveness of the intervention.
⇒ The intervention delivery and assessment will be conducted separately from Mexican Institute of Social Security routine care and health information systems, limiting consideration of implementation requirements.
⇒ Individuals of lower socioeconomic status without smartphones or internet access will not benefit from the intervention.

INTRODUCTION

Breast cancer is the leading cause of cancer morbidity and mortality in Mexico, with nearly 30 000 incident cases and 8000 deaths in 2020.1 Age-standardised mortality from breast cancer has doubled since 2000 and...
continues to increase annually. Patients with cancer who receive healthcare in public hospitals report multiple unmet supportive care needs and deficiencies in the quality of their care: over half report receiving incomplete information, preventing their participation in decision-making and 7 in 10 receive care they consider inadequate to address their physical and emotional needs. Unmet supportive care needs negatively affect patients’ quality of life and are associated with a higher probability of using emergency services and unscheduled hospitalisations.

Patient-centred care is intended to meet the needs, expectations and preferences of patients. To be patient-centred, healthcare providers must be aware of and proactively address patients needs as they arise; therefore, design and evaluation of care models should be informed by assessing patient-reported outcome (PRO) measures. However, previous studies have found that physicians frequently underestimate the severity of patients’ symptoms during cancer treatment, causing unnecessary patient suffering, excess use of emergency services and hospitalisations. Orienting cancer care delivery around PROs has the potential to better address patients’ needs and to reduce the use of emergency services and avoidable hospitalisations, making care more efficient in resource-constrained settings. In Mexico, research has demonstrated that those receiving patient-centred care report notably better health outcomes, but that the major health systems have not integrated PROs within clinical care. Locally validated models focused on PROs are currently lacking.

Digital health information and communication technologies have emerged as a flexible and scalable approach to increasing patient-centred care. When deployed correctly, digital interventions can reduce patient travel time, facilitate access to clinical information and remote monitoring, improve communication between patients and health personnel to detect and address the treatment side effects in a timely manner and promote active participation of patients in their self-care. Digital interventions for patients with cancer have included symptom monitoring, self-care support and digital communication with providers and other patients. In high-income countries, these interventions have demonstrated high patient acceptance and adherence, as well as positive effects on PROs including symptom management.

Research on the design and implementation of digital interventions in Mexico is limited and has not addressed cancer care. It is not yet known whether incorporating PROs within cancer treatment, using digital interventions to support PRO reporting and using clinical care guidelines to respond to patient-reported needs may be feasible and effective within public oncology services in Mexico.

The objectives of this paper are to describe: (1) the design of a two-component intervention for monitoring electronic patient-reported outcomes (ePROs) among patients with breast cancer using a responsive digital application and proactive follow-up by nurses, (2) intervention pilot testing and (3) an individual randomised clinical trial to assess usability and effectiveness of the intervention.

**METHODS AND ANALYSIS**

The study protocol development was guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guideline and the SPIRIT-PRO extension.

**Study setting**

The study will be conducted in one of the largest public oncology hospitals in Mexico, located in Mexico city and operated by the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social (IMSS)). This hospital provides treatment to ~190,000 patients with cancer annually, including ~2000 new breast cancer cases. General and clinical patient data are collected in an electronic health record primarily for aggregate reporting; standard care does not include collection of PROs.

**Patient and public involvement**

Patient involvement in the development of the ePRO application and in debriefing following the pilot test was prioritised to ensure that the content and measurement tools are clear and useful to the patient population. Furthermore, patients with breast cancer will be invited to a webinar about the study findings to engage them in disseminating the study results. However, patient participation in design and conduct of the trial is not typically permitted by the IMSS National Research and Ethics Committees.

**Study population and eligibility criteria**

The study will include women between 20 and 75 years, diagnosed with breast cancer, who have just started or will start neoadjuvant or adjuvant treatment with chemotherapy or radiotherapy within 2 weeks before or after enrolment; who have access to the internet in mobile phone, computer or tablet; and who provide written informed consent (see online supplemental material 1: Consent form). The study will exclude illiterate women and those, who at the time of enrolment, have stage IV breast cancer, blindness or low vision not corrected with glasses, cognitive disability (e.g., Alzheimer’s disease, other dementias or other mental illness with intellectual disability) or severe depression (≥12 points on the Hospital Anxiety and Depression Scale).

**Intervention design**

We designed an ePRO application to capture patient supportive care needs and a clinical care model to proactively meet such needs. We were guided by the Patient Engagement Framework proposed by the National eHealth Collaborative of the USA and focused on informing, involving, empowering, accompanying and supporting patients with cancer through electronic applications. The intervention design also followed Jensen et al’s recommendations for successful monitoring of
patients with cancer’s ePROs and the ePRO monitoring workflow proposed by Basch et al. As shown in figure 1, we adapted this workflow to the resources and processes within IMSS oncology services.

Based on these recommendations, we defined our ePRO intervention as a weekly register of patients with breast cancer’s symptoms and supportive care needs combined with proactive follow-up by nurses guided by predefined clinical algorithms and a weekly cell-phone message providing an educational video from a recognised cancer association or health institution. The study ePRO application uses a responsive web application design emphasising easy-to-use electronic records with a clear interface, clinically relevant health outcomes and automated communication, including reminders to patients to record data and alerts to health professionals regarding moderate-to-severe or worsening symptoms.

**Intervention development**

To develop the intervention content, the lead researcher (SECS) reviewed the available institutional and international evidence-based clinical guidelines for patients with breast cancer’s diagnosis and treatment and identified 20 common symptoms affecting breast cancer women during neoadjuvant and adjuvant chemo and radiotherapy and requiring supportive care from health professionals. These symptoms included (1) pain, (2) fatigue, (3) nausea and/or vomiting, (4) constipation, (5) diarrhoea, (6) anorexia, (7) dyspnoea, (8) insomnia, (9) oral mucositis, (10) pruritus, (11) acute radiodermatitis, (12) palmar-plantar erythrodysesthesia, (13) papulopustular rash, (14) lymphoedema, (15) proctitis, (16) peripheral neuropathy, (17) infusion phlebitis, (18) anxiety and depression, (19) changes in sexuality and other symptoms. After that, SECS proposed an initial set of questions for the weekly symptoms register (95 items grouped into 20 symptom-specific sections) and constructed 21 process-of-care algorithms for proactive follow-up of symptoms by nurses (1 general and 20 symptom-specific).

The study algorithms were developed based on the Dennstädt et al method for creating algorithms for clinical decision-making in oncology. This method consists of seven steps: definition of the environment, description of the existing evidence, definition of the decision strategy, selection of decision criteria, creation of the clinical algorithm, validation and optimisation.

Next, a group of experts validated the contents of the weekly symptoms record and study algorithms. This group included three medical oncologists, one radiation oncologist, two oncology nurses, one psychologist and one health services researcher, all with clinical and research experience in breast cancer treatment. The experts rated the relevance and clarity of the items in the weekly symptom reporting and each algorithm content using a Likert-type scale: (1) not relevant, (2) somewhat relevant, (3) relevant and (4) very relevant. In the case when specific content was rated as not relevant or somewhat relevant, the experts were asked to explain the reason for this negative rating and to provide suggestions for improvement. Two rounds of rating of the record and algorithm contents were conducted to obtain their final versions, for which agreement on validity was achieved (Content Validity Index (CVI) ≥ 0.70).

**Figure 1** ePRO monitoring workflow. ePRO, electronic patient-reported outcome; PRO, patient-reported outcome; SMS, short messaging service.

During the validation process, we made 31 changes to the weekly symptoms record (eg, questions rewording, or deletion, adding response options) and 91 changes to the algorithms (eg, reorganisation of processes, adding or modifying general recommendations). The final CVI for algorithm content ranged between 0.92 and 1.00, while the CVI in each symptom-specific section of the weekly record ranged from 0.82 to 1.00.

After the expert group’s validation of the study materials, we conducted two rounds of cognitive interviews, each with nine patients with breast cancer, to assess the clarity, comprehension and relevance of the content of weekly symptoms records perceived by women. The median age of women participating was 47 years in the first round and 46 years in the second round. Half of women had a post-secondary) education, while the remainder had secondary (27.8%) or primary school (22.2%). Based on the women’s feedback, seven images were added to the weekly record, including visual illustration of pain and fatigue severity using a 6-point smiley face scale and clinical pictures to illustrate symptoms such as acute radiodermatitis (redness and swelling in the radiation therapy area). Ten terms were modified using simple wording or defining a specific term to achieve better clarity.

A professional web development service was hired to programme the responsive web application. The application was developed in HTML5 with CSS, Bootstrap, Java and PHP Style Sheets to receive and manage the collected data. It can be accessed from different electronic devices (eg, mobile phones, tablets, desktop computers) regardless of operating system (iOS, Android, Symbian, Windows Phone, etc), running through a URL that does not require downloading. The web application has interfaces for (1) intervention group, (2) control group, (3) study nurses and (4) research team (administrators). The intervention group interface includes a baseline record of socio-demographic and clinical characteristics, weekly reporting of symptoms and supportive care needs, questionnaires to assess study outcomes and access to videos on breast cancer-relevant topics on the websites of recognised cancer associations and health institutions. The control group interface includes only modules for baseline records of socio-demographic and clinical characteristics and the questionnaires to assess study outcomes. Online supplemental material 2 provides screenshots illustrating the ePRO application content.

The model of clinical care was designed to align with the ePRO application. Symptom reporting will be linked to automated alerts to the study nurses via WhatsApp/short messaging service (SMS)/email. Those who report mild symptoms or supportive care needs will receive automated messages via SMS/WhatsApp or email (based on the participant’s preference) with general recommendations on how to reduce the presented symptoms/needs. Those who report moderate or severe symptoms/needs will be contacted by phone by the study nurse, who will guide the participant based on the clinical algorithms. Examples of non-pharmacological recommendations provided by the study nurses are presented in table 1.

Two nurses will be available in the morning shift and one nurse in the evening shift to contact participants from 08:00 to 20:00, from Monday to Friday. Outside these hours, participants will receive only automated messages via SMS, WhatsApp or email (based on the participant preference) with general recommendations. All participants will be informed that if presenting severe symptoms outside these hours or not receiving a response from the study nurse within 30 min after symptom registration, they should go to the emergency room. Study nurses will be supervised by the lead researcher and study oncologist; all breast cancer treatment decisions will continue to be handled by the IMSS oncologist following standard care procedures.

Training of the study nurses
Prior to the study fieldwork, the lead researcher (SECS) will provide a 1-week training to the three study nurses. In addition to the intervention content, the training will include information on study selection criteria, logistics of patient recruitment, informed consent procedures and retention strategies. Training will be based on a study manual finalised during intervention development.

Study outcomes
Primary and secondary outcome variables are presented in table 2.

Study covariates
Participant demographic and clinical characteristics include age, formal educational attainment (primary school or less and secondary school or higher), marital status, number of people who live in the patient’s home, number of people who provide caregiving to the patient, time since cancer diagnosis (in weeks), cancer stage (I, II or III) and type of treatment (chemo, or radiotherapy), local/regional recurrence, chronic diseases prior to cancer diagnosis (eg, diabetes, hypertension).

Pilot test procedures
We will conduct a pilot test of the intervention with 50 patients with breast cancer. We determined the required sample size in consideration of three planned analyses: usability of the ePRO application (primary outcome), preliminary effectiveness in reducing supportive care needs and trial feasibility in preparation for larger studies. Conservatively assuming 10% attrition, the 45 participants provide sufficient sample to yield a 95% CI of width 14% (margin of ±7) on the mHealth Application Usability Questionnaire (MAUQ) score and 90% probability that the CI width will be no larger than 14 in a future study. Based on prior studies among patients with breast cancer providing an average score of 45 (SD=29) on supportive care needs in the health system information domain (4.5), we will have 80% power to detect an improvement of at least 11 points (45 vs 34) between pre-test and post-test on a one-sided paired comparison with...
Table 1  Examples of non-pharmacological recommendations

<table>
<thead>
<tr>
<th>Symptom/supportive care need</th>
<th>Non-pharmacological recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Keep tracking your pain using a diary; do not self-medicate; use thermal compresses on the site of pain; practice relaxation techniques and improve sleep quality</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Postpone non-essential activities; moderate activities that involve high energy use; use assistive devices to perform tiring activities</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>Practice relaxation techniques; avoid large meals and consumption of fatty, fried or very spicy foods; wear loose and comfortable clothing; avoid strong odours</td>
</tr>
<tr>
<td>Constipation</td>
<td>Consume foods high in fibre daily; increase liquid intake; avoid carbonated beverages and chewing gum; perform gentle abdominal massage</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Drink at least one cup of fluid after each bowel movement; do not self-medicate; eat small portions of foods that are easy to digest; avoid eating dairy products, red meat and high-fat foods</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Do not stay awake late; do not use a computer or other electronic devices before going to bed; avoid large meals and drinking coffee or alcohol before bedtime; practice relaxation techniques</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Practice relaxation techniques; lie down with the upper body raised to a 45° angle by raising the bed or using pillows; use home air purifier; check your oxygenation with an oximeter</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>Do not use mouthwashes that contain alcohol; brush teeth gently or use a damp gauze pad or sponge mouth swab instead of a toothbrush; avoid acidic, fried, bitter, spicy, very salty, spicy or hot foods</td>
</tr>
<tr>
<td>Acute radiodermatitis</td>
<td>Wash the skin daily with lukewarm water and neutral soap without fragrance; without scratching; avoid excessive sun exposure; limit activities with sources that generate heat such as cooking, ironing, taking a hot bath or shower; do not use deodorants, perfumes, fragrances and powders</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>Keep the arm with lymphoedema higher than the heart whenever possible; do not sleep on the affected arm; avoid carrying weight greater than 2 kg; obtain massage performed by a trained specialist</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Avoid falls; verify daily the presence of injuries or scratches in the arms, hands, legs and feet; practice relaxation techniques</td>
</tr>
</tbody>
</table>

alpha set to 0.05 and within-person correlation of 0.5. Finally, the pilot study has a sufficient sample to detect study design problems with an expected prevalence of 6% or greater with 95% confidence.65

Participants will be enrolled within 2 weeks of initiating treatment, provided access and training on the ePRO application and followed for 6 weeks. Participants will also receive a voucher for 1-month prepaid data to support application use. In addition to weekly application use and symptom reporting, study measures will be assessed using questionnaires at baseline and after 4 weeks of follow-up. ePRO application use will be passively monitored for the remaining 2 weeks following the end of the prepaid internet support. Participants will continue receiving care from oncologists according to IMSS standards throughout the pilot and following the study close out. In addition, at the end of the pilot test, up to nine participants, each with incomplete and complete weekly ePRO records, will be contacted and invited to participate in semi-structured feedback interviews on their experiences and difficulties with the application and proactive care and suggestions for improvement. We will conduct structured debriefs with study nurses to identify potential changes in application of the clinical algorithms and other study procedures. At least six key stakeholders within IMSS will be contacted to explore acceptability and alignment of the intervention with organisational priorities.

We will conduct descriptive analysis of socio-demographic and clinical characteristics of initial participants and successfully retained participants compared with all patients with breast cancer within the hospital. We will describe ePRO application use and usability based on the 4-week MAUQ scores and will use paired t-tests to compare supportive care needs between baseline and 4-week assessments. We will refine the ePRO and the study procedures based on the pilot results.

Clinical trial
After finalising the pilot test and adjusting the study application, we will conduct an unblinded, parallel-arm, individual randomised controlled clinical trial. This phase 2 clinical trial focuses on exploring the effect of the intervention on outcomes presented in table 2.

Study groups
The intervention group will be given access to the ePRO application and proactive clinical care, including study
Table 2  Study outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement scale</th>
<th>Pilot test assessments timelines</th>
<th>Clinical trial timelines</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary study outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supportive care needs</td>
<td>SCNS Short Form 34, previously validated in Mexico.5 This scale comprises 34 items and assesses 5 domains: (1) psychological needs, (2) health systems and information needs, (3) physical and daily living activities needs, (4) care needs and (5) needs related to sexuality. It uses a 5-point Likert scale to measure if a patient needs support and the extent of such need. Each domain score is standardised and ranges from 0 to 100, with a high score indicating a high need. The study’s primary outcome will focus on health systems and information supportive care needs domain.</td>
<td>Baseline, 4 weeks</td>
<td>Baseline, 1, 3, 6 and 9 months</td>
<td>Patient self-reported questionnaire</td>
</tr>
<tr>
<td><strong>Secondary study outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global quality of life and breast symptoms</td>
<td>EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30,53 This questionnaire comprises 30 items, and it has been validated among Mexican patients with cancer54 and includes five functional scales (physical functioning, role emotional, cognitive and social), three symptom scales (fatigue, pain, nausea/vomiting), a global quality of life scale and six single items (shortness of breath, loss of appetite, insomnia, constipation, diarrhoea and economic difficulties). The complementary breast cancer questionnaire EORTC QLQ-BR2355 will also be used. This questionnaire comprises 23 items, and has been validated among Mexican patients with cancer.54 It includes five symptom scales (body image, sexual functioning, systemic therapy side effects, breast and arm symptoms) and six single items (sexual enjoyment, future perspective and upset by hair loss). For both questionnaires, linear transformation will be applied to standardise raw scores. The standardised scores range from 0 to 100 for each scale, with the higher scores representing a higher quality of life or higher intensity of symptoms.56 57 The study’s secondary outcome will focus on the global quality of life scale as measured by the EORTC QLQ-C30 and breast symptoms as measured by the EORTC QLQ-BR23.</td>
<td>Baseline, 4 weeks</td>
<td>Baseline, 1, 3, 6 and 9 months</td>
<td>Patient self-reported questionnaire</td>
</tr>
<tr>
<td><strong>Other prespecified outcome measures</strong></td>
<td>Number of visits to the emergency room in the previous month.</td>
<td>Baseline, 4 week 4</td>
<td>Baseline, 1, 3, 6 and 9 months</td>
<td>Patient self-reported questionnaire</td>
</tr>
<tr>
<td>Unscheduled hospitalisations</td>
<td>Number of unscheduled hospitalisations in the previous month.</td>
<td>Baseline, 4 week 4</td>
<td>Baseline, 1, 3, 6 and 9 months</td>
<td>Patient self-reported questionnaire</td>
</tr>
</tbody>
</table>
nurses responding to ePROs and weekly health information videos for 6 months.

Control group participants will be provided with a list of electronic links to videos on breast cancer-relevant topics on the websites of recognised cancer associations and health institutions.

All participants will continue to receive the usual healthcare provided by the hospital. The intervention will last 6 months with 3 months of additional passive follow-up to allow post-intervention monitoring.

Randomisation
The participants will be randomly allocated to the intervention or control groups using the minimisation technique with MS-DOS Minim program. Randomisation will be conducted by a research assistant who will use a pre-prepared list of random numbers to randomise the first six participants. Starting with the seventh participant, randomisation will be carried out using the MS-DOS Minim program. The minimisation technique is recommended as a standard to ensure that clinical trial groups are similar in terms of participant characteristics, such as age, schooling, breast cancer stage and treatment modality.

Intervention implementation
Each week, the lead researcher will obtain a list of patients with breast cancer who have started or will start neoadjuvant or adjuvant treatment with chemotherapy or radiotherapy within 2 weeks from the oncology hospital. Study nurses will use this list to invite all eligible patients with breast cancer to participate in the study. Patients will be invited by telephone to meet at the hospital or the research unit (located within the oncology hospital) to receive study-related information and to confirm eligibility. Those who meet the inclusion criteria will be provided with the option to participate and invited to provide informed consent prior to participation.

Participants will be provided with username, password and access to the intervention or control interface of the responsive ePRO application and training on its use. All participants will be asked to answer the baseline record of socio-demographic and clinical characteristics and questionnaires to assess study outcomes. Intervention arm participants will be asked to complete the weekly register, and will receive weekly reminders via WhatsApp messaging. Study nurses will contact patients without 2 weekly records to encourage adherence to the intervention.

Study nurses will be supported by the study oncologist/oncology resident to ensure adherence to the intervention activities. Additionally, the nurses will be in regular contact with the study team and will record their activities in the corresponding interface of the responsive ePRO application.

Confidentiality
Consent forms with participant signatures and handwritten information such as field notes or other related research materials will be stored in a locked location only accessible by the principal and leader researchers. All electronic data will be stored on password-protected computers. Data will be anonymised prior to the statistical analysis by the research team. Only de-identified data will be used for reporting, publication and dissemination of findings. Data will be erased and destroyed after 5 years, as per IMSS Ethics and Research Committee guidelines.

Study hypothesis
For primary study outcome
Compared with the control group, the intervention group at the 6-month follow-up:

a. Will show lower supportive care needs in the domain of health systems and information based on a 10-point difference in this dimension of supportive care needs.
measured with the Supportive Care Needs Survey (SCNS) Short Form.
For secondary study outcomes
b. Will report better quality of life based on at least a 10-point difference in the global quality of life scale as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ)-C30.
c. Will report lower breast symptoms based on at least a 10-point difference in the breast symptoms scale as measured by the EORTC QLQ-BR23.
For other prespecified outcome measures
d. Will report 20% less frequent use of emergency services and unscheduled hospitalisations.

Sample size
We calculated sample size using Power Analysis & Sample Size (PASS) software based on primary analysis of unadjusted outcomes at the 6-month assessment comparing control and intervention groups using two-sample t-tests allowing for unequal variance, setting alpha to 0.05, power of 80% and a dropout rate of 20%; we conservatively assume SD will be larger in the control arm than found in prior studies. Table 3 presents the additional assumptions and the number of participants to include: to address all study objectives, the required sample size is 205 participants per group.

Data collection and monitoring
Five evaluations will be performed during the trial: baseline, 1, 3, 6 and 9 months. Main study outcome variables will be measured at each evaluation, while the covariates will be collected only at the beginning of the study and application use and usability will be collected throughout the 6 months of ePRO access. We will also document reasons for dropouts and poor adherence. The information on the study variables will be gathered through the corresponding modules of the responsive ePRO application. Data monitoring will be performed by SECS and SVD to inform aspects of trial recruitment and follow-up. There will be no external data monitoring committee due to the minimal risk designation of this study.

Statistical analysis
Data quality will be assessed before statistical analysis (eg, range checks for numerical values). For the primary analysis, we will examine the effects of the intervention on each outcome variable at 6 months using a two-sample t-test. Anyone measured at 3 but not 6 months will have values carried forward or imputed as an intention-to-treat sensitivity analysis. As an additional analysis, we will use generalised estimating equations with autoregressive correlation structure to estimate time-averaged difference in each continuous outcome over all time points, adjusting for baseline measures and clinically and conceptually important baseline characteristics. The sample size required for the primary analyses is powered at 80% with alpha 0.05 to detect effect sizes of 10 points or more in supportive care needs, symptom reporting and quality of life outcomes. The analysis will be performed using Stata V.14.0 statistical software and R package V.3.6.2.

ETHICS AND DISSEMINATION
The study was authorised by the National Research and Ethics Committees of the Mexican Institute of Social Security (R-2021-785-059). Potential participants will sign an informed consent form prior to joining the study. This form contains the information about study objectives, random assignment of participants to intervention or control groups, study content and duration, relevant ethical considerations (eg, voluntary participation, possible risks and benefits, data custody, security and confidentiality protections) and contact information.

### Table 3  Sample size

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Expected control</th>
<th>Expected difference (intervention vs control)</th>
<th>SD (intervention, control)</th>
<th>Participants per group</th>
<th>Enrolment target per group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary study outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health systems and information supportive care needs</td>
<td>37.3 points$^{59}$</td>
<td>10 points</td>
<td>29 points, 35 points$^{59}$</td>
<td>164</td>
<td>205</td>
</tr>
<tr>
<td><strong>Secondary study outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global quality of life</td>
<td>68.8 points$^{59}$</td>
<td>10 points</td>
<td>29 points, 35 points$^{59}$</td>
<td>164</td>
<td>205</td>
</tr>
<tr>
<td>Breast symptoms</td>
<td>25.5 points$^{59}$</td>
<td>10 points</td>
<td>24 points, 29 points$^{59}$</td>
<td>113</td>
<td>141</td>
</tr>
<tr>
<td><strong>Other prespecified outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency services and unscheduled hospitalisations</td>
<td>1.97 visits$^{61}$</td>
<td>0.4 visits</td>
<td>0.4 visits, 0.5 visits$^{61}$</td>
<td>26</td>
<td>33</td>
</tr>
</tbody>
</table>
of the principal investigator and IMSS Ethics Committee (online supplemental material 1).

The trial was registered at ClinicalTrials.gov. Based on the SPIRIT recommendations, any modifications to the protocol that may affect the conduct of the study or the potential benefit or risk of the study participants, such as changes of study objectives, study design, population, sample sizes or study procedures will be submitted as an IMSS IRB amendment to the protocol and modified accordingly on ClinicalTrials.gov. The pilot study began on 15 August 2023; the anticipated start date for the trial is 15 January 2024, with expected completion by the end of 2024. Study findings will be disseminated through publications in peer-reviewed journals, presentations in national and international conferences, a policy-brief to the local authorities and a webinar to patients with breast cancer and health professionals.

**DISCUSSION**

In Mexico, a substantial unmet need exists to improve health services and outcomes for women with breast cancer. Patient-centred ePRO digital interventions have been proven useful for breast cancer care quality improvement in other settings, but have not been tested in Mexico. The Mexican population is well equipped to adopt digital interventions: there are 86.5 million cell phone users in the country, and 79.9% of the population live in urban areas and use the internet, predominantly via smartphone.51 Moreover, the Mexican government has recognised the importance of implementing eHealth strategies to achieve ‘universal and effective health coverage’ in the country.52 The experience of the COVID-19 pandemic has increased familiarity with telemedicine among patients and providers, showing the benefits of digital approaches, and heightened interest among health system policymakers in validated, scalable models of digital, patient-centred care. Despite that, public health services for patients with cancer in Mexico lack modern and innovative options for remote monitoring and control of cancer symptoms, treatment side effects and supportive care needs. Thus, it is imperative to identify feasible and effective digital health interventions to improve cancer care in Mexico.

The proposed intervention has several strengths. We conducted a comprehensive development and validation process drawing on expert input to ensure the intervention content is complete and accurate and on patient perspectives to confirm clarity and relevance. The final content demonstrated high validity. The intervention design is structured around accessibility from the patient’s perspective, relying on a visually attractive web application that can be used on any device regardless of browser or operating system. The pilot test will provide evidence of the preliminary usability of the web-based ePRO application and generate patient and provider perspectives on necessary adjustments to the intervention or study procedures in preparation for the clinical trial. The intervention focuses on early chemotherapy and radiotherapy, representing a critical window in which patients face the most important supportive care needs.

Several limitations can be noted. First, participation is limited to those capable of interacting with the application, excluding those without access to an internet-capable device as well as illiterate patients, those with limited visual acuity and those with cognitive disability or pre-existing severe depression. Uncontrolled severe depression is characterised by persistent apathy, sadness, poor concentration and loss of interest in activities, symptoms that make it difficult to engage with study activities; women with prior diagnosis of depression receiving effective treatment (reporting Hospital Anxiety and Depression Scale <12) are eligible for participation. This prevents generalising to all patients with breast cancer in Mexico; we will report on the demographic composition of study participants compared with all IMSS patients with breast cancer. Second, the intervention does not include patients with stage IV breast cancer. Although these patients have numerous symptoms and unmet supportive care needs, they will not be included due to the more complex care needs and a limited possibility of improvement of their quality of life. Third, the limited working hours of study nurses (08:00 to 20:00) could affect the use of the ePRO application by patients and, therefore, the effectiveness of this intervention; however, 24-hour support would not be feasible for scale up within IMSS clinical care, so understanding effectiveness with this model will be more relevant to further implementation. Third, study participation and completion of assessment tools require time from women undergoing cancer treatment, who may find it difficult to participate, particularly if no benefit is perceived. Finally, the intervention procedures and evaluation will be conducted separately from routine clinical care; if demonstrated to be effective, considerations of cost and implementation feasibility would need to be addressed within IMSS.

Study materials (e.g., content of the ePRO application, clinical algorithms for nurses) are expected to guide the implementations of similar multifaceted ePRO interventions at oncology services of public health institutions in Mexico and other Latin American countries to provide remote monitoring and control of adverse symptoms and supportive care needs of patients with breast cancer, particularly for large oncology hospitals with patient populations similar to the study setting; further local adaptations may be required.

**Author affiliations**

1Epidemiology and Health Services Research Unit CMN Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico
2Oncology Department, Oncology Hospital CMN Siglo XXI, IMSS, Ciudad de Mexico, Mexico
3Radiation Oncology Department, Oncology Hospital CMN Siglo XXI, IMSS, Ciudad de Mexico, Mexico


12 Black N. Patient reported outcome measures could help transform healthcare. *BMJ* 2013;346:mm1167.


27 Ruland CM, Maffei RM, Borosund E, et al. Evaluation of different features of an eHealth application for personalized illness...


