Supportive care for patients with breast cancer by using an interactive app during neoadjuvant chemotherapy -a Randomized Controlled Trial

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SUPPORTIVE CARE FOR PATIENTS WITH BREAST CANCER BY USING AN INTERACTIVE APP DURING NEOADJUVANT CHEMOTHERAPY - A RANDOMIZED CONTROLLED TRIAL

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"I pictured myself lying on a huge wave on a stormy sea and just went with the flow"

Sara Danius speaking in the radio show "Vinter i P1" in 2014 about her breast cancer treatment

ABSTRACT

Background: Patients with breast cancer undergoing neoadjuvant chemotherapy are often treated as outpatients and experience several distressing symptoms and concerns over a long period, which must be managed at home. Routine use of patient reported outcomes facilitates communication with the healthcare of what needs the patient may have. To support patients with cancer during treatment, the use of mHealth has shown promising results in reducing symptoms and improving quality of life.

Aim: To evaluate how an interactive app for reporting and managing symptoms provides supportive care in patients with breast cancer during neoadjuvant chemotherapy.

Methods: Through the app patients report symptoms daily as well as write free text messages. The reports are monitored and responded to by a contact nurse at the clinic. Further, the patients have access to self-care advice and can view their reported symptoms in graphs. This randomized controlled trial was conducted according to the Medical Research Council's framework for complex interventions. In **Study I**, the patients were randomized to an intervention group (n = 74), who used the app during treatment in combination with standard care, and to a control group (n = 75), who received standard care alone. Both groups answered questionnaires regarding symptoms and health-related quality of life before start of treatment and two weeks after end of treatment, to evaluate if the intervention had any effects on the patients' symptoms and health-related quality of life. **Study II** investigated the patients' engagement in using the app. Logged data from the patient's app usage (n = 74) and predictors of usage were analyzed. Telephone interviews were conducted with the patients about how they perceived using the app during treatment. In **Study III**, face-to-face interviews were conducted three months after end of neoadjuvant chemotherapy with patients from both groups (n = 40) about perceptions of care during treatment with or without using the app.

Results: In **Study I**, patients who used the app during treatment perceived less prevalence of symptoms and symptom distress and better emotional functioning two weeks after end of treatment compared with the patients in the control group. In **Study II**, the adherence to reporting in the app was 83%. The components included in the app, such as self-care advice and graphs, were used by most of the patients. Higher age predicted fewer free text messages sent. The app was considered easy to use with a relevant content, which facilitated support for symptom management and own monitoring of symptoms as well as having a close, continuous, and interactive contact with the contact nurse. In **Study III**, results showed that most of the patients, whether they had used the app or not, were satisfied with the care during the treatment. The patients who had used the app perceived it as an added value for support as they were provided easy access to information and communication regarding experienced symptoms with the contact nurse. Moreover, Interaktor facilitated performing self-care by using the self-care advice and promoted own participation in care.

Conclusions: This thesis shows that patients with breast cancer can receive supportive care by using an app such as Interaktor during neoadjuvant chemotherapy. By facilitating interaction and communication with the contact nurse, symptoms can be identified and managed in a timely manner as well as enhancing patients' participation in their own care.

LIST OF SCIENTIFIC PAPERS

I. **Fjell, M**., Langius-Eklöf, A., Nilsson, M., Wengström, Y., Sundberg, K. (2020). Reduced symptom burden with the support of an interactive app during neoadjuvant chemotherapy for breast cancer – a randomized controlled trial. *The Breast, 51,* 85-93.

II. Crafoord, M. T.*, **Fjell, M.***, Sundberg, K., Nilsson, M., Langius-Eklöf, A. (2020). Engagement in an interactive app for symptom self-management during treatment in patients with breast or prostate cancer: mixed methods study. *Journal of Medical Internet Research, 22,* e17058.

III. **Fjell, M**., Langius-Eklöf, A., Nilsson, M., Sundberg, K. (2020). Patient perceptions of care with or without the support of an interactive app during neoadjuvant chemotherapy for breast cancer. *Manuscript*.

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CONTENTS

LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
App	Application for smartphones and tablets
BOCF	Baseline Observation Carried Forward
CCI	Charlson Comorbidity Index
eHealth	Information and communication technology for healthcare
Elston-Ellis	Grading system in breast cancer
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	Estrogen Receptor
ES	Effect Size
HER2	Human Epidermal growth factor Receptor 2
ITT	Intention-to-treat
Ki-67	Marker of proliferation
MDC	Multidisciplinary Conference
mHealth	Mobile health
MRC	Medical Research Council
MSAS	Memorial Symptom Assessment Scale
NACT	Neoadjuvant chemotherapy
PR	Progesterone Receptor
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
RCT	Randomized Controlled Trial
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

1   INTRODUCTION

During my clinical nursing career, I have primarily worked as an oncology nurse with patients with breast cancer at the outpatient department at Karolinska University Hospital (formerly Radiumhemmet). Since the department is research intense, I had the privilege of continuously working together with researchers in both oncology nursing and breast cancer oncology, which has inspired me and laid the foundation for my interest in research. The advances in new treatments have led to increased survival. However, this also means symptoms and concerns for the patients who receive it, which needs to be managed over a long period of time.

In my experiences working as a contact nurse, patients with breast cancer have different needs for support during their treatment and they want to be involved in the care in some way. Information and management of symptoms, as well as having regular contact with and easy access to a contact nurse when needed, is support that seems meaningful for the patients to be able to cope with their disease and treatment. To deliver this support nurses play an important role by using various nursing interventions.

When I was told that the Doctoral School in Health Care Sciences at Karolinska Institutet announced for a doctoral student in a research project focusing on how patients with breast cancer can be supported by using an interactive app in clinical nursing care, I immediately thought that this was the natural step for me to take to gain in-depth understanding and knowledge of how such intervention can be supportive for the patients.

My hope is that the findings in this thesis will contribute to knowledge of how patients with breast cancer undergoing neoadjuvant chemotherapy perceive their situation and care and how they can be supported by making care accessible and communicative as well as enabling participation in their own care according to individual needs.

2 BACKGROUND

2.1 Breast cancer

In Sweden, breast cancer is the most common cancer among women. In 2018, over 7800 women and just over 60 men were diagnosed. The same year around 1500 individuals died because of the disease (The National Board of Health and Welfare & The Swedish Cancer Society, 2018). The median age for getting the disease is 64 years and fewer than five percent are under 40 years old (The Swedish Cancer Society, 2020). Over the years there has been an increase in the number of individuals who are diagnosed with breast cancer and a decrease in mortality (The National Board of Health and Welfare & The Swedish Cancer Society, 2018). This can be explained by early detection of the disease through public mammography screening programs as well as advances in treatments (Cardoso et al., 2019; Nordenskjöld et al., 2018).

2.1.1 Treatment methods for breast cancer

There are several approaches to treating breast cancer. Surgery is commonly performed either before or after different medical treatments. The surgical techniques have evolved aiming to be effective in removing the tumor, but also to improve the cosmetic result and longtime functions (Waks & Winer, 2019). The surgical techniques for breast cancer commonly consist of breast-conserving surgery or mastectomy, which can be combined with reconstruction of the breast (Zurrida & Veronesi, 2015). Breast-conserving surgery aims to remove the tumor with tumor free margins around the tumor, but not the breast itself, while mastectomy removes the tumor as well as the breast. Tumor characteristics, the patient's age, volume of the breast, further oncological treatment, and patient's wishes are some examples of factors that determine which surgical technique should be performed. It has been concluded that besides preventing locoregional recurrence and improving survival, the surgical treatment of breast cancer also focuses on the patients' quality of life and body image (Riis, 2020). During the surgery, a standard procedure is also the sentinel-node biopsy, where a radioactive isotope and blue dye is injected close to the tumor. By doing this, the first lymph node that drains the tumor is identified and examined. If there is no sign of metastasis, an axillary dissection is avoided. This technique not only predicts the status over the entire axilla, it can also prevent the patient from being affected by lymphedema, pain and mobility impairment of the arm, which an axillary dissection may cause (Confederation of Regional Cancer Centres in Sweden, 2020b; Zurrida & Veronesi, 2015). Medical treatments can consist of chemotherapy, which can be combined with targeted drugs (anti-HER2 treatments), and anti-hormonal treatment (endocrine therapy). Radiation therapy is also frequently used after surgery and chemotherapy to eliminate any remaining cancer cells (Confederation of Regional Cancer Centres in Sweden, 2020b). The decision about which treatment should be given is based on several factors such as characteristics of the tumor, such as tumor type, grade, stage of the disease (Elston-Ellis), proliferation rate (Ki-67), hormonal-receptors status (estrogen = ER and progesterone = PR) and HER2 status (human epidermal growth factor receptor 2). The patient's health status and any comorbidities also

affect the decision of treatment (Bourdeanu & Liu, 2015; Colomer et al., 2019; Confederation of Regional Cancer Centres in Sweden, 2020b; Gamucci et al., 2018; Klein et al., 2019).

2.1.2 Chemotherapy

Chemotherapy is a systemic treatment method, where the goal is to destroy cancer cells and stop them from dividing uncontrollably. The treatment is given with different intentions such as curative, which aims to eliminate all cancer cells in the body, as adjuvant, where the goal is to eliminate cancer cells that might be left after surgery, or as neoadjuvant before surgery to shrink the tumor. Chemotherapy given as palliative treatment can help to slow down or stop the progress of the cancer temporarily or relieve symptoms (Fisusi & Akala, 2019; Nilbert, 2013; Schmidt, 2014).

Chemotherapy is given in cycles. The number of cycles and how long the intervals are between them, depends on how long the effect of the chemotherapy lasts, recovery time for the patient and the overall length of the treatment. Common cycles are weekly treatment, every other week or every third week, which means that the total length of the treatment can vary between 12 and 18 weeks. Further, the treatment can be given as single-agent, meaning that only one drug is given, or as multi-agents, where a number of drugs are combined (Chatterjee & Erban, 2017; Colomer et al., 2019; Gianni et al., 2012). This means that there can be many different combinations depending on how the agents work to have effect on the tumor (Waks & Winer, 2019). In Sweden, patients are treated according to recommendations written in the national care guidelines for breast cancer (Confederation of Regional Cancer Centres in Sweden, 2020b). The decisions on which chemotherapy agents should be given, dosages, in which order and cycles are based on results from several clinical trials conducted over the years (Waks & Winer, 2019). Clinical trials are also continuously ongoing to develop and evaluate new treatments. In Sweden, PREDIX II Her 2 and NordicTrip are neoadjuvant clinical trials, where tumor characteristics play a crucial role such as HER2 status or triple negative breast cancer meaning that the tumor is tested negative for hormonal receptors and HER2 (Confederation of Regional Cancer Centres in Sweden, 2020a). Studies based on tumor characteristics as well as individual factors for each patient will hopefully result in knowledge about which treatments will be most beneficial for the individual patient (Falzone et al., 2018).

2.1.3 Undergoing treatment with neoadjuvant chemotherapy

Historically, neoadjuvant chemotherapy (NACT) was introduced in the 1970s (Early Breast Cancer Trialists' Collaborative Group, 2018). This was based on studies with positive results in patients with inoperable tumors who had received NACT before surgery to decrease the size of the tumor to be operable (Mieog et al., 2007). Today, NACT is an established and commonly used treatment in early-stage and locally advanced breast cancer (tumor size from 20 mm to 50 mm or spread to axillary lymph nodes), as well as inflammatory and primarily non-operable breast cancer (Heil et al., 2020; Mrkonjic et al., 2019; Steenbruggen et al., 2017; Teshome & Hunt, 2014). This means that the patients

receiving NACT often have more aggressive characteristics of the tumor (Cain et al., 2017; Graham et al., 2015; Haddad & Goetz, 2015).

In Sweden, the proportion of patients receiving NACT has doubled from nine percent in 2009 to 18 percent in 2018 (Regional Cancer Center Stockholm-Gotland, 2020). The chemotherapy agents given as NACT are predominantly the same as those given as adjuvant (Early Breast Cancer Trialists' Collaborative Group, 2018; Waks & Winer, 2019). Combinations of Anthracyclines, Alkylators, Antimetabolites and Taxanes are commonly given as NACT followed by Taxanes as a single-agent treatment (Confederation of Regional Cancer Centres in Sweden, 2020b). If the tumor has shown to be HER2 positive, anti-HER2 drugs such as Trastuzumab and Pertuzumab is added to the treatment (Chatterjee & Erban, 2017; Colomer et al., 2019; Gianni et al., 2012). In recent years, interest in adding immunotherapy to chemotherapy has risen even in the neoadjuvant setting after showing positive results in treatment of metastatic breast cancer (Adams et al., 2019; Schmid et al., 2020). Immunotherapy uses components of the patient's own immune system to detect and destroy cancer cells (Koury et al., 2018). If a patient responds well to NACT, the prognosis of survival increases (Klein et al., 2019; Li et al., 2019; Romero et al., 2013). Clinical trials using immunotherapy aim to investigate whether the prognosis can improve even further (Garcia-Aranda et al., 2019; Mina et al., 2019).

Neoadjuvant chemotherapy is considered both effective and safe. Besides the benefit of reducing tumor size to facilitate breast conserving surgery rather than mastectomy, which can decrease morbidity associated with axillary surgery, NACT allows to treat possible micro metastases early and provides valuable prognostic information (Cain et al., 2017; Caparica et al., 2019; Curigliano et al., 2017; Haddad & Goetz, 2015). When NACT is completed, the patient undergoes surgery to remove the primary tumor. A decision on whether further treatment is warranted is also taken for example more chemotherapy, radiation therapy and/or anti-hormonal therapy (Bourdeanu & Liu, 2015).

Despite the benefits, chemotherapy is associated with treatment-related side-effects causing several distressing symptoms and concerns (Bergh et al., 2001; Fisusi & Akala, 2019; Pondé et al., 2019). Chemotherapy does not have the ability to distinguish between cancer cells and normal cells. Cancer cells grow fast like many of the normal cells in the body such as in the blood and hair, but also cells in the mouth and gastrointestinal tract. When chemotherapy is given, the normal cells are also affected which cause symptoms (Nilbert, 2013). Depending on which chemotherapy agents are used, dosages, number of treatment cycles, individual factors such as age and comorbidity as well as coping strategies and social support, the patients experience of prevalence, frequency and severity of symptoms can vary (Gibbons & Groarke, 2018; Lai et al., 2017; Miaskowski et al., 2014). Some patients complete the treatment smoothly and can live a relatively normal life during treatment while others experience many symptoms and concerns, which causes great suffering (Lai et al., 2017). Frequently patients express having multiple symptoms simultaneously (Browall et al., 2017; Denieffe & Gooney, 2011; McKenzie et al., 2011;

Tiezzi et al., 2017), commonly between 10 to 32 symptoms (Miaskowski et al., 2014; Ward-Sullivan et al., 2017), which can be associated with both the treatment and the illness itself (Bower, 2008; Davis & Kirkova, 2008; Galipeau et al., 2019; Kirca & Kutlutürkan, 2018; McFarland et al., 2018; Miaskowski et al., 2017; Pearce et al., 2017) (Table 1). These symptoms and concerns affect the patient's physical, psychological, and social well-being and subsequently have a negative impact on quality of life (Avis et al., 2017; de Ligt et al., 2019; Karimi & Brazier, 2016; Tang et al., 2018).

Table 1. Commonly perceived symptoms and concerns by patients undergoing chemotherapy.

• Anger	• Lack of energy
• Anxiety	• Nausea
• Breathing difficulties	• Nervousness
• Changes in taste and smell	• Neutropenia
• Cognitive disturbances	• Numbness or tingling in hands and feet
• Constipation	• Oral mucositis
• Depression	• Pain
• Diarrhea	• Sadness
• Fatigue	• Sleeping difficulties
• Fear	• Vomiting
• Hair loss	• Worry

Note. The symptoms and concerns presented in Table 1 are from Bower (2008); Davis and Kirkova (2008); Galipeau et al. (2019); Kirca & Kutlutürkan (2018); McFarland et al. (2018); Miaskowski et al. (2017) and Pearce et al. (2017).

Even though perception of symptoms during chemotherapy for breast cancer is well known, how patients perceive symptoms and quality of life during NACT has not been studied to the same extent (Beaver et al., 2016; LeVasseur et al., 2020). The symptoms perceived associated with NACT may not differ that much since the chemotherapy agents given are the same as for adjuvant treatment. To be considered though is that patients planned for NACT are relatively young and may have to balance own needs against their families, manage financial difficulties and maintain their careers (Adams, 2010; Beaver et al., 2016; Hamer et al., 2017). The chemotherapy treatment often starts quickly after diagnosis, and the patients must cope with a rapid transition from being well to feeling ill while also dealing with the shock of the cancer diagnosis. Another stressful factor when undergoing NACT is the knowledge that the cancer is remaining in their body during the treatment (Beaver et al., 2016).

2.2 Supportive cancer care

In cancer care, supportive care is a concept that is frequently used, however there is no consensus over what it really entails (Cramp & Bennett, 2013; Hui, 2014). Often supportive care is used interchangeably with palliative care or hospice care (Hui, 2014). Also mentioned as integrated in supportive care are rehabilitation, secondary cancer prevention

and survivorship (Multinational Association of Supportive Care in Cancer [MASCC], 2020). All interpretations of supportive care have similarities such as multi-professional care for the patient, but there are large differences in how the services are performed and the patient population that receive it (Hui et al., 2013). In the early 1990s, the Supportive Care Framework for Cancer Care was developed by Fitch (2008), as a tool for healthcare professionals to define what type of help patients with cancer might require and how delivery of services should be approached and assessed according to patients' individual needs, response to the situation, coping and adaption (Fitch, 2008). The supportive care needs differ from patient to patient depending on factors such as age, stage of disease, social and cultural context, and individual perceptions, as well as change over time, but regardless of what, the needs must be handled appropriately and timely (Loibl & Lederer, 2014). The goal is to provide the best possible care which is accessible for all patients.

Being diagnosed with breast cancer is often described as a shocking and overwhelming experience turning everyday life upside down, and as the forthcoming treatment begins, it affects the patients in several ways (Curtis et al., 2014; Landmark & Wahl, 2002). It has been concluded that patients have unmet supportive care needs during their treatment (Cardoso et al., 2013; Schmid-Büchi et al., 2013), which can be described as the difference between a patients perceptions of the support and the actual support that is required or desired (Hubbard et al., 2015) as well as possibly not receiving supportive care that is adequate (Cardoso et al., 2013; Schmid-Büchi et al., 2013). Patients with breast cancer often describe supportive care needs concerning how to cope with the disease, such as psychological and practical support and information about the treatment and the disease, related symptoms and how they can be managed (Fiszer et al., 2014; Loibl & Lederer, 2014). The patients may perceive impaired well-being and quality of life if symptoms are uncontrolled and there is also a risk of poor treatment outcomes due to delay, dose reduction or if the treatment needs to be cancelled. Moreover, patients may need distressing visits to the emergency department or need care that requires hospitalizations (Lai et al., 2017; McKenzie et al., 2011; Tang et al., 2018; Wyatt et al., 2015). Therefore, prevention and management of symptoms related to the cancer and its treatment constitutes a large part of supportive care in patients with cancer. The management includes both physical and psychological symptoms perceived by patients from diagnosis through treatment to post-treatment care (Loibl & Lederer, 2014). According to The Symptom Management Model developed by Dodd et al. (2001), symptoms can be effectively managed if they are assessed based on severity, cause, and treatability.

2.2.1 Perspectives on supportive care

Within nursing, health is considered as a key concept (Wärnå-Furu, 2017) and closely related to the concept of a human being. The human being is viewed as one unit where physical, psychological, existential, and social dimensions interact with each other (Lindwall, 2017). When a human being becomes a recipient of care he or she is commonly referred to as a patient (Kasén, 2017). Health is based on the holistic perspective of a

human being, which means that perceptions of health are subjective, have different meanings for different patients and can change their character over time. Moreover, health and illness do not have to be opposites. Even though a patient has an illness, the patient can perceive health (Ekebergh, 2015). Therefore, it might be conflicting that in nursing literature how patients with breast cancer perceive their situation and treatment is commonly described from the perspective of illness. An explanation is that reflections on their own health are usually not made when feeling well, but when they are affected by illness, the awareness of their own health increases, as the illness may interfere with daily life (Ekebergh, 2015). Due to illness, unmet needs, inability to take care of oneself and difficulties in adapting to the new situation are perceptions that often occur among patients (Meleis, 2011).

Patients with breast cancer describe that to feel supported during treatment, they request communication and interaction with healthcare professionals, easy access to the care as well as information and help to manage symptoms related to the treatment (Droog et al., 2014). Since perceptions of being diagnosed with breast cancer and the forthcoming chemotherapy are highly subjective as well as entailing a prolonged and complex care, it is crucial that the patients are provided with appropriate supportive care that each patient requests and needs (Brédart et al., 2013). There are nurse-led interventions conducted to support patients with breast cancer (Chan et al., 2020; Charalambous et al., 2018; Tuominen et al., 2019). The majority of the interventions are randomized controlled trials (RCTs) or controlled before and after studies. Commonly they involved teaching or provision of information and nurse-led follow up by assessing and monitoring symptoms and providing advice for those symptoms and subsequently reporting back to the physician. Primarily, the interventions were delivered face-to-face, over the telephone or online (Chan et al., 2020; Charalambous et al., 2018; Tuominen et al., 2019). Among the interventions described by Chan et al. (2020), Charalambous et al. (2018) and Tuominen et al. (2019), teaching or provision of information and nurse-led follow up during treatment were interventions that showed statistically significant positive effects on health-related quality of life and symptom burden. However, many had small sample sizes, inappropriate study designs, insufficiently described methods, and poorly reported results sections, making it hard to make interpretations and recommendations. It is therefore concluded that more research is needed to gain better insights into which interventions are effective and can then be further evaluated (Chan et al., 2020; Charalambous et al., 2018; Tuominen et al., 2019).

To be considered is that, as most of the patients with breast cancer receive their treatment as outpatients, they are required to manage their situation at home over a long time period (Lai et al., 2017; McKenzie et al., 2011). Enhancing self-care is one nursing intervention that is of special importance in those patients (Coolbrandt et al., 2018; McCorkle et al., 2011). Studies have shown that performing self-care during treatment for cancer has several advantages. It can relieve symptoms, improve quality of life, help patients cope with the treatment as well as being advantageous for compliance with further treatments (Davis et al., 2018; Hammer et al., 2015; Hernandez Silva et al., 2019; Howell et al., 2017; van Dijck

et al., 2016). This can in the long run help patients achieve a faster return to daily activities and work (Pryce et al., 2007). Moreover, performing self-care can enhance interaction and communication with healthcare professionals, and by letting the patients take their own actions in managing symptoms related to treatment, patient participation can be achieved (Howell et al., 2017).

The concept of patient participation is not well defined and various terms such as patient collaboration, patient involvement, partnership and patient empowerment are used interchangeably. Patient participation is often associated with decision making and does not always include the various aspects in which the patient can participate in healthcare (Longtin et al., 2010). In this thesis, patient participation focuses on the individual patient receiving nursing care, the collaborative relation between the patient and the contact nurse, shared information and knowledge, and active engagement in their own care (Angel & Frederiksen, 2015; Sahlsten et al., 2008).

Even if the nurse has the responsibility to support the patients during treatment, the patients are also expected to participate in their own care (Tinetti & Basch et al, 2013), such as making decisions or expressing opinions about their treatment, sharing information with the healthcare professionals, asking questions and managing their own health (Longtin et al., 2010; Vahdat et al., 2014). However, it is crucial to remember that patients might have different needs for participation (Frank et al., 2009). Some want to participate, and some want to stay passive (Cohen & Botti, 2015; Ringdahl et al., 2017). Patient participation should therefore be considered on an individual basis depending on the patients' needs, wishes and situation (Angel & Frederiksen, 2015; Engqvist Boman et al., 2018). By taking each patient's needs for participation into consideration and where there is collaboration and mutual communication between the patient and healthcare professionals, the supportive care becomes person-centered (Jordan et al., 2018; Santana et al., 2018). This means that the focus is on the patient behind the disease, rather than solely on the disease (Kaasa et al., 2018).

2.2.2 Patient-reported outcomes – subjective symptom reporting

Patients' perceptions of symptoms related to chemotherapy are as described highly subjective and can only be recognized by the patient without interpretation by the healthcare professionals (Dodd et al., 2001; Rhodes & Watson, 1987). The symptoms can be perceived in several dimensions such as prevalence, frequency, severity, bother, intensity, and distress (Henoch et al., 2018). Using patient-reported outcomes (PROs) is a strategy to gain a holistic view of the patients perceived symptoms. Patient reported outcomes can include symptoms, a patients physical, psychological, social and emotional functioning, and other reports concerning the patients' health (U.S. Department of Health and Human Services FDA, 2006). The use of PROs has increased in cancer care (Howell et al., 2015). To measure PROs, instruments called patient-reported outcome measures (PROMs), are used commonly as self-report questionnaires (Weldring & Smith, 2013).

Evidence has shown that routine use of PROMs by patients to report their symptoms and concerns can facilitate early detection of symptoms and impact of treatment, improve communication between patients and healthcare professionals, addressing the patients' needs, and improve patient satisfaction (Berry, 2011; Berry, Blumenstein, et al., 2011; Kotronoulas et al., 2014; Maher, 2013; Snyder et al., 2014; Valderas et al., 2008) and participation in care (Chen et al., 2013; Howell et al., 2020). When used in clinical practice it is important that the questions used for assessment are tailored and relevant for the context in which they are used (Snyder et al., 2014). Since patients with breast cancer undergoing chemotherapy perceive various symptoms to various degrees, measuring PROs can better identify those patients who would benefit from actions taken with additional supportive care (Davis et al., 2018).

2.2.3   mHealth – a digital solution

Today digital health solutions within eHealth and mHealth are commonly used in cancer care (Charalambous, 2019). eHealth is a broader concept and involves internet and related technologies for delivering and enhancing health services and information (Eysenbach et al., 2001). eHealth has also been described as using digital tools to exchange information digitally to achieve and maintain health (Hofflander, 2020). Mobile technology, which refers to devices such as smartphones and tablets where various applications (apps) can be downloaded, have become a large part of people's daily lives (Jeon & Park, 2015). This development has led to an increased use of mobile technology within healthcare called mHealth (Blake, 2013; Park, 2016). mHealth has been defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" (World Health Organization [WHO], 2011). There are several reasons why the use of mHealth in healthcare has increased. The smartphones or tablets have powerful technical capabilities, people are attached to their phones and carry them everywhere (Klasnja & Pratt, 2012). Smartphones can also be used in large samples, accessing hard-to-reach groups and have the potential to be cost effective (Blake, 2008).

Due to the rapid development within mHealth it is today possible to integrate and collect PROs in such devices instead of using paper-based questionnaires (Kaasa et al., 2018), which can decrease the risk of missing data, recall bias and transcription errors (Benze et al., 2019). Further, using digital solutions such as mHealth for reporting PROs in real time gives an opportunity to address and monitor patients' unmet needs as well as support patients in management of symptoms through self-care advice. Moreover, mHealth helps increase communication between the patients and healthcare professionals and provides information about the treatment and related symptoms (Aapro et al., 2020; Kruse & Beane, 2018; Richards et al., 2018; Rowland et al., 2020).

There is increasing evidence showing that the patients with cancer using digital health such as mHealth are supported in various ways. Patients often appreciate to report symptoms to the nurse during their treatment (Beck et al., 2017; Egbring et al., 2016) and consider the

systems as usable, acceptable, and feasible (Heynsbergh et al., 2019; Moradian et al., 2018). These systems offer patients to interact with the healthcare professionals by regular self-reporting and monitoring of symptoms during treatment. Further, alerts are sent to the healthcare professionals according to predefined levels, which the healthcare professionals responds to by contacting the patient (Basch et al., 2007; Denis et al., 2014; Drott et al., 2016; McCann et al., 2009; Weaver et al., 2014). mHealth can also improve communication and interaction with the healthcare professionals as well as enhance the opportunity for participating in care (Vo et al., 2019). By monitoring the symptoms, patients get the opportunity to discuss them with the healthcare professionals, who also can act on them within a short period (Drott et al., 2016). This has in patients with different cancer diagnoses such as breast, prostate genitourinary, gynecologic, lung, and colorectal cancer, lymphoma, and multiple myeloma, been shown to be effective in reducing symptoms, improving quality of life and survival (Basch et al., 2016; Denis et al., 2019; Denis et al., 2017; Ruland et al., 2010). mHealth can also be used to support patients in symptom management by providing information and self-care advice (Escriva Boulley et al., 2018; Foley et al., 2016; Hernandez Silva et al., 2019; Kearney et al, 2009; McCann et al., 2009).

2.2.4 Engagement and adherence using mHealth

As interventions with mHealth to support patients with cancer have increased, it is essential to understand how these interventions operate and how usage is experienced and can be enhanced to interpret its eventual benefits (Doherty, 2019; Eysenbach, 2005; Gomolin et al., 2020; O'Brien et al., 2008; Perski et al., 2017). Usage and user experiences of mHealth interventions can be described as engagement (Perski et al., 2017), which is influenced by several interacting factors such as a patient's skills, understanding, demographics, internet access, online environment and intervention components such as technical and design features. If the patient perceives the interventions as relevant, usable, helpful, and interactive, persistent engagement is achieved (Short et al., 2015; Sieverink et al., 2017).

Related to engagement is adherence, which can be described as the degree to which the patients followed or used the intervention as it was planned (Donkin et al., 2011). There are several approaches to measure adherence such as number of logins, views on websites and modules completed, which depend on the purpose and design of the intervention. High levels of adherence within interventions in mHealth have been shown to positively correlate with improved outcomes (Donkin et al., 2011). Moreover, high levels of adherence were reached in patients with cancer reporting symptoms on a tablet in connection with clinical visits (Basch et al., 2017). The need to examine how patients adhere to and perceive symptom reporting and monitoring via mHealth when at home between treatments has been stated (Rincon et al., 2017; Warrington et al., 2019).

2.3 The Interaktor app

The app Interaktor used in the studies focuses on the patient perspective and was inspired by different aspects of person-centered care and patient participation in care (Frank, Asp, Fridlund et al., 2011; Olsson et al., 2013). Considering the different needs patients may perceive during treatment for cancer, the app was developed with the intention to support them in real time with information, provision of self-care advice to manage symptoms and easy access to the healthcare professionals. This would reinforce communication and interaction with the healthcare professionals as well as enhance patient participation in care.
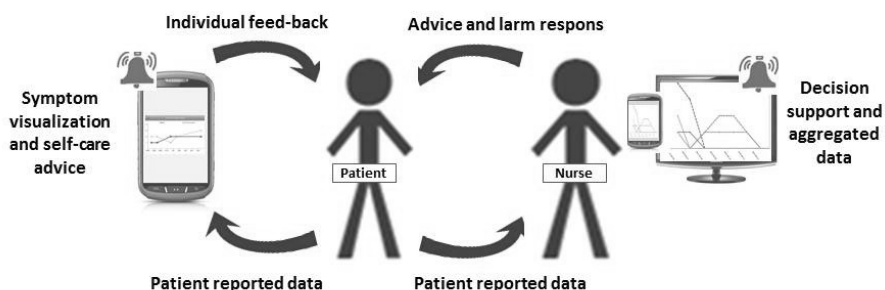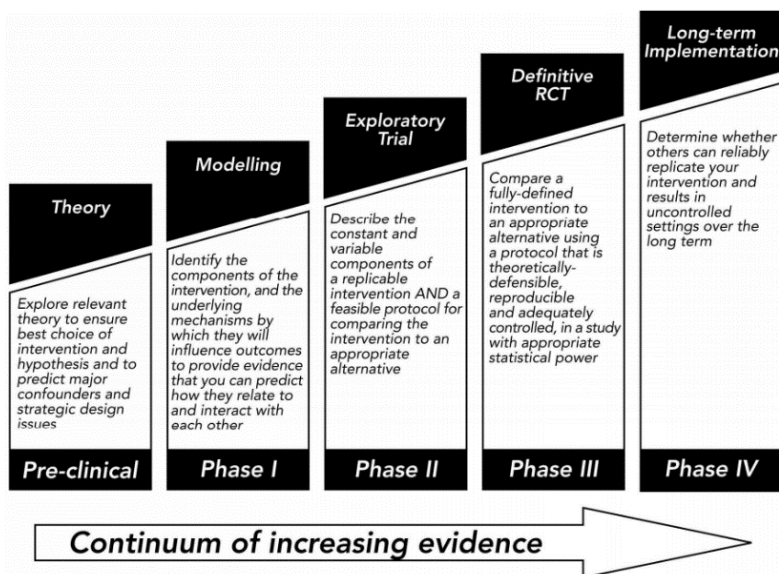

Figure 1. Illustration of the idea of the Interaktor app and web interface (Langius-Eklöf, Crafoord, et al., 2017; Sundberg et al., 2015).

The app is interactive and the components are: 1) regular assessment of self-reported symptoms, 2) a risk assessment model sending alerts for symptoms of concern, 3) continuous access self-care advice and links to relevant websites for additional information, 4) graphs of reported symptom history, and 5) a connected web interface for the contact nurse to monitor the patient's reports in real time (Figure 1). Interaktor was initially developed in a collaboration with the research group and a health management company specialized in new innovative care solutions. Further it was developed to be adaptable depending on setting and target group. To get access to the app it is downloaded onto a smartphone or tablet through the operating systems Android and iOS. To get access to the content, an individual log in with username and pin code is required.

The development and test of Interaktor was underpinned by the framework of the Medical Research Council (MRC) for evaluating complex interventions (Figure 2) (Craig et al., 2013; Medical Research Council, 2000). In relation to the initial phases of the framework, Interaktor was developed by 1) identifying existing evidence, defining and understanding the problem and the context, 2) feasibility or pilot testing to test procedures, 3) evaluation by assessing effectiveness (Craig et al., 2013; Medical Research Council, 2000). In the first phase, literature reviews in combination with interviews with patients and healthcare professionals were conducted to decide the content of the app (Blomberg et al., 2016;

Gustavell et al., 2017). In the second phase feasibility studies were made to test Interaktor (Sundberg et al., 2015; Gustavell, Langius-Eklöf, et al., 2019). Finally, in the third phase, were randomized controlled trials (RCTs) to evaluate the effectiveness of Interaktor (Langius-Eklöf, Crafoord, et al., 2017).

Long-term Implementation

Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term

Definitive RCT

Compare a fully-defined intervention to an appropriate alternative using a protocol that is theoretically-defensible, reproducible and adequately controlled, in a study with appropriate statistical power

Exploratory Trial

Describe the constant and variable components of a replicable intervention AND a feasible protocol for comparing the intervention to an appropriate alternative

Modelling

Identify the components of the intervention, and the underlying mechanisms by which they will influence outcomes to provide evidence that you can predict how they relate to and interact with each other

Theory

Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues

| Pre-clinical | Phase I | Phase II | Phase III | Phase IV |

Continuum of increasing evidence

Figure 2. Description over the phases of the MRC framework. From *A framework for development and evaluation of RCTs for complex interventions to improve health* by Medical Research Council, 2000, (https://mrc.ukri.org/documents/pdf/rcts-for-complex-interventions-to-improve-health/). CC BY 2.0.

Interaktor has been tested in different samples and settings such as in patients with prostate cancer undergoing radiotherapy (Hälleberg-Nyman et al., 2017; Langius-Eklöf, Christiansen, et al., 2017; Sundberg et al., 2015; Sundberg et al., 2017), pancreatic cancer after surgery (Gustavell, Sundberg, et al., 2019; Gustavell et al., 2020) and in older persons receiving home-based healthcare (Göransson et al., 2018; Göransson et al., 2020).

3 RATIONALE

Patients with breast cancer undergoing chemotherapy usually perceive several distressing treatment related symptoms over a long period and often report unmet supportive care needs in the management of them. As most patients are treated on an outpatient basis, it is necessary for the patients to manage symptoms at home. If these symptoms are not properly managed it may result in impaired well-being and reduced quality of life as well as poor treatment outcomes if the treatment for example must be delayed or interrupted. The contact nurse has the responsibility to promote patients' health during treatment. Therefore, it is imperative to ensure that the patients' symptoms and supportive care needs are identified, assessed, and managed regularly in a timely manner, which requires a well-functioning communication between the patients and the contact nurse. There is a clear increase in patients receiving NACT and new treatments and combinations are constantly being developed, which means that the support for the patients must also be adapted to this development. There are studies of nursing interventions for supporting patients with breast cancer during treatment, but many have different methodological weaknesses such as small sample sizes and poor study designs. Moreover, studies regarding patients' perceptions of symptoms and related supportive care needs during NACT are few, which may reflect a lack of support services for this population.

Promising results of, for example, improved symptoms, quality of life and increased interaction with healthcare professionals have been seen in patients with cancer who have used eHealth as a way of reporting their symptoms to the healthcare professionals. It is reasonable to believe that patients undergoing NACT may benefit from using mHealth as support for appropriate and timely care and this needs to be investigated further.

4 OVERALL AND SPECIFIC AIMS

The overall aim of the thesis is to evaluate how an interactive app for reporting and managing symptoms provides supportive care in patients with breast cancer during neoadjuvant chemotherapy.

The thesis is based on three studies with the following aims:

Study I

The aim was to evaluate whether the use of the interactive app Interaktor improves patients' levels of symptom burden and health-related quality of life during neoadjuvant chemotherapy for breast cancer.

Study II

The aim was to describe engagement with the Interaktor app among patients with breast cancer during their treatment.

Study III

The aim was to describe patients' perceptions of care with or without the support of an interactive app during neoadjuvant chemotherapy for breast cancer.

5 METHODS

5.1 Design

The design for this thesis originates from one randomized controlled trial (RCT) including both quantitative and qualitative approaches. The first study is experimental, where effects of the intervention are assessed and evaluated. The second study involves both a quantitative and qualitative approach to describe the patients' engagement in the intervention. The third study has a qualitative approach of patients' perceptions of care and use of the intervention. An overview of the included studies, samples, and the methods used for data collection and analyses are presented in Table 2.

Table 2. Overview of included studies in the thesis.			
Study	**Sample**	**Data collection and outcomes**	**Data analysis**
I	Patients with breast cancer undergoing NACT (n=149) - Intervention group n = 74 - Control group n = 75	Sociodemographic and clinical data MSAS EORTC QLQ-C30 Logged data from app usage	Descriptive statistics Student's t test Chi-square test Fischer's exact test ANCOVA
II	Patients with breast cancer undergoing NACT (n=74) [Patients with prostate cancer (n=75)*]	Sociodemographic and clinical data Logged data from app usage Structured individual interviews	Descriptive statistics Mann-Whitney U test Chi-square test Fischer's exact test Multiple regression analysis Conventional content analysis
III	Patients with breast cancer undergoing NACT (n=40) - Intervention group n = 21 - Control group n = 19	Sociodemographic and clinical data Semi-structured individual interviews	Descriptive statistics Thematic analysis
RCT=Randomized controlled trial; MSAS=Memorial Symptom Assessment Scale; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire; ANCOVA = Analysis of covariance * = Population is not included in this thesis			

5.2 Interaktor – Breast cancer – NACT version

The content of the app for patients with breast cancer during NACT needed to capture symptoms important to patients and healthcare professionals. This version of Interaktor was developed in two phases. In the first phase, a review of literature was conducted regarding current research and prevailing clinical guidelines concerning symptoms, symptom management and self-care advice associated to breast cancer and NACT, as well as discussions with the healthcare professionals at the clinics. In the second phase, the app was pilot tested during April 2015 in eight patients and interviews were conducted with both patients and healthcare professionals for optimizing the app and web interface before start

of the RCT. The optimization concerned adjustments of alerts levels, changes and corrections of texts for some self-care advice, addition of self-care advice, adjustments in the web interface to make the patients reports more manageable. An illustration of screenshots from the patient view in the final version of the app is presented in Figure 3.
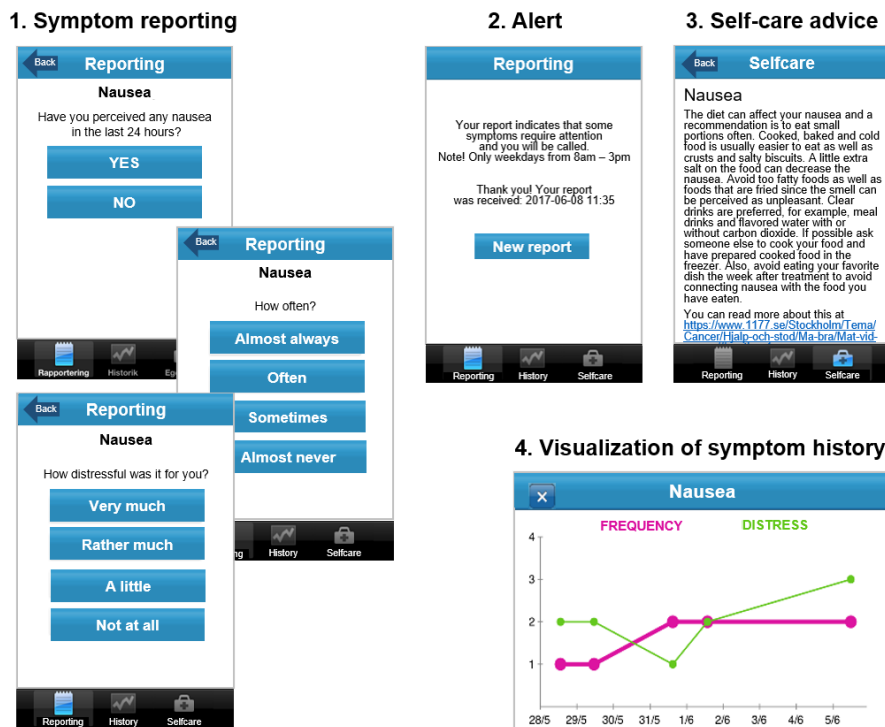
Figure 3. Screenshots of the Interaktor app adapted for patients with breast cancer undergoing NACT.

5.2.1 Symptom reporting

The symptom reporting questions are inspired by a standardized questionnaire assessing different dimensions of symptoms perceived by patients undergoing treatment for cancer and they address prevalence, frequency and distress level of symptoms perceived during the last day (Portenoy et al., 1994). For example, "Have you perceived nausea in the last 24 hours?" If the answer is "yes", the patient is asked about how often the symptom is prevalent by rating the frequency (almost always, often, sometimes and almost never) followed by how distressing the symptom is by rating distress level (very much, rather much, a little and not at all). The reported symptoms are immediately transferred via a secure server approved by the Swedish Data Protection Authority, to a linked web interface where the contact nurse can monitor the patient's reports in real time. Reporting in the app is supposed to be made at least once a day with no limits in the number of submitted

reports. If a report has not been submitted before 2 p.m., a notification is sent out to remind the patient to report.

The app contains assessment of 14 self-reported symptoms commonly prevalent during chemotherapy such as fever, breathing difficulties, pain in the body, numbness/tingling in hands and feet, nausea, vomiting, diarrhea, constipation, oral problems, depression, anxiety/worry, fatigue, sleeping difficulties, and swelling/pain/redness in the arm (related to the peripherally inserted central catheter line for chemotherapy administration). Furthermore, a free text message question "Other symptoms or concerns to report?" is included. The symptoms fever and pain/swelling/redness in the arm are only assessed by reporting prevalence. The symptoms constipation, oral problems, depression, anxiety/worry, and sleeping difficulties are only assessed by reporting distress level.

5.2.2 Alerts

The alerts in the risk assessment model are triggered depending on how the symptom is reported by the patient according to level of prevalence, frequency, and distress. All alerts are triggered after a report. Symptoms and their levels set to generate alerts in this version are shown in Table 3. There are two kinds of alerts, yellow and red. Yellow alerts are sent when symptoms are less severe and require a contact nurse to contact the patient during the day, and red alerts are sent in cases of greater severity, and require contact within one hour since this can mean a potential risk to the patient's health and wellbeing. The alerts are sent to a mobile phone at the clinic by text message (SMS), which leads to a contact nurse contacting the patient to discuss the symptom and further actions. The alerted symptom for each patient can be viewed in the web interface as well as being documented regarding the actions taken after an alert. The symptoms numbness/tingling in hands and feet, fatigue and sleeping difficulties are not set to trigger alerts. Often these symptoms are perceived frequently over a long period and could therefore lead to triggering alerts with each submitted report. Moreover, even though those symptoms can be perceived as distressful by the patients, they are not considered to pose an immediate risk to their health.

Symptom	Rated as		Type of alert

Table 3. The risk assessment model for symptoms set to generate alerts in the version of Interaktor for patients undergoing NACT for breast cancer.

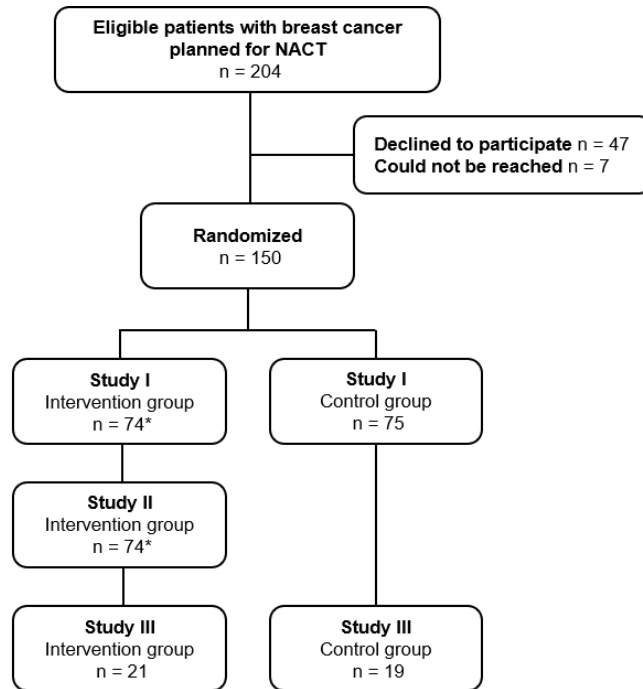| Symptom	Rated as		Type of alert
Fever	Occurrence	"Yes"	Red
Breathing difficulties	Frequency	"Often"	Yellow
	Frequency	"Almost always"	Red
Pain in the body	Frequency	"Almost always"	Yellow
Numbness/tingling in hands and feet	N/A		N/A
Nausea	Frequency	"Often"	Yellow
	Frequency	"Almost always"	Red
Vomiting	Frequency	"Often"	Yellow
	Frequency	"Almost always"	Red
Diarrhea	Frequency	"Almost always"	Yellow
Constipation	Distress	"Very much"	Yellow
Oral problems	Distress	"Rather much"	Yellow
Depression	Distress	"Very much"	Yellow
Anxiety/worry	Distress	"Very much"	Yellow
Fatigue	N/A		N/A
Sleeping difficulties	N/A		N/A
Swelling/pain/redness in the arm	Occurrence	"Yes"	Yellow

N/A = Not applicable means that no alert is triggered for the symptom.

5.2.3 Self-care advice and symptom history graphs

In the app, the patient has continuous access to 17 evidence-based self-care advice, as well as links to relevant websites with information related to assessed symptoms and other areas of concern. If an alert is triggered, a notification suggests to the patient to read related self-care advice. Moreover, the patient has the possibility to monitor own reported symptom history over time in graphs (Figure 3).

5.3 Setting and sample (Studies I – III)

In Stockholm region, investigation and treatment of breast cancer is performed at three breast centers: Karolinska University Hospital, Södersjukhuset and Capio St. Göran Hospital. The breast centers focus on the patient's path through the care from screening and diagnostics, through treatment to rehabilitation and follow-up (Regional Cancer Center Stockholm-Gotland, 2018). Recruitment and inclusion of the patients were performed at the oncological departments at Karolinska University Hospital and Södersjukhuset.

Figure 4. Samples in respective studies.

In **Study I**, the sample size was calculated from the results of a previous study on patients with prostate cancer (Sundberg et al., 2017) as there were no data in this population. With an effect size (Cohen's *d*) difference of 0.54 at the end of treatment in the primary outcome of symptom burden with 90% power at $P < 0.05$, 71 patients in each group were estimated in this study. Between June 2015 and March 2017, 204 patients newly diagnosed with breast cancer and planned for NACT were found to be eligible when screened through the medical appointment lists. Inclusion criteria were patients aged over 18 years, diagnosed with non-metastatic breast cancer and able to read and understand Swedish. Exclusion criteria were patients with a documented cognitive dysfunction. When asked about participation, 47 patients declined, and seven patients could not be reached. In total, 150 patients were consecutively included for randomization in the study. The patients were equally randomized into an intervention group or a control group. One patient in the intervention group was excluded after randomization and introduction to the app due to a change of treatment to primary surgery instead of NACT. The final sample therefore consisted of 74 patients who received the intervention in combination with standard care and 75 patients who received standard care alone (control group) (Figure 4).

Study II includes 74 patients from the intervention group who used the app. Of those 73 patients were interviewed, as one patient declined to participate in the telephone interview. The other included sample was patients from the intervention group (n = 75) of a similar RCT

on patients with locally advanced prostate cancer during treatment with radiotherapy. The two RCTs were conducted simultaneously, however, this thesis only reports on the sample consisting of patients with breast cancer undergoing NACT.

Study III includes 21 patients from the intervention group and 19 from the control group. Initially, a consecutive sampling strategy with an equal number of patients from both the intervention group and the control group at the two hospitals was adopted in the first 20 patients. To capture a range of patients' characteristics such as age at inclusion, residential area, marital status, highest education level, occupation and treatment duration in weeks, a strategic sampling was then used in the remaining 20 patients from both groups at the hospitals. Four patients declined to participate in the face-to-face interviews (intervention group n = 2 and control group = 2).

5.4 Standard care

In Sweden, all patients diagnosed with breast cancer are discussed at a multidisciplinary conference (MDC). During an MDC, various professions responsible for the patients' care are gathered to discuss appropriate treatment to gain best treatment results (Confederation of Regional Cancer Centres in Sweden, 2020b).

Patients who have been recommended NACT during an MDC have their initial visit with a physician at the oncology clinics. According to a standardized care process for breast cancer, NACT starts approximately two weeks after the patients are diagnosed. During the treatment period, the patients have visits with the physician before each chemotherapy treatment to assess the patients' health status and the tumor response to the treatment. Most patients undergoing chemotherapy for breast cancer are treated on an outpatient basis, which means that they receive their treatment at the oncology clinic and then return home between treatments (Confederation of Regional Cancer Centres in Sweden, 2020b).

5.4.1 Contact nurse

According to the National Cancer Strategy for the Future (The Swedish Government Official Reports, 2009), it has been decided that all patients diagnosed with cancer shall be assigned a contact nurse within the clinic where the care takes place. According to Confederation of Regional Cancer Centres in Sweden, 2020b, the purpose of the contact nurse is to guide and support the patients through investigation, treatment, and rehabilitation, to improve both information and communication between the patients and healthcare professionals (Confederation of Regional Cancer Centres in Sweden, 2020b). Before the patients started NACT, they were assigned a contact nurse with whom the patients had a visit either directly after the initial visit with the physician or booked a couple of days after the consultation with the physician, depending on the routines at the respective clinic. During these visits to the contact nurse the patients were given verbal and written information about NACT, related symptoms and how to manage them, practical information such as forthcoming planning and

appointments to the physician and treatments, information about the peripherally inserted central catheter line, where to get a wig, sickness payment, healthcare journeys and psychosocial contact. The patients were also offered a guided tour to orientate themselves better at the clinic. Contact information was given to all patients where to call during all hours of the day and to contact the emergency department in case of severe symptoms related to the treatment. If the patients had questions or other concerns related to the treatment, they were encouraged to call their contact nurse at the clinic during working hours on weekdays (8 a.m. to 4 p.m.) or recommended to use an online eHealth system "1177 Vårdguiden", offering different services for information, advice or contact with healthcare (Confederation of Regional Cancer Centres in Sweden, 2020b).

5.5 Procedure (Studies I – III)

During the patients' first visit at the oncology clinics, they received written information about the study from the assigned oncology contact nurse or physician. The patients were then contacted by the researcher and asked about participation. For patients who agreed to participate, a meeting was arranged with the researcher before starting NACT. During this meeting, the patients filled in informed consent and a baseline questionnaire. Subsequently, randomization was performed by sequentially drawn opaque sealed envelopes containing a card with the treatment allocation. The envelopes were opened in front of the patient. Prior to the randomization process, the envelopes had been shuffled by an independent individual. Depending on which group the patients were randomized to, more detailed study information was given to the patient. Both groups of patients received standard care and only the intervention group reported in the app (Figure 5).
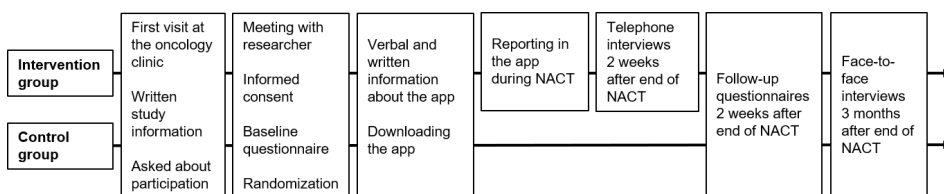
Figure 5. Flowchart of the procedure for study I-III.

The patients in the intervention group were individually informed how to use Interaktor both verbally and in writing. Patients who had their own access to a smartphone or tablet got help to download the app on their device and received an individual login for access to the content of the app. Two patients borrowed a smartphone from the research group to use during the study period. The patients were shown how to report symptoms in the app and were shown the self-care advice and the graphs of previous reports. A detailed written manual with illustrations on how to use the app was given to the patients to take home, as

well as contact information to the researcher in case of questions or concerns about the app and the study. The patients were instructed to submit a report at least once a day on weekdays starting on their first day of NACT and continuing until two weeks after end of NACT. Total reporting time was approximately 18 weeks. Furthermore, patients were carefully informed that the contact nurses at the clinic would monitor and respond to alerts triggered during working hours (8 a.m. to 4 p.m.) on weekdays and in case of an alert they would only be contacted during these hours. If emergency healthcare attention was needed outside these hours, the patients were instructed to contact the clinic according to standard care procedure. To be able to monitor and manage the patients reports and alerts, the contact nurses at the clinics received brief training on how to use the connected web interface before the RCT started. This training consisted of an individual overview with each contact nurse where they were provided verbal and written instructions on how to use the web interface as well as practical exercises on fictitious patients.

All patients were informed about the respective follow-up procedure according to the group they were allocated to. After the end of reporting, telephone interviews were conducted with the patients in the intervention group. Further, questionnaires to be filled in two weeks after end of NACT in both the intervention and control group as well as individual face-to-face interviews with a sample of patients from both the intervention and control group conducted three months after end of NACT. When the patients agreed to take part in the RCT, they had been informed they could later be contacted and asked to participate in interviews.

As the study was ongoing, NACT occasionally had to be interrupted for some patients. This was due to several reasons such as no tumor response during treatment (intervention group n = 2, control group n = 3), or too severe symptoms to continue the treatment (intervention group n = 5, control group n = 3). In these cases, surgery was performed earlier than planned. If it was detected that patients' disease had spread, this led to a switch of treatment to other chemotherapy agents or anti-hormonal treatment. This was detected in six patients (intervention group n = 2, control group n = 4) after cycle two to six depending on chemotherapy regimen. The study procedure during these circumstances was that patients who had surgery performed earlier reported in the app until the day before surgery (intervention group) and had the follow up questionnaire sent out according to original planning (intervention and control group). Patients with detected spread of disease reported in the app (intervention group) and had the follow-up questionnaire sent out according to the original planning (intervention and control group), thus two weeks after when it was planned that the NACT would end.

5.6 Data collection (Studies I – III)

The overall project includes different sets of data: sociodemographic and clinical data of included patients, outcomes concerning symptoms and health-related quality of life, logged

data on the patients' app usage and individual interviews concerning perceptions of using the app as well as perceptions of care with or without using the app.

Sociodemographic data including age, residential area, marital status, education level and occupation was obtained from the baseline questionnaires. Clinical data concerning menstruation status, tumor characteristics such as histologic grade of the tumor (Elston-Ellis), human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) status, proliferation rate (Ki-67), type of chemotherapy regimen, treatment duration in weeks, completion of planned cycles of NACT and reasons for early treatment discontinuation, were obtained from the electronic medical records. Any medical conditions of each patient were also collected at baseline from the electronic medical records to calculate comorbidity score using Charlson Comorbidity Index (CCI). Comorbidity score predicts mortality in patients with a range of different comorbidities. The CCI encompasses 19 medical conditions related to heart, liver, kidney and lung disease, cerebrovascular disease, dementia, diabetes, malignancies, and AIDS. Each condition has a score based on a relative risk of death within a year. The scores are totaled to yield the comorbidity score, with a range between 0 and 37. A higher value corresponds to greater comorbidity (Charlson et al., 1987).

In **Study I**, symptoms were assessed through self-reported questionnaires at baseline before randomization, and two weeks after end of NACT by using the Swedish version of The Memorial Symptom Assessment Scale (MSAS) (Browall et al., 2013), which was developed to measure the multidimensional perception of 32 common cancer-related symptoms in oncology patients (Portenoy et al., 1994). Twenty-four symptoms assess prevalence (if a symptom is present or not), frequency (how often it is present), severity (how severe the symptom is perceived) and distress (how bothersome the symptom is perceived). Eight symptoms assess only prevalence, severity, and distress. Each symptom is rated as being present (0) or absent (1) during the past week. If a symptom is present, frequency and severity are rated on a four-point rating scale from 1 = rarely to 4 = almost constantly and distress on a five-point rating scale from 0 = not at all to 4 = very much. Higher scores indicate greater frequency, more severity and higher distress. The MSAS also features four subscales: Global Distress Index (MSAS-GDI), which measures overall symptom distress, includes the average of the frequency of four psychological symptoms (feeling sad, worrying, feeling irritable and feeling nervous) and the distress of six physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation and dry mouth). The Physical Symptom Subscale (MSAS-PHYS), which measures physical symptoms, includes the average of the frequency, severity and distress of 12 symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness). The Psychological Symptom Subscale (MSAS-PSYCH), which measures psychological symptoms includes the average of the frequency, severity and distress of six symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable and difficulty concentrating). Total MSAS score (TMSAS), which also measures overall symptom distress, includes the

average of the symptom scores of all 32 items including frequency, severity and distress. The MSAS has been widely used in clinical trials to assess symptoms and is therefore well-validated and reliable (Browall et al., 2013; Portenoy et al., 1994). To ensure reliability, internal consistency was measured for all subscales by using Cronbach's reliability coefficient α. All subscales showed a Cronbach's alpha of > 0.80 at baseline and two weeks after treatment completion, which was considered as acceptable (Field, 2017).

Health-related quality of life was assessed through self-reported questionnaires at baseline before randomization, and two weeks after end of NACT by using the Swedish version of The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (version 3.0), which measures health-related quality of life during the past week (Aronson et al., 1993). The questionnaire includes 30 items, where 28 of them have four response alternatives: not at all, a little, quite a bit and very much. Two (2) of the items have seven response alternatives from very poor to excellent. Furthermore, the 30 items are divided into one global health status scale/quality of life, five functional scales exploring physical, role, emotional, cognitive and social functioning, as well as eight symptom scales assessing fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea and one item measuring financial impact. A high score in the global health and functional scales represents a high level of health-related quality of life and functioning, whereas a high score in each of the item and symptom scales represents high levels of symptoms or problems (Aronson et al., 1993). This instrument is widely used, well validated and has shown good reliability for assessing health-related quality of life in patients with cancer (Aronson et a., 1993; Sitlinger & Zafar, 2018). Internal consistency was measured for all subscales by using Cronbach's reliability coefficient α. All scales showed a Cronbach's alpha of > 0.72 at baseline and two weeks after treatment completion, which was considered as acceptable (Field, 2017), except for nausea/vomiting at baseline (α = 0.47) and after treatment completion (α = 0.61).

For **Studies I** and **II**, logged data was collected through app usage and included the patients' submitted reports, symptoms reported, triggered alerts, views of self-care advice, and free text messages sent. The logged data was hosted on a secure server and was accessible and extracted in an encrypted Microsoft Excel 2013 file. At the time of this RCT, it was not possible to log data on clicked links or viewed graphs for later retrieval.

In **Study II**, individual telephone interviews were conducted with the patients in the intervention group after their final report in Interaktor, about perceptions of using the app. A semi-structured interview guide was used focusing on patients' perceptions of usability and utility of using the app and its components. Questions such as "What was it like to report in the app?" and "How have you experienced that the technology has worked" were asked as well as questions specifically related to the components of the app such as "Have you used the self-care advice?" and "Have you used the graphs to follow your symptom history?" Follow-up questions were used to deepen the patients' responses. The telephone interviews were conducted between November 2015 and August 2017 and lasted between

10 and 20 minutes, during which notes of the answers were made in the template of the interview guide. All telephone interviews were conducted by the author of this thesis.

For **Study III**, individual face-to-face interviews were conducted three months after end of NACT with patients from both the intervention and the control group. The interviews took place in a secluded room at both oncology clinics and followed a semi-structured interview guide covering different aspects of patient participation such as the relationship between patient and the healthcare professionals, patients' information needs, self-care, and caretaking (Angel & Fredriksen, 2015; Frank, Fridlund, Baigi, et al., 2011). Examples of questions asked to the patients were "How did you perceive the contact (care relationship) between you and the healthcare professionals during the treatment period?", "Do you feel that you have received enough information regarding your care and treatment?" and "How have you experienced your encounters with the healthcare professionals?". In addition, the patients in the intervention group were asked about the significance of using the app during the treatment. The patients were requested to speak as freely as possible and depending on the extent of their answers, follow-up questions were used to get more in-depth responses from the patients. The interviews were audio-recorded and lasted between 14 and 61 minutes, with a median of 27 minutes. All interviews were conducted between January 2016 and August 2017 and the majority of them were conducted by the author of this thesis.

5.7 Data analyses (Studies I – III)

The statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 24, Windows version. A p-value < 0.05 was considered as statistically significant in all analyses.

In **Studies I** and **II**, descriptive statistics were used to analyze the sociodemographic and clinical data. Between-group analyses were performed using Chi-square and Fisher's exact tests for categorical variables and Student's t-test for continuous variables. For continuous variables that were not normally distributed (**Study II**), Mann-Whitney U test was used.

In **Study I**, the items in the MSAS questionnaire were processed according to Portenoy et al. (1994). In the initial step, a score (MSAS score) for each symptom is calculated. If a symptom is absent, the score for that is 0. If a symptom is present, the score is 1. To determine the MSAS score for each present symptom, the average of the scores on frequency, severity and distress for the symptom is calculated. This initial calculation forms the basis for further calculation of the MSAS subscales. Percentages were calculated of the prevalence of the symptoms between the intervention group and control group at baseline and two weeks after end of NACT by using Chi-square test. When analyzing health-related quality of life, the items in EORTC QLQ-C30 were processed according to the EORTC QLQ-C30 scoring manual (Fayers et al., 2001). The principle for scoring in all scales is the same. Initially, the average of the items in the respective scale is calculated, which is the

raw score. Thereafter the raw scores are linearly transformed so that the scores range from 0 to 100.

At baseline there were no questionnaires or single items missing in MSAS and EORTC QLQ-C30. At two weeks after end of NACT, some patients were lost to follow-up in both groups. Five questionnaires were missing in the intervention group (6.8%) and four questionnaires in the control group (5.3%). To handle missing data, a modified intention-to-treat (ITT) approach was used, which allows exclusion of randomized patients if it is justified (Abraha & Montedori, 2010; Gupta et al., 2011; Montedori et al., 2011; Polit & Gillespie, 2010). This was the case in this RCT, since one patient was excluded after being ineligible after randomization and therefore not included in the analyses. Missing values in MSAS and EORTC QLQ-C30 at two weeks after end of NACT were replaced with the baseline values using the baseline observation carried forward method (BOCF) (Liu-Seifert et al., 2010; Petroff, 2017). Complete case analyses were also performed for MSAS and EORTC QLQ-C30 to make the results from both approaches visible.

To assess between-group differences in MSAS and EORTC QLQ-C30, analysis of covariance (ANCOVA) was used adjusting for baseline values.

To calculate the magnitude of the effect between the two groups, Cohens d effect size (ES) was calculated by subtracting the group means and dividing the result by the pooled standard deviation (intervention group mean – control group mean/SD$_{Pooled}$). A value of $0.2 – 0.5$ is often interpreted as small effect, $0.5 – 0.8$ as medium effect and ≥ 0.8 as large effect (Cohen, 1988; Sullivan & Feinn, 2012).

In **Studies I** and **II**, the logged data of the patients' app usage during treatment concerning submitted reports, triggered alerts, views on self-care advice, and free text messages sent, were analyzed with descriptive statistics using Microsoft Excel 2013. Adherence to report was calculated as the number of weekdays a patient submitted a report (excluding multiple daily reports) divided by the number of weekdays a patient was intended to report. Adherence was presented as a mean percentage for the whole group.

To investigate whether age, comorbidity, marital status, and education level predicted usage variables of the app such as adherence to daily reporting as intended, total number of alerts triggered, total views on self-care advice, and total number of free text messages sent, multiple regression analysis was conducted. Marital status was dichotomized and coded as single/living apart = 0 and married/cohabiting = 1. Education level was dichotomized and coded as high school/secondary school = 0 and college/university = 1. Since all usage variables were positively skewed, these were normalized using natural log transformation (log^e) (Altman, 1990).

The telephone interviews concerning perceptions of using the app were analyzed with an inductive approach using conventional content analysis (Hsieh & Shannon, 2005). First, all the interview notes were read several times to get to know the entire data set. A data sheet

was compiled with the patients' answers. The data sheet was reviewed repeatedly, and systematically coded. Thereafter, the codes were sorted based on similarity into subcategories and combined based on content into overarching categories. During the analytical process, the authors of the study continuously discussed and reviewed the analysis to come to a consensus.

In **Study III**, the face-to face interviews concerning patients' perceptions of care with or without using Interaktor were analyzed with an inductive approach using thematic analysis as described by Braun and Clarke (2006). First, the recorded interviews were transcribed verbatim and the texts were read through several times to become familiar with the data and the whole. Initially each group was analyzed separately, starting with the intervention group, followed by the control group. Statements from the patients regarding perceptions of care and the app were systematically coded throughout the entire dataset and transferred into a coding sheet. A code could consist of a few words or a whole sentence. After the statements from the two groups had been coded, the codes were then discussed between the authors of the study. Since there were mainly similarities in the statements between the two groups, the codes were merged into one coding sheet and tagged with an identification so that they could be distinguished according to group. Analysis continued by sorting and putting together similar codes from both groups and themes were created. The codes included in each theme were then reviewed to see if the theme worked well in relation to included codes.

6 ETHICAL CONSIDERATIONS

In this thesis, all studies were carried out according to the ethical principles of the Helsinki Declaration (World Medical Association, 2013) as well as The Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460) (The Swedish Riksdag, 2003). Central in the Helsinki Declaration is that there must be a balance between the benefits of the research and the protection of the participants. Further, the participants' right to autonomy, justice and informed consent must be ensured. In RCTs, it is also of importance that the intended participants are informed about the procedure and its purpose, as well as understand what it means to be randomized to an intervention or control group. The Act concerning the Ethical Review of Research Involving Humans involves managing personal data considered to be sensitive information. Furthermore, there are several ethical considerations that need to be made when using mHealth in research, such as the large volumes of data from the patients, which need to be stored and managed so as to ensure anonymity and confidentiality. Access to mHealth, regardless of socioeconomic status or physical or mental impairments, and evaluation of safety and effectiveness are also important considerations (Botrugno, 2019; Carter et al., 2015). All studies included in this thesis have also undergone ethical examination and were approved by The Regional Ethical Review Board of Stockholm, Sweden (Reg.no: 2013/1652-31/2) and (Reg.no: 201712519-32).

In Studies I – III, the patients received written information about the study in connection with their first visit to the oncology clinic. A couple of days later, the patient was contacted by a researcher who answered any questions about the study and asked if the patient wanted to participate. For patients who agreed to participate, a meeting was arranged prior to the start of NACT. At the meeting, the patients signed a written informed consent and were informed that participation was voluntary and that they could withdraw from the study at any time without specifying a reason, which would not influence the forthcoming care and treatment. Further specific verbal and written information was given to the patients depending on which group they were randomized into, such as how to use the app and what the follow-up meant in terms of questionnaires and interviews.

The patients were also informed that all collected data would be handled confidentially. To avoid potential threats to autonomy and integrity, the inclusion process and data collection were performed by researchers who were not involved in the patients' care. As the patients had been randomized, they were given a specific individual code. When analyses of the data were performed it was therefore not possible to determine which ratings or statements had been made by a specific patient. Also, the results are presented so that individual patients cannot be identified. All collected data was stored and accessible only to researchers involved in the RCT. The list of the codes was stored separately from the other collected data to prevent the identity of the patients from being revealed.

Patients who were randomized to use the app and did not have access to a smartphone or tablet could borrow such a device throughout the reporting period. Moreover, the patients

who used the app were provided an individual login with username and password to get access to the content in the app, and the contact nurses who monitored the reports received a username and password to get access to the web interface. Besides app usage, the patients' names and personal identity number were registered in the web interface to ensure easy access for the contact nurses to the patients' medical records. Involved researchers had access to the web interface for registering new patients and for monitoring at regular intervals to ensure that alerts had been responded to. Appointed staff at Health Navigator (the company who assisted with the development of Interaktor) also had access to the web interface for technical support. The data from the use of the app and web interface was logged and stored on a secure server hosted by Health Navigator. The server was approved by The Swedish Data Protection Authority. To prevent personal information from the logged data being disclosed to unauthorized persons, data files were encrypted when sent from Health Navigator to the researchers for data management.

It posed no risks for the patients to participate in the RCT. All patients received standard care and the patients who were randomized into the intervention group used the app as a complement to standard care. The patients were instructed to report during office hours and were carefully informed who to contact if any severe symptoms or problems related to the treatment occurred outside these hours. The patients were also encouraged to contact the researcher in case of questions or concerns regarding the study. There was also knowledge among the researchers to refer the patients' further if such needs arose, for example if a researcher was contacted by the patients in case of severe symptoms or need for contact with the healthcare professionals.

Research such as this RCT involves patients who are in a vulnerable situation. Not only do they have a potentially life-threatening illness. They may also experience multiple distressing symptoms and concerns related to both illness and treatment and at the same time struggle to make everyday life work. Therefore, it is fundamental that research is conducted in an ethical way. For example, when being interviewed about personal perceptions of the app and care, this can be sensitive and trigger unpleasant emotions and memories. There was an awareness about this as the researcher had extensive experience of working with this group of patients. It is also important to recognize that patients treated at larger oncological clinics at university hospitals are often asked to participate in several studies at the same time. This implies a risk that the patients become burdened with different studies because they feel obliged to participate in research as they might feel dependent on the healthcare professionals. Also, patients planned for NACT often start the treatment shortly after being diagnosed, which means they have limited time to think and make a decision to participate in the study. On the other hand, it would be unethical to not ask all eligible patients about participation. Therefore, the need for sufficient information regarding study participation is crucial to facilitate the patients' decision making.

7 RESULTS (STUDIES I – III)

This section contains a summary of the results from all three studies conducted in Phase III (Definitive RCT) in the MRC framework (Craig et al., 2013; Medical Research Council, 2000). More detailed results of each study are presented in the publications attached in the last section of this thesis.

7.1 Sociodemographic and clinical data (Study I)

In **Study I**, there were no statistically significant differences between the intervention group and the control group in sociodemographic and clinical data at baseline (Table 4). The average treatment duration of NACT in both groups was 15 weeks (Intervention group *SD* = 4.77, range = 3-34; Control group *SD* = 2.60, range = 3-26). Further, most of the patients completed NACT as planned (intervention group 88 % and control group 87%).

Table 4. Sociodemographic and clinical data at baseline (n = 149).

	Intervention group (n = 74)	Control group (n = 75)
Age at inclusion, years		
Mean (SD)	48 (10.6)	50 (11.6)
Range	27-73	30-77
Marital status, n (%)		
Married/Cohabiting	61 (82.4)	57 (76.0)
Living alone	13 (17.6)	18 (24.0)
Highest education level, n (%)		
University	50 (67.6)	44 (58.7)
Secondary school	18 (24.3)	25 (33.3)
Primary school	6 (8.1)	6 (8.0)
Occupation, n (%)		
Working	57 (77.0)	48 (64.0)
On sick leave	12 (16.2)	14 (18.7)
Retired/Unemployed	5 (6.8)	13 (17.3)
Type of chemotherapy and combinations, n (%)		
EC	3 (4.1)	1 (1.3)
EC + DOC or EC + weekly Paclitaxel or TAC	37 (50.0)	38 (50.7)
FEC + DOC or FEC + weekly Paclitaxel	9 (12.2)	13 (17.3)
Gemcitabine + Carboplatin	2 (2.7)	1 (1.3)
DOC or weekly Paclitaxel	11 (14.9)	14 (18.7)
DOC + Carboplatin	1 (1.4)	0 (0)
DOC + Trastuzumab Emtansine	2 (2.7)	2 (2.7)
Trastuzumab Emtansine	9 (12.2)	6 (8.0)

Abbreviations
EC = Epirubicin, Cyclophosphamide
DOC = Docetaxel
TAC = Docetaxel, Doxorubicin, Cyclophosphamide
FEC = Fluorouracil, Epirubicin, Cyclophosphamide

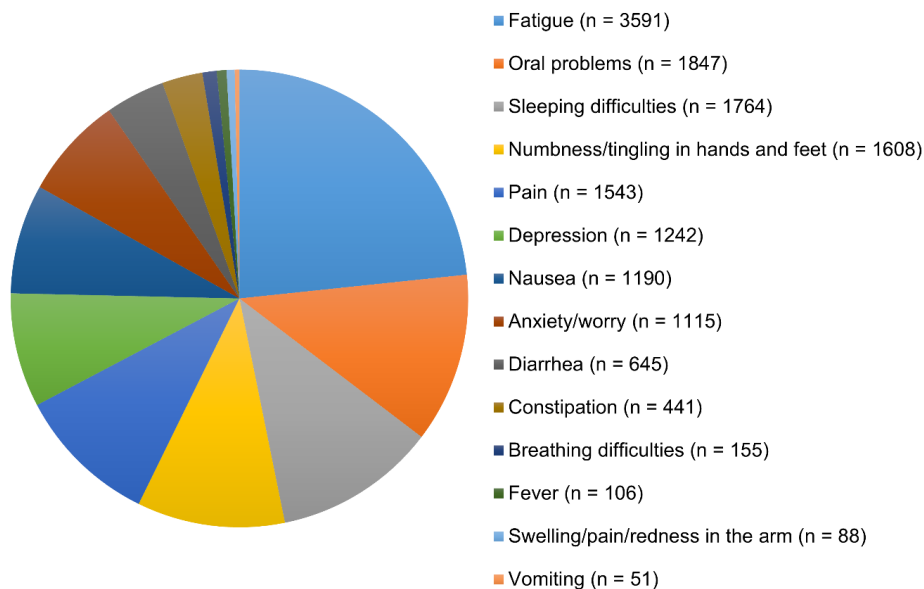## 7.2 Impact on symptoms and health-related quality of life (Study I)

Before start of NACT, the intervention group rated statistically significant higher prevalence of difficulty sleeping (p =.047) and lower prevalence of difficulty swallowing (p = .044) than the control group. In the MSAS subscales there were no statistically significant differences between the groups before start of NACT. At two weeks after end of NACT the intervention group rated statistically significant lower prevalence in nausea (p = .041), vomiting (p = .037), and feeling sad (p = .003) compared with the control group. In the subscales of MSAS, overall symptom distress (MSAS-GDI), was rated statistically significant lower in the intervention group (p = .004, d = 0.34) than in the control group. Regarding physical symptoms (MSAS-PHYS), the intervention group rated statistically significant lower levels (p = .031, d = 0.27) in comparison with the control group. Further, the intervention group rated statistically significant lower scores in the total MSAS (p = .033, d = 0.26) than the control group did. In the subscale measuring psychological symptoms (MSAS-PSYCH), there were no statistically significant differences between the groups.

There were no statistically significant differences between the intervention group and the control group in the EORTC QLQ-C30 at baseline. At two weeks after end of NACT, the intervention group rated statistically significant higher emotional functioning (p = .008, d = 0.30) than the control group. In the remaining four functional scales: physical, role, cognitive and social scale, there were no statistically significant differences between the groups. In the symptoms scales the intervention group rated statistically significant lower levels in nausea and vomiting (p = .007, d = 0.40), appetite loss (p = .027, d = 0.35), and constipation (p = .007, d = 0.43) in comparison with the control group.

7.3 Logged data from app usage (Studies II and III)

The patients used the app for a median of 106 days (range 22-183 days). The median adherence to report symptoms was 83% (**Study II**).

In **Study I**, the patients using the app reported a total number of 15386 different symptoms during the study period. Fatigue was the most reported symptom (n = 3591), followed by oral problems (n = 1847), and sleeping difficulties (n = 1764) (Figure 6). Each patient reported on average two prevalent symptoms per day.

- Fatigue (n = 3591)
- Oral problems (n = 1847)
- Sleeping difficulties (n = 1764)
- Numbness/tingling in hands and feet (n = 1608)
- Pain (n = 1543)
- Depression (n = 1242)
- Nausea (n = 1190)
- Anxiety/worry (n = 1115)
- Diarrhea (n = 645)
- Constipation (n = 441)
- Breathing difficulties (n = 155)
- Fever (n = 106)
- Swelling/pain/redness in the arm (n = 88)
- Vomiting (n = 51)

Figure 6. Distribution of the total number of reported symptoms during the study period (n = 15386).

In total, 71 out of 74 patients (96%) triggered at least one alert with a median of 7 alerts (range 1-210) during the study period. Of the triggered alerts 1094 (86%) were yellow and 182 (14%) were red.

All patients viewed the self-care advice in the app at least once with a median of 11 various self-care advice out of the 17 self-care advice available. The total number of views were 1075 of which 362 (34%) were made after the patients had been notified in the app with suggestions to read related self-care advice when an alert was triggered. The most common self-care advice viewed were related to oral problems (n=196), nausea (n=126) and pain (n=114) (Figure 7).
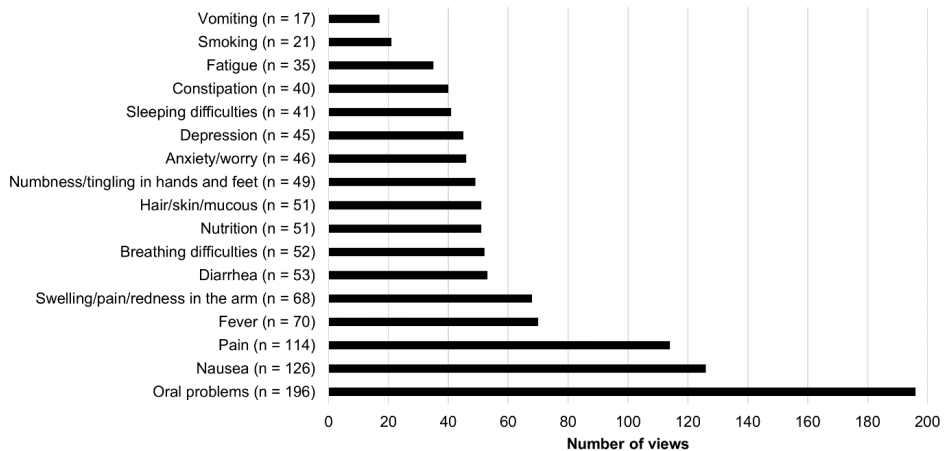
Figure 7. Distribution of the total number of self-care advice viewed during the study period (n = 1075).

The free text function was used by 93% of the patients and concerned symptoms which were not assessed in the app, requesting or declining contact, care-related information, and issues linked to the app or to reporting. The use of the function varied. Some patients wrote short messages, while others wrote long descriptions.

7.4 Predictors of app usage (Study II)

The multiple regression showed that none of the regression models in the analysis was statistically significant, meaning that patients characteristics age, comorbidity, marital status, and education level did not predict usage of the app (adherence to daily reporting as intended, total number of alerts, total views on self-care advice, and total number of free text messages sent). Only one single characteristic; higher age predicted a decreased total number of free text messages sent ($p = .040$)[*].

[*]Misprint in the published paper "Engagement in an interactive app for symptom self-management during treatment in patients with breast or prostate cancer: mixed methods study" (Study II).

## 7.5 Perceptions of using the Interaktor app (Study II)

The patients expressed that the app was easy to use with few technical problems during the study period and went quick to report in. The content in the app was considered by most of the patients as relevant. They described that the symptom assessment component included most of their perceived symptoms during treatment and reporting went quick. Some patients lacked symptoms to report such as headache and the symptom pain was considered as too broad. The free text component was appreciated and perceived as useful to add such

symptoms or other concerns to the contact nurse. There were discrepancies in how patients perceived to report in the app on a daily basis. Many patients described symptom reporting as a way of keeping a diary, which made them reflect on their wellbeing as well as becoming aware of symptoms. Most patients considered reporting as more necessary during days when they felt ill, however it could sometimes be stressful. A few patients described that reporting in the app during days when they felt well was a negative reminder of their illness. During these days it could also be difficult to remember to report and therefore the reminder notification was appreciated. Using the graphs also enabled self-monitoring of reported symptoms. Patients perceived the graphs as useful for comparing symptoms and detecting patterns in symptoms over time, which facilitated planning of activities during days when they felt well. The graphs also made it visible that many days were trouble-free.

Most patients who used the app described it as a facilitator for support during NACT. Reporting symptoms and in case of an alert being called by a contact nurse was perceived as having a continuous, close, and interactive contact with the contact nurse, which created feelings of being monitored, safe, acknowledged and cared for. It also decreased the need for patients to contact the clinic by themselves, where they had to search for the right number to call or be put on hold. However, there were some patients who expressed wishes that alerts were monitored and responded to around the clock, and several wanted the possibility to choose for themselves whether a contact nurse should call them or not. Other components described as supportive by most of the patients were the self-care advice and the links to websites. The self-care advice was considered valuable, applicable, and informative. Reading the advice gave the patients an idea of what symptoms were normal and what they could expect during NACT. It also gave information on how to perform self-care to relieve or manage symptoms, which allowed them to participate in their care. There were requests for more comprehensive information on psychological symptoms and dietary advice.

7.6 Patients' perceptions of care with or without using the Interaktor app (Study III)

The thematic analysis of the patients perceptions of care during NACT and the role of the Interaktor app resulted in four overarching themes: "The healthcare context", "Being a recipient of care", "Taking an active role as a patient", and "The value of the app" (Figure 8).
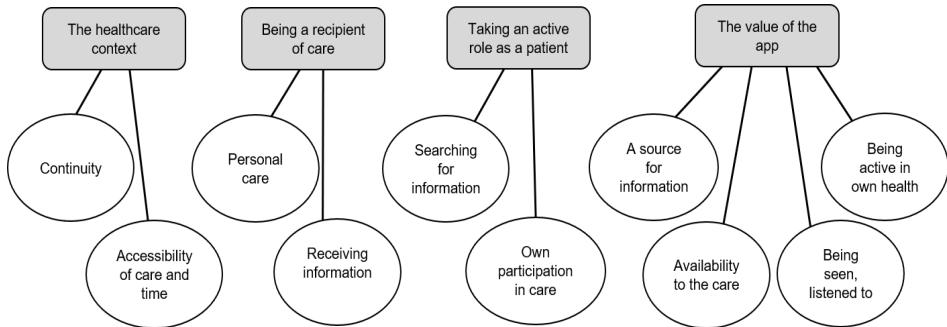
Figure 8. Illustration of themes and subthemes that emerged from the thematic analysis.

The patients expressed the contact nurse as valuable and supportive during treatment and as the reason for patients perceiving continuity. When there was a lack of continuity the patients described not knowing who their contact nurse was or having to meet too many different healthcare professionals, which created feelings of confusion and insecurity. Perceived accessibility was described by the patients by knowing who to contact if they needed and that it was easy to get in touch with the healthcare professionals. Receiving enough time during visits or over the telephone was also expressed. Some patients described that they had not received contact information to the healthcare professionals or that it was hard to get in touch with the healthcare professionals because of occasionally switched off telephone or that the contact nurse returned the patients' calls late or not at all. There were also patients who perceived not getting enough time during consultations with the healthcare professionals or having the opportunity to ask questions.

The patients described the atmosphere at the oncology clinics in several positive terms such as friendly and warm. Moreover, they perceived having a dialogue with the healthcare professionals where both parts could ask and answer questions as well as have discussions. Patients expressed they felt trust, safety and were encouraged, as the healthcare professionals were interested in their wellbeing, listened to them, and treated them with respect and empathy. A few negative experiences leading to feelings of being one of a crowd were described by patients such as coldness and disinterest among the healthcare professionals, not being taken seriously or having to remind the healthcare professionals repeatedly regarding booking appointments with a physician or for treatments or prescriptions of medicines. The patients perceived being satisfied with the information they

received about the treatment and related symptoms, self-care, and planning, making them prepared for the treatment. However, sometimes the information was either perceived as too extensive, which was hard to take in, or insufficient, leaving unanswered questions.

Patients described being active in searching for more information than they had been provided with by the healthcare professionals. Commonly the internet was used for that purpose. Moreover, patients described participating in their own care in different ways. The patients described being satisfied of being a passive receiver of care and trusted the healthcare professionals and accepted the treatment and planning since the highest priority was to get well. Patients who expressed having participated in their own care described this as performing self-care, being able to plan daily activities by having a treatment plan and discussing different matters regarding their care with the healthcare professionals. Occasionally participation in care was perceived by patients as difficult, especially since everything from diagnosis, treatment decision and planning to start of treatment happened so quickly.

The patients who used the app perceived it as an easy and accessible source of information during treatment. Normal and expected symptoms caused by the treatment were explained in the app and the patients expressed being able to follow the self-care advice to manage symptoms instead of contacting the contact nurse. Further, the information and the links in the app were considered as a good complement to the information provided by the healthcare professionals. Using the app was also perceived as a safe, easy, and convenient way to get in contact with the contact nurse by being contacted directly in the event of severe symptoms. The patients stated that using app led to feelings of being seen and listened to. When reporting symptoms, the patients shared the information about their health condition with the contact nurse who monitored their reports and responded in case of severe symptoms. The patients described that using the app enabled them to take actions in their own care, such as performing self-care when symptoms occurred so as to feel better. By reporting symptoms, the patients described being active and being given the opportunity to daily reflect on their health. By being conscious and aware of symptoms and their patterns, self-planning was facilitated, and patients discovered that many days were trouble-free, which patients perceived as positive and comforting.

8   DISCUSSION

8.1   Results discussion

The main finding in this thesis is that the patients received additional support for managing symptoms and awareness of their own health by using the Interaktor app for supportive care during treatment with NACT. The patients used the app as intended and described it as easy to use, enabling access and interaction with the contact nurse and participation in their own care.

8.1.1   Supportive cancer care by using Interaktor during neoadjuvant chemotherapy

During the time of the RCT in this thesis all patients with breast cancer who underwent NACT received structured standard care at the clinics, including information about the treatment and routine follow-up by the contact nurse and physician. The patients were satisfied overall with the care they received during NACT, regardless of whether they had used the app or not. The patients described being supported by the contact nurse, who played an important role in providing them with information about the treatment and how symptoms should be managed, as well as being a person who they could contact when needed, according to the National Cancer Strategy for the Future (The Swedish Government Official Reports, 2009). Nevertheless, it emerged that using the app gave additional valuable supportive care during the treatment in several ways, which perhaps further reinforced the patients' satisfaction with the care. This can explain why the patients in the intervention group rated a significantly lower prevalence in symptoms and symptom burden as well as showing significantly better emotional functioning in comparison to the control group two weeks after the end of NACT. Other studies of patients with prostate cancer during radiotherapy and patients with pancreatic cancer after surgery using Interaktor have shown similar results (Gustavell et al., 2020; Sundberg et al., 2017). It has previously been shown that emotional well-being can be supported by using mHealth (Dahlberg et al., 2018; Maguire et al., 2015). Symptoms in patients with lung cancer receiving radiotherapy were monitored while they were at home and they were either contacted or could contact the nurse by an app (Maguire et al., 2015). In the other study, patients were using an app for assessment of the quality of recovery after day surgery where they could request to be contacted by a nurse (Dahlberg et al., 2018). Moreover, it has been shown that patients with different cancer diagnoses had fewer visits to emergency departments, stayed on chemotherapy for a longer period and even increased survival (Basch et al., 2016; Denis et al., 2017).

The most significant reduced symptoms and concerns in the RCT were feeling sad, nausea, vomiting, appetite loss and constipation, which are all common and related to chemotherapy and often perceived as distressing (Browall et al., 2017; Ward Sullivan et al., 2017). The self-care advice for nausea was one of the most read pieces of advice and as previously suggested, it is very probable that it was useful for prevention and early

management of this symptom (Dranitsaris et al., 2017; Navari & Aapro, 2016). Reduced symptoms for patients during treatment are beneficial not only for their well-being and quality of life, but also for the clinical care such as compliance with the chemotherapy regimen for longer, which can improve treatment outcomes (Bouchard et al., 2018; Davis et al., 2018). It has been described that a key aspect in supportive care for breast cancer during treatment is identification and management of symptoms (Zdenkowski et al., 2016). The Interaktor app enables daily reporting of symptoms as well as the opportunity for patients to reflect on their well-being, which renders early identification of symptoms from both the patients and the health care professionals. There were different opinions among the patients as to whether daily reporting was necessary, depending on how severely the symptoms were perceived. It is understandable that patients might think that it is more necessary to report symptoms when feeling unwell. Reflections over one's own health are often made when feeling ill because the illness interferes with daily life (Ekberg, 2015). However, some patients stated the importance of highlighting days when they were feeling well, since this can become a positive reminder that there are days during the treatment which are trouble-free. Having the opportunity to visualize reported symptoms in graphs can enhance symptom awareness even more as the symptom patterns were visualized, which also facilitated the planning of activities.

Irrespective of whether they were using the app or not, patients expressed that the information they received about the treatment and how symptoms should be managed was sometimes hard to digest, because of the overload of information that had been provided on only a few occasions. Furthermore, it is known that patients treated with chemotherapy have difficulties in concentrating and remembering, which may inhibit their necessary understanding of the treatment (Ibrahim et al., 2019; Myers, 2012). The patients described that Interaktor provided them with easy access to additional information and self-care advice, which enabled them to read the information whenever they needed. It has been emphasized that supportive care requires relevant and accessible information to meet the informational needs the patients might have whenever they have them Droog et al. (2014), Fiszer et al. (2014), and Loibl and Lederer (2014).

The interviews revealed that the patients received support in performing self-care since the app gave them access to relevant advice for them to act on to obtain symptom relief. Moreover, it was comforting to be able to discuss self-care actions with their contact nurse. Digital solutions such as mHealth need to have an interactive function to facilitate communication between patients and healthcare professionals (Shaw et al., 2017) and having easy access to healthcare can provide timely supportive care (Hammer et al., 2019).

Encouraging patients to perform self-care can attain symptom control and influence quality of life in a positive direction. However, it has been concluded that many patients with conditions such as cancer need support to perform self-care (Hoffman, 2013). The essence of self-care for patients with breast cancer is to understand the information on how to perform it (Engqvist Boman, 2017). Moreover, to gain understanding, the relevance of the

information provided in a dialogue with the healthcare professionals is imperative. This is especially important in outpatient-based care when there is less access to support from the healthcare professionals (Engqvist Boman et al., 2018).

According to Swedish legislation, healthcare should as far as possible be designed and implemented in consultation with the patient. Further, if a patient participates by performing certain care and treatment actions, this must be based on the patient's own wishes and individual conditions (The Swedish Riksdag, 2014). The findings in this thesis show that patients from the whole group were sometimes content to be passive receivers of care. Rather, patients described their wish to get well and that this was prioritized, so that they trusted and accepted everything that had been decided and planned regarding treatment. When patients talked about taking an active role, it concerned searching for information, performing self-care and having discussions with the healthcare professionals. Descriptions from the patients using the app revealed that using the self-care advice to take their own actions in symptom management enhanced participation in their own care. Participation can be enhanced even further when the actions in symptom management are taken in collaboration with the healthcare professionals (Howell et al., 2017). In the present RCT patients described feeling like an active participant when being contacted by a nurse in the event of severe symptoms, which were then discussed. This led to feelings of being safe, seen and listened to. These results are consistent with the findings in studies of other versions of Interaktor, as well as in studies evaluating similar interventions (Gustavell et al., 2020; Göransson et al., 2018; Hälleberg-Nyman et al., 2017; Maguire et al., 2015; Weaver et al., 2014). According to Angel and Frederiksen (2015) participation must be based on the patients' individual needs and it has to be made clear when patients have to participate, if it is possible and when patients can participate in their own care. This is a challenge since there must be a balance between safety and legal parameters versus the patients' wishes, abilities and preferences to participate (Tobiano et al., 2015). For the patients who had used the app, it was obvious that using Interaktor allowed them to participate in their own care in different ways, which seems to have been supportive and improved the patients' health and well-being.

8.1.2 The importance of engagement in mHealth

The adherence of reporting symptoms in the app as intended was high, which is comparable with results from patients with prostate cancer using Interaktor during radiotherapy and patients with pancreatic cancer after surgery (Langius-Eklöf, Christiansen, et al., 2017; Gustavell, Sundberg, et al., 2019). These are positive findings since high levels of adherence in using mHealth have been shown to be associated with improved outcomes (Donkin et al., 2011). High adherence has also been reported in patients with various cancer diagnoses using mHealth to support their needs related to cancer and treatment (Richards et al., 2018). In contrast to these results it has been shown that patients with chronic conditions such as diabetes, epilepsy, obesity, and mental health problems using web-based interventions had an average adherence of 50% (Kelders et al., 2012). It has been shown

that social support and level of education influence the usage of web-based interventions, where high levels of social support and education are associated with an increase in engagement (Eysenbach, 2005; Perski et al., 2017; Ryan et al., 2018). In this thesis, a higher age of patients predicted a decrease in number of free text messages sent. However, it has been suggested by Rai et al. (2013) that demographic variables may be too broad to indicate usage motives for mHealth. To reach a high adherence an intervention needs to be meaningful and relevant to use in clinical care (Rose & Bezjak, 2009; Short et al., 2015). The notification sent out to remind the patients to report may have had a positive impact on adherence. Patients expressed the notification as being helpful in reminding them to report in the app. It is also important that the interventions are co-created with patients and healthcare professionals (Rose & Bezjak, 2009). By doing this, valuable experiences and needs are highlighted, and interventions can be developed to better suit the patient and improve engagement in the intervention (Boyd et al., 2012). During the development phase for the version of Interaktor in this thesis, the app was pilot tested during which both patients and healthcare professionals shared their suggestions to optimize the app.

All patients who were randomly selected to use Interaktor were given instructions and practiced reporting in the app on one supervised occasion. This is a strength and reflects the user friendliness of Interaktor. It has been argued that when implementing new systems such as mHealth, it is essential that the patients are provided with supervised training on several occasions to be comfortable in using them (Seto et al., 2012). However, in this RCT, the introduction of Interaktor seems to have been sufficient, considering the regular reporting and frequent use of the different components of the app as described previously and below.

Most of the patients who used Interaktor said it had been easy and convenient and was considered as an accessible source of information with negligible technical problems. This is emphasized by Dennison et al. (2013) showing that by using mHealth, the support becomes more accessible compared to computer-based systems since the patients can easily carry smartphones or tablets with them. It is estimated that around 90% of households in Sweden have access to a smartphone (The Swedish Internet Foundation, 2019). In the present RCT, only two patients needed to borrow a smartphone because they did not own such a device. Furthermore, all components in the app had been applied with a high, although, individual degree of usage. All symptoms included in the app were reported at some time and all self-care advice were viewed at least once by all patients. Only a few patients perceived the reminder as negative, where they felt that being required to report during days when they were feeling well could be a negative reminder of their illness. Despite this, most patients preferred to report their symptoms during days when they felt ill even though it occasionally was stressful. But since the app was perceived as easy to use and reporting was quick, this was not a major issue.

When an alert was triggered, the patients were called by a contact nurse. Most of the patients expressed that this made them feel safe and acknowledged, but sometimes they

perceived it as unnecessary and wanted to choose for themselves whether to be contacted or not, especially if the same symptom occurred over several days. When Interaktor was tested in patients with pancreatic cancer, two approaches were tried regarding who should be responsible for initiating the contact (Gustavell et al., 2018). The first one was the same approach as in this RCT. In the other approach, after submitting a report, the patients could choose if they wanted to be contacted by a contact nurse. Results revealed that opinions about the approaches differed between the patients and it was concluded that since patients with pancreatic cancer have a poor prognosis and often perceive severe symptoms, the responsibility to contact the healthcare professionals should not be put on the patients. Results from another study show that patients with different cancer diagnoses may find it hard to estimate when their symptoms are considered to be serious and thereby needing contact with the healthcare professionals (Jansen et al., 2015). Considering these findings, it was concluded by Gustavell et al. (2018) that alerts should continue to be triggered and responded to by a nurse. In the app, the patients can send a free text message if they do not wish to be contacted by a contact nurse. In the future development of Interaktor, a more convenient way to communicate the need to be contacted and why, could be integrated into the risk assessment model. This may also prevent the patients from adjusting their reports by reporting lower frequency and distress levels of symptoms in order to avoid being contacted by a contact nurse.

There were some suggestions for improvement given by the patients. Some patients proposed to add additional symptoms, such as headaches and that the symptom pain should be divided into several categories depending on the cause, such as pain in the breast caused by the remaining tumor and pain in muscles and joints caused by the chemotherapy. Also, there were suggestions to extend the self-care advice about diet and psychological symptoms. However, when adding symptoms for assessment there must be a balance between relevant symptoms to report and the time it takes to report. The component with the free text function gave the patients the opportunity to report additional symptoms or concerns that were not assessed, which could address the lack of individually-related symptoms or concerns. In the future, it will be important to develop the app to be even more individualized for example to enable them to add or exclude symptoms and self-care advice according to their specific needs (Moradian et al., 2018). Updating information regularly according to each patient's progress during the treatment trajectory can also be a way to meet individual needs even more and maintain personal relevance (Short et al., 2015).

8.2 Methodological discussion

8.2.1 Design

This thesis represents phase III underpinned by the MRC framework (Craig et al., 2013; Medical Research Council, 2000), where the app was evaluated. Both quantitative and

qualitative approaches were used, which is considered as a strength as it gives knowledge and insights of an intervention from several angles. Using a qualitative approach is useful as a complement to the quantitative approach, to gain a deeper understanding of why the intervention is supportive for the patients (Medical Research Council, 2000) not least when evaluating the use of mHealth apps (de Korte et al., 2018; Vo et al., 2019).

8.2.2 Setting and sample

The RCT was conducted in an outpatient setting and involved women with breast cancer treated according to structured national care guidelines. The results in this thesis may limit the generalizability of the results to all other groups of patients with breast cancer. However, Interaktor can be adapted to other samples and settings and has been shown to be acceptable, feasible and clinically significant in men with prostate cancer, women and men with pancreatic cancer and in older persons receiving home based care (Algilani et al., 2017; Gustavell, Langius-Eklöf, et al., 2019; Göransson et al., 2018; Langius-Eklöf, Christiansen, et al., 2017).

To include a sufficient number of patients in the RCT, a sample size calculation was conducted to estimate the sample size for Study I. As there was no data available from the current population, the sample size was calculated from the results of a study on patients with prostate cancer (Sundberg et al., 2017), which may have an impact on the results. However, as the power was calculated on the primary endpoint symptom burden and on patients with cancer it was considered as relevant for the sample size calculation in this RCT.

The inclusion criteria for the RCT were broad with the intention to include all patients planned for NACT. For pragmatic and safety reasons, patients had to be able to read and understand Swedish and be cognitive able to participate. In total, 47 eligible patients declined to participate in the RCT. Even though they were not asked the reason for declining, the patients spontaneously expressed that the main reasons were lack of energy or interest or that they were already participants in other studies. At baseline, the intervention group and control group did not significantly differ in sociodemographic- and/or clinical data, which shows that randomization worked properly. Dropout rate during the study was considered to be low and was similar in both groups which could reflect an opinion among the patients that it was a relevant study and their interest to contribute to nursing research.

8.2.3 Questionnaires

Two questionnaires were used to evaluate whether the app had impact on patients' symptoms and health-related quality of life. The questionnaires MSAS and EORTC QLQ-C30 are both well validated and reliable questionnaires developed for patients with cancer (Aronson et al., 1993; Browall, et al., 2013). The internal consistency was very good overall except for the symptom scale nausea/vomiting in EORTC QLQ-C30. Similar results of low Cronbach's alpha for nausea/vomiting in the EORTC QLQ-C30 have been shown in

other studies with non-malignant pain (Fredheim et al., 2007) and in general populations using EORTC QLQ-C30 (Derogar et al., 2012; Michelson et al., 2000). It is common that scales with few items have small alphas (Field, 2017).

The RCT showed relatively small effects in the symptom subscales and in the emotional functional scale of the EORTC QLQ-C30, although some of the symptom scales almost reached medium effects. Interpretations of the EORTC QLQ-C30 scales have suggested that a mean change of >10% in the scores within the groups is considered as clinically meaningful and classifies the patients' scores into improved, stable or worsened (Osoba et al., 1998; Osoba et al., 2005). Using this method to interpret the scores in this RCT revealed improved, stable and worsened scores in the functional and symptom scales for both groups. This may help when deciding appropriate supportive care for the patients and can therefore be clinically relevant even if the results showed small effects.

It can be discussed why two such comprehensive questionnaires were used. First, symptoms and symptom burden were assessed with the MSAS. Since it is known that symptoms directly influence quality of life (Browall et al., 2013) the EORTC QLQ-C30 was also used. This questionnaire is suitable to assess health-related quality of life in populations with cancer (Aronson et al., 1993). Also, the MSAS questionnaire is appropriate for use in both clinical assessment of patients' symptoms and in research (Browall et al., 2013). In the RCT, the MSAS was used both as questionnaires which the patients responded to and as an inspiration when developing the symptom reporting questions in the app, where prevalence, frequency and distress levels were assessed. Moreover, MSAS was considered as appropriate and relevant to use in the patients included in this RCT since it includes symptoms commonly perceived during chemotherapy. Assessing symptoms from several dimensions, where the patient's individual perceptions of the symptoms are in focus, is also the concept behind using PROs (Basch et al., 2016; Chen et al., 2013). It was discussed whether to use other questionnaires for assessing symptoms and health-related quality of life, such as FACT-B and EORTC QLQ-BR23. However, they include items concerning symptoms perceived after surgery and during antihormonal treatment, which were not relevant considering the context in which Interaktor was used in this RCT (Nguyen et al., 2015). In this thesis, it was chosen to report only the ratings of prevalence of the symptoms and the subscales in the MSAS. In clinical care, when the contact nurse needs to assess and communicate a patient's symptoms, it is recommended to use all three dimensions of frequency, severity and distress to gain a detailed picture of the patient's symptom profile (Pettersson et al., 2014).

Analysis of covariance was performed adjusting for baseline values. By adjusting for baseline covariates, the precision of the outcomes improves (Steingrimsson et al., 2017). Results in the thesis showed significant differences between the intervention group and the control group in symptoms and health-related quality of life. There is always a risk that the results are due to chance rather than a factual difference. The risk of drawing inaccurate conclusions from the results is determined by setting a level of significance. If the

significance level had been set to 0.01 (1%) instead of 0.05 (5%), the risk of drawing conclusions that a difference exists when there is no actual difference is reduced even more, however differences calculated with a t-test are harder to detect (Field, 2017). Reporting statistical significance only describes whether there are differences between two groups. Therefore, in **Study I** effect size was calculated, which is important to gain even further information of how much the intervention affects the patients (Sullivan & Feinn, 2012).

In studies there is always a risk of missing data. No questionnaires were missing at baseline, however, after end of NACT, five complete questionnaires were missing in the intervention group and four in the control group. A strength in the statistical analysis was to use a modified intention-to-treat analysis approach to handle the missing data. To replace missing data, BOCF was used as imputation method. This method was chosen since it is suitable when patients drop out after baseline assessment, as well as when there are low levels of missing data, mainly because this is a well-known conservative method and there is a risk of either under- or overestimating the results (Liu-Seifert et al., 2010; Petroff, 2017; Shao et al., 2009). Therefore, a complete case analysis was also performed. Analyses using both methods revealed similar results, which is a strength of the study results. The overall dropout rate in the RCT was considered as low (6%) and the personal relevance and contribution to research expressed by the patients may have played an important role in motivating them to participate in the study. Also, if the questionnaires were not responded to by the patients' they were reminded by researcher up to three times. This procedure was however very rare.

8.2.4 Logged app data

Analyses and assessment of logged data within mHealth interventions are important to get insights into the patients' usage behavior throughout an intervention (Eysenbach, 2005). It is not only important to assess when and how often the patients use the app it is also vital to assess how the patients use the app, to gaining further knowledge of the effectiveness of mHealth (Stragier et al., 2019). In the RCT, the patients' app usage was logged except clicked links and viewed graphs, which may be a limitation to gain an overall picture of how Interaktor was used and is something that will be taken under consideration in forthcoming studies of Interaktor. However, conclusions of how the links and graphs were used can be made from the interviews conducted with the patients after the reporting period had ended.

8.2.5 Interviews

To establish trustworthiness in the qualitative approach in this thesis, the criteria credibility, confirmability, dependability, and transferability according to Lincoln and Guba (1985) were considered. Credibility in qualitative data refers to the truth in the data, analysis, and interpretation of the results and since the researcher is the instrument in the analysis, it is important to know the researcher's knowledge and preunderstanding (Polit & Beck, 2016). The present author, who performed all telephone interviews and most of the face-to-face

interviews and related transcriptions, had both theoretical knowledge and practical experience of working with patients with breast cancer during NACT. The analyses in **Studies II** and **III**, were made with an inductive approach and therefore, it was important to be aware of the pre-understanding as this may affect the analysis and reported results. To increase credibility, analyses were conducted in transparency with the other researchers, by continuously reviewing and discussing the analysis with each other to come to consensus and to ensure that the categories and themes covered the data and responded to the study aims.

In **Study II**, telephone interviews with the patients who had used the app were conducted shortly after the patients' final report to ensure the patients remembered the use of the app as much as possible. A potential weakness is that the interviews were not audio recorded and analysis was made from the notes taken during the interviews. This may affect confirmability of the findings, which means accuracy of data and that the findings are in line with what the patients said (Polit & Beck, 2016). However, the interview guide was developed so that the questions generated short answers but still captured the usability and utility of the app and were easy to write down in the template of the interview guide. Also, the researcher who conducted all interviews wrote down the patients' statements with accuracy to capture as much as possible of the patients' own words in the statements. Data from the analyses revealed richness in the material sufficient to get a deeper understanding of how the patients used the app.

In **Study III**, all face-to-face interviews were conducted in a secluded room at the oncology clinics according to the patients' wishes. Often the patients had various visits planned at the clinics relating to their illness and treatment, so the interviews were planned to be conducted in connection with these visits for reasons of convenience. Also, given that the interviews were conducted over a period of one and a half year, this was something that may positively affect dependability, which means the stability of findings over time indicating the care and treatment were performed in a similar way. However, in the last interviews it was noted that no new information was added, which indicates saturation of data (Polit & Beck, 2016). To establish dependability further, most interviews were conducted by the researcher of this thesis who followed a semi-structured interview guide, which, as far as possible, ensured that the interviews were conducted in a similar way. A weakness in **Study III** is that the interviews were conducted three months after end of NACT, which may have led to difficulties for the patients to remember how the treatment period was perceived with or without the use of Interaktor. However, the data from the interviews testified that the patients remembered the period well and were able to deliver rich descriptions of how they perceived the care and use of Interaktor.

In **Study II**, conventional content analysis according to Hsieh and Shannon (2005) was chosen to analyze the telephone interviews. The method was chosen since it is suitable for describing a phenomenon where limited knowledge exists (Hsieh and Shannon, 2005), which was the case in **Study II** where researchers wanted to gain understanding of how

patients perceived using Interaktor. In **Study III**, thematic analysis according to Braun and Clarke (2006) was chosen to analyze the face-to-face interviews. This method is considered as a flexible method when interpreting the data. Also, it is recommended for investigating patients views and experiences as well as for large sets of data that can be approached by sorting them into broad themes, which was the case in **Study III** (Braun & Clarke, 2006; Nowell et al., 2017).

Transferability is described as the counterpart of the term generalizability in quantitative research and refers to the extent the results can be transferred to other samples and settings than the ones studied (Polit & Beck, 2016). The interviews in **Study II** and **III** both included large samples with a wide range of sociodemographic and clinical characteristics of the patients and the descriptions from the patients were considered as rich. These aspects strengthen the possibility of transferability of the results.

9 CONCLUSIONS

The findings in this thesis show that patients with breast cancer undergoing NACT receive individual supportive care by using an interactive app such as Interaktor. Reduced symptoms and increased emotional functioning were achieved through provision of information and self-care advice, the monitoring of symptoms and easy access to healthcare professionals.

Patients were highly engaged in using the app and it enabled them to share knowledge and discuss their health with the contact nurse as well as taking their own actions to better cope with the treatment. Enhanced communication and interaction with a contact nurse promoted patients to participate in their own care.

Overall, both study groups stated they had been satisfied with the care during treatment, reflecting a well-organized healthcare. Notwithstanding, using an interactive app provided additional value for support and therefore has high relevance for use in clinical practice.

10 CLINICAL IMPLICATIONS

This thesis provides increased knowledge that patients with breast cancer can be supported by using an interactive app during NACT to support self-care between treatments. Reporting symptoms regularly to the healthcare professionals enables them to identify the patients' distressing symptoms early so they can be discussed with the patients and thereby timely and supportive care can be provided. This is important as symptom relief will very possibly lead to increased wellbeing and quality of life, as well as a better understanding of how to take part in their own care. Further, enabling patients to monitor their reported symptoms over time and reflections over their health can facilitate planning of activities based on how they usually feel between the treatments.

Patients with breast cancer will most likely continue to receive their care and treatment on an outpatient basis in the future and mHealth can provide supportive care for those patients as well as address the different needs the patients have, and through that support more person-centered healthcare.

To implement technology such as mHealth, its value as additional supportive care for the patients must be highlighted and widely spread to patient organizations, clinicians, stakeholders, and politicians. An implementation process must be carefully planned and conducted by involving all concerned parties responsible for the care for patients with breast cancer.

The findings in this thesis also provides knowledge that might facilitate collection of PROs in clinical practice even further, since mHealth is accessible and convenient for the patients to use.

11 FUTURE RESEARCH

The next step to take with the breast cancer version Interaktor would be phase IV (Long term implementation) according to the MRC framework to integrate the use of Interaktor into clinical practice, where a goal is that all patients should be offered to use the app during their treatment and then identifying those who are interested to do so. As part of this phase, co-creation with the clinical settings should be conducted to investigate how the nurses perceive working with innovations such as mHealth to support patients and how nursing interventions such as Interaktor can facilitate their work to provide the right supportive care to the right patients at the right time. Also, a health economic evaluation of the app and its use needs to be conducted to provide information regarding the economic outcomes when using the app.

It would also be interesting to further study the use and value of Interaktor during the follow-up phase of patients with breast cancer. It is known that patients perceive lack of support and often feel abandoned and outside of the healthcare in the aftermath of the long treatment period. It is during this phase late effects and symptoms of chemotherapy and radiation therapy occurs. Also, it is common today that patients undergoing antihormonal treatment during ten years after chemotherapy, surgery, and radiation therapy. This treatment often causes symptoms, and the patients are followed-up once a year for symptom control, mammography, and prescription renewal of antihormonal drugs. There is therefore reason to believe that an app like Interaktor can be a complement during this follow-up by early identifying symptoms and providing self-care to prevent the patients from stop taking their medication because of symptoms.

12 SVENSK SAMMANFATTNING (SUMMARY IN SWEDISH)

Bakgrund

Patienter med bröstcancer som genomgår neoadjuvant cytostatikabehandling upplever ofta flertalet besvärande symtom som kan påverka deras livskvalitet negativt under en lång tid. De flesta patienter får sin vård och behandling i öppenvård vilket innebär att symtom orsakade av sjukdom och behandling måste hanteras av patienterna hemma. Om symtom inte hanteras i tid finns förutom risk för sämre livskvalitet även risk för att behandlingen måste skjutas upp eller i värsta fall avbrytas, vilket kan resultera i sämre behandlingsresultat. Många patienter upplever att de saknar tillräcklig information och stöd för att hantera sina symtom under behandlingen. För att möta detta behöver såväl symtom som patienternas behov av stöd identifieras, utvärderas och hanteras. Ett sätt att göra det är genom mHälsa till exempel smartphones, då rapportering av symtom via digital teknik har visat sig kunna öka interaktion och kommunikation med vården samt minska symtom och förbättra livskvalitet hos patienter med cancer.

Syfte

Det övergripande syftet med denna avhandling är att utvärdera hur en interaktiv app för rapportering och hantering av symtom kan ge stödjande vård till patienter med bröstcancer under neoadjuvant cytostatikabehandling.

Appen Interaktor

Fokus för appen är patientperspektivet genom att stötta med information, egenvårdsråd och öka tillgängligheten till vården och därmed främja patientens delaktighet i sin egen vård. Innehållet i appen är utvecklat utifrån litteratur av aktuell forskning inom området, rutiner och riktlinjer samt intervjuer och diskussioner med patienter och personal på klinikerna. Appen är interaktiv där patienten gör dagliga skattningar av förekomst, frekvens och besvärsgrad av symtom som är vanligt förekommande under neoadjuvant cytostatikabehandling. Patientens rapportering överförs via en säker server till ett webbgränssnitt där en kontaktsjuksköterska kan se vilka symtom som patienten har rapporterat samt även läsa fritextmeddelanden från patienten. Om patienten rapporterar symtom av svårare grad, går ett larm till kontaktsjuksköterskan som sedan ringer upp patienten för att ge stöd eller råd. I appen har patienten också tillgång till egenvårdsråd och internetlänkar för ytterligare information om hur symtom kan hanteras. Patienten kan också via grafer se sina rapporterade symtom.

Metod

Utvecklingen och utvärdering av appen följer ett ramverk för komplexa interventioner. Denna avhandling innefattar fas III i ramverket, vilket är en randomiserad och kontrollerad studie (RCT) för att utvärdera appen och omfattar i sin tur tre delstudier med såväl

kvantitativ som kvalitativ ansats. I **Studie I** ingår 149 patienter som randomiserades till en interventionsgrupp (n = 74) och en kontrollgrupp (n = 75). Patienterna i interventionsgruppen rapporterade sina symtom i appen under den neoadjuvanta behandlingstiden i kombination med sedvanlig vård. Patienterna i kontrollgruppen erhöll endast sedvanlig vård. Båda grupperna fyllde i enkäter avseende symtom och livskvalitet före start av behandling och två veckor efter avslutad behandling som sedan analyserades sedan för att utvärdera och jämföra interventionens effekter på patienternas skattade symtom och hälsorelaterad livskvalitet. I **Studie II** undersöktes patienternas användningsmönster av appen under behandlingstiden. Studien omfattar samtliga patienter som använde appen (n = 74). Loggade data från användningen av appen analyserades samt om det fanns faktorer som påverkade användningen. Telefonintervjuer gjordes med patienterna efter avslutad rapportering för att undersöka deras upplevelse av att använda appen. I **Studie III** intervjuades patienter från båda grupperna (n = 40) tre månader efter avslutad behandling avseende deras upplevelser av vården under behandlingstiden med eller utan stöd av appen.

Resultat

Resultaten i **Studie I** visade att patienterna som använde appen under behandlingstiden upplevde färre symtom såsom illamående, kräkningar, aptitlöshet, förstoppning och nedstämdhet samt hade mindre oroskänslor, irritation och nedstämdhet två veckor efter avslutad behandling jämfört med de patienter som inte använt appen. I **Studie II** visade resultaten att patienternas följsamhet att rapportera sina symtom som planerat var 83%. De vanligaste symtomen som rapporterades i appen var trötthet, munproblem och sömnsvårigheter. Fritextfunktionen användes av majoriteten av patienterna. Samtliga patienter läste egenvårdsråden i appen där munproblem, illamående och smärta var de vanligaste lästa råden. Den enda faktorn som påverkade användningen av appen var att ju högre ålder patienterna hade desto färre antal fritextmeddelanden skickades. Patienterna upplevde appen som lättanvänd med relevant innehåll och de flesta ansåg att daglig rapportering var som mest betydelsefullt de dagar de mådde dåligt. Egenvårdsråden ansågs värdefulla och lättillgängliga för att stötta patienterna i att utföra egenvård av upplevda symtom. Graferna möjliggjorde egen monitorering av symtom som underlättade för planering av dagliga aktiviteter. Att rapportera och använda appens olika funktioner beskrevs av patienterna som att få möjlighet att reflektera över sin egen hälsa, ha en nära, kontinuerlig och interaktiv kontakt med kontaktsjuksköterskan vilket upplevdes som tryggt, att bli sedd och vara delaktig i sin egen vård. Resultaten i **Studie III** visade att patienterna överlag var nöjda med vården som de fått under den neoadjuvanta cytostatikabehandlingen, oavsett om de använt appen eller inte. Patienterna beskrev ibland brist på kontinuitet som innebar att de träffade olika vårdpersonal under sin behandlingstid eller att de inte visste vem deras kontaktsjuksköterska var. Patienterna upplevde också tillfällen med svårigheter att nå vårdpersonalen när de behövde. Att vara delaktig i sin egen vård upplevdes i varierande grad beroende på vilket behov de hade. De patienter som använde appen beskrev den som ett mervärde och fungerade som ett stöd under behandlingen. Detta stöd uttrycktes

som en lättillgänglig källa för information om behandling och egenvård och erbjöd ett lätt sätt att komma i kontakt med vården vid svårare symtom. Patienterna upplevde även att appen möjliggjorde kommunikation och delaktighet i vården genom att rapportera symtom och utföra egenvård för att må bättre

Slutsatser

Patienter med bröstcancer kan under pågående neoadjuvant cytostatikabehandling få stöd utifrån individuella behov genom att använda en interaktiv app som Interaktor. Interaktion och kommunikation mellan patient och kontaktsjuksköterska underlättas genom att patienten rapporterar symtom i hemmet och blir kontaktad av en kontaktsjuksköterska på kliniken vid svårare symtom. Patienten får möjlighet att reflektera över sin egen hälsa, har enkel tillgång till information och egenvårdsråd samt har möjlighet att följa sin symtomrapportering via grafer. Detta gör att symtom kan identifieras och hanteras tidigt vilket kan leda till att patienten upplever symtomminskning och förbättrad livskvalitet samt känner sig trygg, sedd, omhändertagen och delaktig i sin egen vård. Även om patienterna i studien uppgav att de var nöjda med vården som de hade fått under behandlingstiden, beskrevs användandet av appen ge ett mervärde och utgjorde ett lättillgängligt, relevant och värdefullt stöd under behandlingen. Avhandlingens resultat visar att det är högst motiverat att rekommendera användning av en interaktiv app under cytostatikabehandling för bröstcancer för de patienter som så önskar.

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