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**INDIVIDUALISED CARE FOR PATIENTS
WITH BREAST OR PROSTATE CANCER
AIDED BY AN INTERACTIVE APP: A FRAME
OF PROCESS EVALUATION**

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**Karolinska
Institutet**

Stockholm 2023

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Published by Karolinska Institutet.

Printed by Universitetservice US-AB, 2023

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ISBN 978-91-8017-091-8

INDIVIDUALISED CARE FOR PATIENTS WITH BREAST OR PROSTATE CANCER AIDED BY AN INTERACTIVE APP: A FRAME OF PROCESS EVALUATION

Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public at Hörsal 2 (H2 Grön) Alfred Nobels allé 23, Huddinge, September 21st, 2023, at 13:00 AM

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Abstract

Background: Patients receiving outpatient cancer treatment often experience distressing symptoms and unmet needs. Collecting patient-reported outcomes via apps (ePROs) facilitates patient-clinician communication regarding symptoms and is recommended in clinical guidelines. Previous studies of an interactive app (Interaktor) for individualised symptom management show reduced symptom burden for patients undergoing breast and prostate cancer treatment.

Aim: To contribute to the knowledge of the value of implementing ePRO in clinical practice by studies framed as a process evaluation of an intervention for individualised symptom management assisted by Interaktor.

Methods: Following the Medical Research Council framework for process evaluation of complex interventions, qualitative and quantitative data were collected along two randomised controlled trials (RCTs). Patients receiving neoadjuvant chemotherapy for breast cancer (N=149), and radiotherapy for prostate cancer (N=150) were randomised to standard care with or without intervention. Intervention group patients reported symptoms and concerns daily by questionnaire and free text. The app included self-care advice and symptom history graphs. Oncology nurses responded to alerts triggered by severe symptoms. **Study I** investigates which and how patients engaged, by analysing adherence and usage predictors from logged data and telephone interviews with patients. **Study II** analyses the effects on patients' perceptions of individualised care and health literacy by questionnaires. **Study III** assesses if the intervention is cost-effective according to the Swedish National Board of Health and Welfare. Cost-effectiveness analyses (CEA) estimate gains in Quality-adjusted life-years (QALYs), intervention costs, and the patient's healthcare utilisation as obtained from the Stockholm Council database. Acute healthcare use is also explored.

Results: **Study I** shows that adherence to daily symptom reporting was 83 %; most patients used the self-care advice and free text. Patients regarded the app easy to use and helpful for self-management. Marital status, age, education level, and comorbidity were associated with usage variations. **Study II** shows no between-group differences in individualised care or health literacy among patients with breast cancer. Intervention group patients with prostate cancer rated their support for decision control as more individualised than their control group, and their ability to seek, understand and communicate health information improved. **Study III** shows the intervention produced significantly more QALYs, although the effect was small. The weekly intervention cost per patient was low. The cost-effectiveness depended on the type of healthcare costs studied. The intervention was cost-effective for patients with breast cancer if non-acute healthcare costs were excluded, and for patients with prostate cancer, considering all healthcare costs. Healthcare costs varied greatly. Patients with breast cancer who used the app had more acute visits for fever. Patients with prostate cancer who used the app had fewer acute visits for urinary problems.

Conclusions: Patients used and valued Interaktor as promoting assurance and participation in care. Using the app can positively affect care individualisation and health literacy for patients with prostate cancer during radiotherapy. It may be beneficial to increase the individualisation of features and settings for patients with breast cancer. The intervention may be cost-effective, but to show if healthcare savings can be achieved requires a larger study.

List of scientific papers

- I. 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(8), e17058.
- II. Crafoord, M.T., Sundberg, K., Nilsson, M. I., Fjell, M., & Langius-Eklöf, A. (2023). Patients' Individualized Care Perceptions and Health Literacy Using an Interactive App During Breast and Prostate Cancer Treatment: Two Parallel Randomized Controlled Trials. *CIN: Computers Informatics Nursing*, February, 3.
- III. Crafoord, M.T., Ekstrand, J., Sundberg, K., Nilsson, M.I., Fjell, M., Langius-Eklöf, A. (2023) ePRO and Interactive Support during Breast or Prostate Cancer Treatment: Health Economic Evaluation from two RCTs. *Manuscript*.

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List of abbreviations

AI	Artificial Intelligence
App	Application Software program
ARV	Reimbursed private practices
B-RCT	Breast cancer trial
CCI	Charlson Comorbidity Index
CCHL	Critical and Communicative Health Literacy
CEA	Cost-effectiveness analysis
CI	Confidence Interval
CT	Chemotherapy
DRG	Diagnose-related group
DV	Dependent variable
EBRT	External beam radiotherapy
ED	Emergency Department
e-health	Health care practices using the Internet.
EHR	Electronic Health Record
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient-Reported Outcome
EQ-5D 3L	EuroQol 5 Dimensions 3 levels
EQ-5D(P) 3L	EuroQol 5 Dimensions, 3 Level (Predicted according to response mapping algorithm)
FHL	Functional Health Literacy
FU-Q	Follow-up Questionnaire
GDP	Gross Domestic Product
GPBM	Generic preference-based measure
HRQOL	Health-Related Quality of Life

ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental Cost-effectiveness ratio
ICS	Individualised Care Scale
ITT	Intention-to-treat
IV	Independent variable
KPP	Cost per patient
m-health	Health care practices supported by mobile devices
MRC	Medical Research Council
NACT	Neoadjuvant chemotherapy
NBHW	National Board of Health and Welfare
<i>P</i>	Probability-value
P-RCT	Prostate cancer trial
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QALY	Quality-Adjusted Life Year
RCC	Regional Cancer Center
RCT	Randomised Controlled Trial
RT	Radiotherapy
SEK	Swedish Krona
SIMKOST	Simulated Cost (for healthcare visit)
SPSS	Statistical Package for the Social Sciences
VAL-OVR	VAL- Database for outpatient care
VAL-SLV	VAL-Database for inpatient care
WHO	World Health Organization
wt	Weeks of treatment
£	British Pound
€	Euro

1 Introduction

In 2016 I was admitted to the Doctoral School of Health Care Sciences at KI to take part in a project for individualised symptom management assisted by an interactive app for patients undergoing breast and prostate cancer treatment. The intervention had been developed and was being evaluated in two recently started randomised controlled trials following the Medical Research Council framework for complex interventions (Campbell et al., 2000; Craig et al., 2013). I had worked as a nurse specialised in operating room nursing and had completed a master's degree in medical science. My interest in digital technology in the healthcare setting led me to apply for this project.

My research plan did not include the effectiveness of the intervention but focused on the value of the intervention to patients and healthcare. During my research education, I read about the concept of process evaluation (Moore et al., 2015), and when the updated framework was published (Craig et al., 2019), I saw a possibility to present the studies in my research plan within a process evaluation frame. This was possible since the project had been rigorously designed with mixed methods and since data had been collected in line with the recommendation (Moore et al., 2015). Knowledge about how the intervention was implemented in the trials must be made available to guide decision-makers in future implementation efforts. I hope this thesis will be a valuable contribution to reaching this goal. While this thesis was being written, it has been shown that the intervention had positive effects on symptom burden.

2 Background

2.1 Complex Interventions and the MRC framework

It is widely acknowledged that non-pharmacological interventions need to be firmly evaluated. Research projects should verify that interventions are effective, achievable, and durable (Campbell et al., 2000; Pfadenhauer et al., 2017; Rycroft-Malone, 2004). An intervention can be regarded as complex if it includes multiple, interacting components or if delivering the intervention require flexibility. Also adding to the complexity of an intervention are the number of involved groups or organisational levels, and the number of outcomes aimed. Following an established approach, such as a framework or guidelines, can aid the evaluation of complex interventions (Campbell et al., 2000; Craig et al., 2013). The original Medical Research Council (MRC) framework focused on the randomised controlled trial (RCT) and favoured a phased approach, alike drug development research, but with iterative features (Campbell et al., 2000). The three phases for development, testing and implementation were: i) defining and understanding the problem and the context, ii) developing the intervention, and iii) developing and optimising the evaluation. The framework advocated incorporating qualitative data to promote successful implementation.

Guideline updates since the original framework have increasingly emphasised the need to investigate and understand processes (Craig et al., 2008; Craig et al., 2013; Skivington et al., 2021). The model has become more iterative, less like the pharmacological

research process, and pays greater attention to the context. For example, examining how the intervention is implemented in the trial can explain lack of success, show unforeseen impacts, and help to advance the intervention by displaying whether contextual factors are connected to diverging effects. The most recent update was collaboratively authored by the MRC and the National Institute for Health Research (NIHR) (Skivington et al., 2021). The authors recommend real-world implementation outcomes to verify intervention theory, promote understanding of key functions and challenges related to implementation.

2.1.1 Process evaluation

The MRC framework for process evaluations (Moore et al., 2015), is foremost aimed at public health interventions, but can also be used when researching healthcare interventions. It focusses on three areas classified as implementation, mechanisms of impact, and context. Implementation is about examining if actual implementation of the intervention corresponds to how it was intended. Mechanisms of impact includes testing and exploring how effects are produced. Context is about how the context influences the results and how the intervention is put into practice, which impact on generalisability. Knowledge from the three process evaluation areas aid interpretation of the outcomes and making generalisations beyond the specific context. Studies can be based on different research designs. Quantitative measures can be used to test key process variables, pre-hypothesised mechanisms of impact, and contextual moderators. Qualitative methods can be used to obtain experiences of the intervention, and unforeseen cause and effect. They can also add to, verify, or generate theory, and discover implementation differences. Moore et al. (2015) write that some authors recommend that process data is analysed and reported before the trial outcomes are known, to avoid biased interpretation.

2.1.2 Health economic evaluation

The latest update of the MRC guidance framework highlights supplementary economic evaluations for policymakers, preferable from a societal perspective are important (Skivington et al., 2021). The need to research the economic impact of interventions so funding decision-makers are guided towards implementing cost-effective care interventions has also been emphasised by authors within the context of digital health and cancer care (Granja et al., 2018; Rising et al., 2018; Sullivan et al., 2011).

One type of health economic evaluation that can guide policy makers is a cost-effectiveness analysis (CEA) (NICE, 2022a). A CEA¹ compares interventions on the costs and health outcomes by estimating how much it costs to gain one unit of a given health outcome. A health outcome commonly used in CEA is Quality-Adjusted Life Years (QALY) (NICE, 2012, 2022c). QALYs are a generic measure of disease burden that includes life quality and quantity. One QALY corresponds to one year in perfect health,

¹ A CEA that involves a generic health outcome like Quality-adjusted life years is generally called a cost-utility analysis (CUA) but in this thesis the term CEA will be used.

and zero equals dead (NICE, 2022b). NICE recommends using generic preference-based measures (GPBMs) of HRQoL to assess health technology and, for enhanced comparability, prefers the Euro-QoL 5 dimensions EQ-5D² (Longworth et al., 2014; NICE, 2022c). The result of a CEA is reported as an incremental cost-effectiveness ratio (ICER) (NICE, 2013, p. 55) which illustrates the difference in the change in mean costs in the intervention group divided by the change in mean outcomes in the current care group. Many national cost-effectiveness thresholds range between one to three times the gross domestic product (GDP) per capita (Cameron et al., 2018). In Sweden the GDP per capita 2022 was \$55,873.2 according to the World Bank (2023) which is €50,286 (if \$1=€.90). But, even if an intervention is cost-effective from a societal perspective, resource limitations often limit implementation decisions on a local level (Henriksson et al., 2018).

2.2 Breast and Prostate Cancer

2.2.1 Incidence

Worldwide, every third person gets cancer during their lifetime (Ferlay et al., 2020). Breast and prostate cancer are the most frequent globally (WHO, 2021), and in the Nordic countries, they account for more than half of all cancer incidences (NORDCAN, 2019a, 2019b). They are predicted to be the most frequent cancers over the next ten years (Soerjomataram & Bray, 2021). In Sweden, the median age for women to receive a breast cancer diagnosis is 64 (Cancerfonden, 2021a), and the mean age to receive a prostate cancer diagnosis is 69 (Cancerfonden, 2021b). Both breast and prostate cancer are treated and often completely cured, most commonly by surgery, radiotherapy, and / or chemotherapy in combination with long-term hormonal therapy. In 2018, the relative 10-year survival rate for both cancer diagnoses were 86 % (Cancerfonden, 2021a, 2021b).

Regardless of age, the psychosocial experience of receiving a breast or prostate cancer diagnosis involves emotional shock, fear, and uncertainty (Campbell-Enns & Woodgate, 2017; Farrington et al., 2019). Uncertainties and worry can be about disease progression, risks concerning one's perceived female or masculine identity, not wanting to burden others, or how the disease and treatment will affect caring responsibilities for children, a partner, or a parent (Campbell-Enns & Woodgate, 2017; Farrington et al., 2019; Fiszer et al., 2014; Nathoo et al., 2018; Sharpley et al., 2018).

2.2.2 Treatment and symptoms

2.2.2.1 Breast cancer

Breast tumours are commonly removed surgically, but radiation, hormone and chemotherapy (CT) drugs are also used to treat breast cancer (RCC, 2020a). CT can be given before (neo-adjuvant, NACT) or after (adjuvant) the tumour has been surgically

² During the time of the thesis NICE updated their preferred measure of health-related quality of life. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l>

removed (RCC, 2020a). CT drugs are associated with several symptoms (Nyrop et al., 2019) which mainly occur in areas with fast cell turnover. They include hair loss, diarrhoea/constipation, changes in taste and smell, and painful gum inflammation (Jairam et al., 2019; Wagland et al., 2015). Another kind of tissue with fast cell turnover is bone marrow, leading the immune system to be negatively affected. This means an increased risk of aggressive infections with rapid and life-threatening progress unless treated (Koenig et al., 2020). Symptoms also include fatigue, depression, and anxiety (Nyrop et al., 2019; Rha & Lee, 2020). Patients may experience multiple simultaneous symptoms (Sullivan et al., 2018).

CT for breast cancer is usually administered in 1–3 weekly cycles during 12–18 weeks (RCC, 2020a). Symptoms typically display a roller coaster pattern following the administration cycle (Chen et al., 2018; Rha & Lee, 2020), with the highest symptom burden occurring in the week following the infusion, declining until the next week after that (Rha & Lee, 2020). This pattern has been observed in both physical and emotional symptoms, including fatigue and depression (Rha & Lee, 2020), with daily fatigue peaking around day 3–5 in the cycle (Jim et al., 2011). Intraday patterns for fatigue have also been observed, with increasing levels of fatigue later in the day (Jim et al., 2011; Johnstone et al., 2019).

2.2.2.2 Prostate cancer

Most prostate cancers develop slowly and rarely generate symptoms before the tumour presses into the urethra, causing urinary problems (Malinowski et al., 2019). Low-risk prostate cancer can be treated conservatively (surveillance), while high-risk prostate cancer is typically treated by surgery or radiotherapy (RT) and antihormonal treatment (Mottet et al., 2021). RT delivers radiation that forms electrically charged (ionising) particles to the tumour area. The ionising particles injure the cancer cells (Connell & Hellman, 2009). Most commonly, RT is delivered from outside the body (external beam radiation, EBRT), but radioactive sources, sealed in catheters or seeds, can also be inserted into the tumour (internal radiation or brachytherapy). The dose is divided (fractionalised) to allow normal cells to repair themselves in between (Mottet et al., 2021). A typical radiotherapy regime consists of daily fractions over several weeks. It takes time (Connell & Hellman, 2009) (hours, days, or weeks) before cancer cells start to die, after which they continue dying for months after the treatment.

During radiotherapy for prostate cancer, symptoms arise predominantly in the treated area. Urinary symptoms are common, can be highly bothersome, and have been identified as main predictors for variations in patients' psychological wellbeing during treatment (Budaus et al., 2012; Jairam et al., 2019; Lehto et al., 2017). Symptoms are urinary leakage, increased urinary frequency, urinary irritation, and blood in the urine (Blomberg et al., 2016; Farhood et al., 2019; Lehto et al., 2017; Rha & Lee, 2020; Rose, 2011). Infrequently a patient's lower colon can become chronically inflamed (radiation proctitis), causing considerable suffering for the patient (Kishan & Kupelian, 2015).

Pertinent to prostate cancer is that it mainly occurs at an older age when patients are predisposed to multimorbidity and polypharmacy (Bluethmann et al., 2016; Keats et al.,

2021). In addition, old age correlates to cognitive problems so increased social care needs may necessitate treatment plan adjustment (Cancer Research UK, 2018).

2.2.3 Symptom management

Since most cancer treatments are outpatient-based (Cancerfonden, 2018, 2019), patients must to a degree self-manage their physical, cognitive, and psychological symptoms (Howell et al., 2020; Magalhaes et al., 2020). Self-management of symptoms includes preventing, recognising, reducing, or relieving symptoms via self-care (Hammer et al., 2015; White et al., 2019).

Theoretically, a symptom has been conceptualised as a subjective experience of a change from normalcy and symptom distress is the negative concern felt when experiencing a symptom (Dodd et al., 2001). Symptom distress relates to a worry about the disease, prognosis, or side effects. It can also be psychosocial, emotional, spiritual, or financial (Holland et al., 2013). Symptom distress affects how patients manage their symptoms by prompting them to relieve the distress-causing symptom. The most distressing symptoms are not always the most difficult (Fu et al., 2004). Symptoms are important indications to the caregiver of a problem (Dodd et al., 2001; Holland et al., 2013). Patients experience cancer treatment symptoms uniquely in a contextually and individually shaped process, which means individuality of symptoms, their frequency, their severity, and of the meanings, beliefs, and expectations regarding symptoms which are ascribed by the patient. The experience, in turn, influences self-care and coping strategies (Hsiao et al., 2014; King-Okoye et al., 2017; Liu et al., 2021; Magalhaes et al., 2020). Newly diagnosed patients battling for acceptance may suffer more negative emotions regarding a given symptom. Cancer treatment-related symptoms may also be experienced as manifest an opportunity for cure and, as such, feel acceptable (Coolbrandt et al., 2016). When symptoms reduce a patient's life quality too much, the patient may change their symptom-management behaviour for example to become more passive (Coolbrandt et al., 2016; Hsiao et al., 2014; Magalhaes et al., 2020).

Symptom management is fundamental for patients undergoing breast and prostate cancer treatment since poorly controlled symptoms affect patients' recovery processes and may require that treatments be paused, leading to adverse patient outcomes (Devlin et al., 2017; Di Maio et al., 2022; Jairam et al., 2019). It is clearly demonstrated that patients with prostate cancer (Orom et al., 2018; Prashar et al., 2022; Smith-Palmer et al., 2019) as well as with breast cancer (Lai et al., 2017; Martínez Arroyo et al., 2019; Mokhatri-Hesari et al., 2020) often have unmet informational, physical, and emotional needs during their disease trajectory. Undiagnosed symptoms impact the patients' quality of life and recovery, and patients with cancer often experience symptoms and problems during a long time after their treatment (Lehto et al., 2017; Lo-Fo-Wong et al., 2020; Matthews & Semper, 2017; Miller et al., 2019; Steentjes et al., 2018).

An individual patient's symptom experience cannot be foreseen by clinicians, since it depends on several factors including dose, age, and comorbidity (Davis et al., 2018; Miaskowski et al., 2014). There is even some evidence that symptoms can vary

depending on the patient's genetic profile (Bayer et al., 2020). Studies have shown that when clinicians and patients undergoing cancer treatment rate the patients' symptoms, score congruence is rather low and clinicians have a tendency to underestimate patients' symptoms (Di Maio et al., 2015; Nyrop et al., 2020).

Several studies have examined health care use among patients with cancer, and it has been established that when patients undergoing cancer treatment experience poorly controlled symptoms, preventable emergency department (ED) visits and hospitalisations occur (Henry et al., 2021; Mills et al., 2020; Prince et al., 2019; Smith et al., 2019). However, when studies about patients with cancer in various stages of their disease are reviewed, large variations are seen. Lash et al. (2017) systematically reviewed studies conducted in the United States that reported unplanned ED visits in patients with cancer, excluding patients in palliative settings. Twenty observational studies were identified, and the proportion of patients with an unplanned ED visit ranged from 6– 83 %. Another systematic review of studies of adult patients receiving systemic therapy in an outpatient setting found that nearly a third of the patients were hospitalised at least once for treatment-related causes, and more than 40 % when all causes were included. Hospitalisations were most frequent during the first cycle, and the median length of stay was 6.5 days. Patients in clinical trials were hospitalised to a lesser extent (Prince et al., 2019).

There is a lack of studies that examine the reasons for such visits, and this area needs to be investigated more (Lash et al., 2017; Prince et al., 2019). Comorbidities, age, and treatment regimen have been the most frequently evaluated factors. While age does not appear to be significantly associated with hospitalisations or ED visits, comorbidities have been shown to be significantly associated with hospitalisations and ED visits (Lash et al., 2017; Prince et al., 2019). Being male, having more symptoms, undergoing chemotherapy treatment (as opposed to other treatment modalities), and being unmarried have been reported as predictive factors in single studies (Lash et al., 2017).

An evaluation of ED visits in 240 patients starting systemic anticancer therapy in a community-based cancer centre found that half of the patients contacted the cancer centre for advice regarding side effects, and that about 20 % made a total of 58 ED visits (Henry et al., 2021). When independent physicians reviewed the patient's medical records, most of the visits were classified as avoidable per predefined classification. The most common cause(s) during avoidable ED visits included gastrointestinal symptoms, which represented nearly half of the visits – others included pulmonary symptoms, musculoskeletal symptoms, and fever and chills. The most common causes for unavoidable visits were indicators of sepsis, severe pulmonary or gastrointestinal symptoms, paclitaxel reactions, and suicidality. Nearly half of the ED visits resulted in hospital admissions. Comparison of patients with an ED visit versus those without showed that significant factors associated with visiting the ED were the use of cytotoxic agents (as compared to targeted agents or immunotherapy), more agents, higher (Eastern Cooperative Oncology Group, ECOG) performance status and cancer type (upper GI cancer, more than one type of cancer, and hematologic malignancies).

The current front line in cancer care is to systematically integrate patient-reported outcomes (PROs) in clinical practice as the foundation for care planning and evaluation of treatment success (Di Maio et al., 2022). A PRO is a patient's report about a consequence of disease and/or its treatment. PROs can include perceptions of health, well-being, a physical or psychological symptom or functioning. Patient-reported outcome measures (PROMS) are tools, such as standardised questionnaires or interview schedules, being used to collect PROs. ePROs or ePROMs refer to when PROs are collected through electronic (digital) means (Coons et al., 2009; van Egdom et al., 2019).

2.2.4 ePRO interventions

2.2.4.1 Digital health

The umbrella term digital health includes the terms e-health and m-health (WHO, 2018). e-health refers to using the internet and associated technologies for health services and information (eHälsomyndigheten, 2022; Eysenbach, 2001; WHO, 2011), and m-health means health practices using wireless technology, such as smartphones, tablets, and wearable devices (Park, 2016; World Health Organization, 2011). Digital Health also encompasses advanced computing sciences like artificial intelligence (AI), genomics, and big data (WHO, 2018).

Apps (short for applications) are software programs for computer, smartphone, or tablet devices, and act as a medium for interaction via interfaces. Apps are becoming increasingly accessible as smartphone ownership rates grow worldwide. For the whole of Europe, smartphone ownership rates were at 70 % in 2018 (Pew Research Center, 2018). The accessibility of high-speed mobile networks has strongly impacted rates of out-of-home internet use (Ofcom, 2018). In 2018 the Pew Research Centre (2018) reported that Sweden had the highest prevalence of internet access through a smartphone, (96 %). During the pandemic, what has been named a shock digitisation occurred in Sweden. After that, pensioners, and persons over 76 years began using the internet more for e-shopping, social media, and digital healthcare services. A national survey showed that 70 % of > 76-year-olds have used a digital care service, and most are positive (The Swedish Internet Foundation, 2020).

Until recently, most research literature reviews about ePRO and digital supportive care interventions did not differentiate between mobile or non-mobile systems, but mobile systems are increasingly focused on in literature reviews (Osborn et al., 2019; Putranto & Rochmawati, 2020; Richards et al., 2018; Silva et al., 2015; Silva et al., 2019). Classifying systems based only on the technical trait, wireless or non-wireless, may constitute a limitation, as it fails to discriminate between interventions significant from a patient's perspective regarding convenience. For example, reporting symptoms via a stationary computer at home may be more of a mobile experience for the patient compared to reporting symptoms via a wireless computer tablet in a clinic.

2.2.4.2 Historical perspective

Research literature of particular relevance for this thesis dates back to the nineties when anticancer chemotherapy treatment shifted from inpatient to outpatient settings

(Dollinger, 1996). One early computer-based intervention for patients undergoing chemotherapy treatment for breast cancer was described 1993 (Gustafson et al., 1993). The intervention featured weekly quality of life assessments, a breast cancer article library, a discussion group, and the possibility to anonymously mail a cancer counsellor. Surveys from women who had used the intervention in pilot studies indicated that the intervention was regarded as supportive.

Even some time after the launch of high-speed networks, issues concerning the reliability of technology posed a limiting factor for ePRO and influenced dependability (Varshney, 2007). For example, McGee and Gray (McGee & Gray, 2005) reported that only a few study participants described having experienced some problems related to modem telephone connection, but analysis of the logged data showed that all participants except one had at least one modem failure, and the number of successfully sent reports were not significantly higher than the number of failed sends.

In 2012 Johansen et al. (2012) systematically reviewed the state of the art regarding ePRO systems and concluded that there was robust evidence for feasibility. Six studies were in the context of cancer. None of these were classified as including support for self-management but instead focused on clinician monitoring. When all identified studies of ePRO were considered (including cancer, respiratory, cardiovascular, and diabetes) considerable clinical effects like reduced symptom distress and increased HRQOL were shown, but RCTs and study protocols were needed to rule out selective reporting bias (Johansen, Berntsen, et al., 2012). Parallel to scientific efforts, clinical implementations had already taken place by early adopters. Jensen et al. (2013) identified 33 unique ePRO systems already implemented in clinical cancer care and classified the systems accordingly: those for monitoring of patients during active cancer treatment and those for use across the treatment and survivorship phases. In total, 18 systems allowed patients to report from their homes only or from their home and the clinic. Most systems sent real-time alerts to providers based on patient reports, and around half also sent alerts to patients. Most systems alerted a physician, but some could render automated referrals to other staff, such as pharmacists and social workers. Forty-four per cent were integrated into the patient's electronic health record (EHR) (Jensen et al., 2013).

From the earliest ePRO studies until now, the research literature mirrors a changing clinical landscape with increased demands on self-management. A shift can be seen, from interventions aiming to support clinicians' management of patients to interventions more focused on supporting patients to self-manage (Johansen, Henriksen, et al., 2012; Warrington et al., 2019b). Currently most ePRO interventions also include symptom information, features for self-monitoring and patient-healthcare provider communication (Warrington et al., 2019b).

2.2.4.3 Effects of using ePRO

During the last five years, studies of the effects of using ePRO to support patients with cancer have accumulated, and there is now substantial evidence that using ePROs in

clinical outpatient cancer care positively impact patients' HRQOL, functioning, symptom management and even overall survival (Lu et al., 2023). Several studies are of good quality, although studies that score high on power analysis and effect sizes are fewer (Saeed Moradian et al., 2018). There are also some limitations concerning the evidence that stem from the challenges for blinding (Lu et al., 2023). ePRO for patients with cancer also show patient acceptance, and that patients perceive them as helpful and easy to use (Cho et al., 2021; Rincon et al., 2017).

2.2.4.4 ePRO system characteristics

Many ePRO systems are based on the Common Terminology Criteria for Adverse Events (Basch et al., 2014) or the European Organisation for Research and Treatment of Cancer Questionnaires (EORTC)(Aaronson et al., 1993) (Cho et al., 2021). There have also been interventions with a focus on lifestyle (Soto-Perez-De-Celis et al., 2018; Uhm et al., 2017) and mental health (Kim et al., 2016). For example, the so-called Pit-a-pat app (Kim et al., 2016), which has demonstrated adequate accuracy in screening for depression through daily patient ratings of sleep satisfaction, mood and anxiety by a sleep journal, visual analogue scales and face emoticons 😊 😞 (Kim et al., 2016; Min et al., 2014).

Most ePRO interventions are for several cancer diagnoses and few specially target patients undergoing active treatment for breast or prostate cancer, although these patient populations are among the largest (Rincon et al., 2017). Cruz et al. (2019) identified three randomised studies and six nonrandomised studies of apps for patients undergoing breast cancer treatment. Two apps enabled the patients to communicate symptoms to the healthcare via symptom reports; three apps featured remote consultations with a healthcare professional. The studies did not form robust evidence about clinical effects but strongly demonstrated acceptability.

For the current thesis literature review, randomised studies about ePRO interventions that target patients undergoing treatment for prostate cancer were not found, but single-arm feasibility studies have been described for patients in follow-up care (Tran et al., 2020) and for patients receiving palliative systemic treatment (Appleyard et al., 2021). Both interventions featured items from validated HRQOL instruments. The intervention for men in follow-up care was based on a smartphone app where patients could complete weekly reports of urinary, bowel, sexual and hormonal symptoms for 12 weeks. The intervention for patients receiving palliative care included an option to complete the PRO from home or in the clinic, monthly for 3 months via web or smartphone (Tran et al., 2020). A conference abstract reports on patient interviews about symptom experiences and the impact of androgen therapy treatment which will be used to draft a PRO tool for patients with prostate cancer (Chladek et al., 2022), so more developments are likely to follow.

Increasingly, ePRO systems are smartphone-based (Osborn et al., 2019; Putranto & Rochmawati, 2020; Richards et al., 2018; Silva et al., 2019). Since smartphone-based interventions are more accessible (e.g., than desktop computers), patients' non-usage, which has been a challenge in research of digital interventions (Eysenbach, 2005;

Ventura et al., 2017), will be less of a challenge (Escriva Bouley et al., 2018; Warrington et al., 2019b). As non-usage has been an obstacle, researchers who have developed digital health interventions have had to seek knowledge from human-computer interaction (Lalmas et al., 2014) and foremost this has been through the concepts of adherence and engagement. They have become a research area to investigate how patients' use of digital interventions can be understood and promoted (Kelders et al., 2012; Kelders et al., 2020; Sieverink et al., 2017; Warrington et al., 2019b).

2.2.4.5 Adherence and engagement in digital health

In medical treatment, adherence refers to *"the extent to which a person's behaviour – taking medication, following a diet, and executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* (Sabate, 2003, p. 17). Some authors have used the more authoritative nomenclature compliance (Judson et al., 2013), but adherence is more established (Donkin et al., 2011; Ryan et al., 2018). It has been emphasized that adherence in relation to digital health interventions should be seen as usage level in relation to a rationalised and operationalised level of use as intended by the creators (Kelders et al., 2012; Sieverink et al., 2017). Adherence is currently conceptualised as a process that cannot be assessed statically, for instance, by measuring total exposure at the end of the intervention but rather throughout the entire procedure (Sieverink et al., 2017). Contrasting each individual's usage to the intended usage generates an adherence percentage, which can be compared to other interventions (Kelders et al., 2012). Methods for analysing log data through visualisation have also been described (Arden-Close et al., 2015; Morrison & Doherty, 2014). Compelling patients to adhere to an intended level of use of a digital intervention may be challenging (Beatty & Binnion, 2016; Eysenbach, 2005).

Engagement is a concept that integrates the subjective experience of using and the behaviour of using, although conceptual agreement can be improved (Perski et al., 2016; Warrington et al., 2019a). Perski et al. (2016) proposed the definition *"Engagement....is (1) the extent (e.g. amount, frequency, duration, depth) of usage and (2) a subjective experience characterized by attention, interest and affect"* (Perski et al., 2016, p. 258). The rationale for engagement is that usage metrics alone cannot reveal why specific usage patterns occur and therefore engagement is assessed by a mixed methods approach that combines objective usage metrics with subjective perceptions of use via interviews, usability tests, or other methodologies (Lalmas et al., 2014; Sieverink et al., 2017).

According to a model by Short et al. (2015), both intervention-, individual- and external aspects influence engagement. Intervention aspects comprises technical and design such as persuasive design, tailoring, credibility, and rewards. Individual aspects may involve demographics, psychosocial factors, and internet self-efficacy. An external aspect can be access (Short et al., 2015). Regarding empirical support for the model by Short et al., research about the effect of intervention features on engagement show some evidence that notifications or prompts (Alkhalidi et al., 2016) and the ability to self-monitor (Lee et al., 2018) can increase engagement.

2.2.4.6 Health economic evaluations of ePRO

It has been hypothesised that ePRO during cancer treatment has the potential to decrease patients' healthcare utilisation, through more timely management of symptoms and adverse events and reductions in secondary healthcare utilisation (Iribarren et al., 2017; Nixon et al., 2018; Peltola et al., 2016). CEAs are increasingly done along clinical trials of digital health interventions to determine their impact on QoL and assess healthcare services' outcomes (Gentili et al., 2022). However, to date studies are scarce, and results are inconsistent (Lizán et al., 2021). In a study by Basch et al. (2016), fewer participants in the intervention group visited the ED compared to the control group. Lizee et al. (2019) reported the cost-effectiveness and costs of ePRO in follow-up care of patients with lung cancer. The study found that the average annual cost of the conventional follow-up, including consultations, imaging, and trips, was lower per patient in the experimental arm compared to the control arm, and that the intervention was deemed as cost-effective, it was also shown that intervention group patients had more prolonged overall survival (Denis et al., 2019).

Not long ago, a cost-effectiveness analysis from the perspective of the healthcare provider, was made alongside an RCT of an ePRO system in patients treated with chemotherapy for colorectal, breast and gynaecological cancer (Velikova et al., 2021). Health state utilities were obtained at multiple timepoints. To estimate direct costs, patients' health care utilisation, collected via medical records, was converted into costs based on pharmacopeia reference values. The intervention group patients had higher costs at 12 weeks, and lower costs at 18 weeks (primary endpoint) but the difference was not significant. Subgroup analysis indicated more cost-effectiveness in patients undergoing treatment with curative intent as opposed to patients with metastatic disease (Velikova et al., 2021).

2.3 Individualised symptom management support and patient engagement

Care ethics and the moral underpinning of nursing places the patient in the centre and responds to the individual patient's experience of health and illness (Abdellah, 1960; O'Rourke et al., 2019; Van Servellen & McCloskey, 1988). Supporting patients to self-manage symptoms and dealing with illness-related concerns in a highly patient-centred manner are included in the concept of individualised care (Kousoulou et al., 2019; Suhonen, Efstathiou, et al., 2012; Suhonen et al., 2005). Individualised care includes support to patients in the clinical situation, relating to physical and psychological care needs, abilities, capabilities, the meaning of illness, feelings, and affective states. Individualised care also includes supporting patients in their personal life situations by considering employment, cultural background, daily activities, and family involvement. Lastly, support for decision control is included by attention to illness and treatment, having alternatives, making choices, and expressing views, opinions, wishes, and proposals (Suhonen et al., 2005).

Individualised care has been conceptualised as situated at the end of a continuum of increasing patient-centredness (Lauver et al., 2002; Suhonen et al., 2000). Personalised interventions are at the onset of the continuum and deploy a single characteristic, like an individually addressed information letter. Targeted intervention aims at individuals with one or several shared features. Tailored interventions are even more customised to individual traits or preferences and have more possible alternatives. Still, the distinction between tailored and targeted interventions can be clouded. Individualised care is, although guided by delineated components, so highly adapted to individuals' situations that no two patients may even receive the same care. Instead, the care is determined by the nurse-patient interaction (Lauver et al., 2002; Suhonen et al., 2000).

The terms individualised, person, and patient-centered are at times used interchangeably within nursing literature (Eklund et al., 2019). Ekman et al. (2011) positioned the concept person-centred care as an approach to design care for the individual patient needs by considering the context, history, and uniqueness of the patient through patient narratives and partnership. Although different concepts prevail, the conjoint focus is on the nurse's ability to approach and adapt care to the unique person (Eklund et al., 2019; Ekman et al., 2011; Radwin, 1995). Patient-centred care shares values with person-centred care but is more used in contexts emphasising the dimensions of functional and effective patient-carer-cooperation like information exchange and shared understanding (Eklund et al., 2019). Patient-centred care has gained explicit recognition within cancer care (Wolfe, 2001), but the term is also used in medical research about patient-physician interaction (Mead & Bower, 2002).

Health literacy encompasses the ability to find and evaluate the credibility and quality of information (Papadakos et al., 2018). A fundamental aspect of the individualised care areas clinical situation and decision control relates to a patients' health literacy, since individualised care consider what the patient wants to know about their treatment, that they understand the information that they receive, and that they are supported in an individual manner in making decisions (Suhonen et al., 2000). Health literacy skills also involve the ability to express health concerns, describe symptoms understandably for health care professionals, ask relevant questions, and fully understand the available medical information (Martensson & Hensing, 2012; Sykes et al., 2013). Low health literacy is associated with less receipt of prescribed chemotherapy, less information-seeking behaviours, higher information needs, and more service utilisation (Papadakos et al., 2018). Patients with cancer often have complex treatment plans, making health literacy skills vital (Lee et al., 2021; Papadakos et al., 2018; Tremont et al., 2020).

Nurses are at the forefront of clinical symptom management and support for patients in cancer treatment. Since the transition from inpatient to outpatient cancer care, they have used the telephone to support patients during cancer treatment (Kwok et al., 2022; Moretto et al., 2019; Ream et al., 2020). Nurse-led telephone interventions are accepted by patients, can reduce cancer symptoms and improve patients' self-care (Liptrott et al., 2018; Suh & Lee, 2017) but they have not demonstrated positive effects on patient satisfaction, adjustment or patient-centred outcomes (Liptrott et al., 2018; Suh & Lee,

2017). A vital policy discussion today concern how healthcare can be practically shaped and organised so that it to a higher degree responds to individual patients' needs and preferences (Cancer Research UK, 2018; eHälsomyndigheten, 2016; Forum, 2014; SBU, 2017). Also, within the healthcare this is a focus for much discussion. Santana et al. (2018) suggest that care structures and processes that recognise the patient as an expert in their health, foster communication, and generate partnership are important. This is done by actively seeking and gathering information from the patient about their health, needs, and preferences, and by sharing information with them.

Patient engagement refers to structures that foster and support patients' active and informed care participation to enhance the quality, safety, and patient-centredness of care (Barello et al., 2016; Fumagalli et al., 2015; Higgins et al., 2017; WHO, 2016). Such structures enable patients to be knowledgeable partners in their own care and to have resources to manage and control aspects that influence their health (Calvillo et al., 2015; Fumagalli et al., 2015). These structures impact by providing patient education, access to information and reliable advice so as to support patients in making informed decisions (Wagland et al., 2019), and through reducing anxiety (Campbell-Enns & Woodgate, 2017; S Moradian et al., 2018; Wagland et al., 2019).

The WHO describes patient engagement as processes nurturing patients' active care involvement (WHO, 2016). However, in a definition used by Higgins et al. (2017), patient engagement is described as both a process and behaviour; both wanting to and actively participating in one's care in an individualised way in collaboration with a healthcare provider. This definition was based on a review of how the concept has been used in health research literature. The review identified four inherent elements to patient engagement. The elements necessary for patient engagement were that the care was tailored to the patient, and that the patient can access the resources that they need. It was also inherent that the relationship between the healthcare provider and the patient was supported and continually encouraged, and that the healthcare provider was dedicated to practicing high-quality care (Higgins et al., 2017). The need for patient engagement has been emphasised by patient organizations and in health care strategies (Forum, 2014; Fumagalli et al., 2015; SBU, 2017; WHO, 2016).

Over the past decade, policy makers have encouraged an intensified use of technology within cancer care to increase the quality and patient-centredness of care (Ganz, 2014; Klöcker et al., 2015; Lee et al., 2015; Olsson et al., 2004; WHO, 2011). Nurses are also increasingly developing and researching digital supportive care interventions like apps containing symptom information, features for self-monitoring and patient-nurse communication. Nevertheless, nurses also worry that e-health will adversely affect nurse-patient interaction (Rouleau et al., 2017). Partly, this connects to care-related philosophical assumptions that e-health objectifies patients or makes them invisible (Barrett et al., 2015; Skär & Söderberg, 2018). Empirical research concerning patient-centred outcomes is needed to optimise and strengthen the theory of digital supportive care interventions (Kelders et al., 2012; Olsson et al., 2013; Sieverink et al., 2017). A growing body of literature has investigated the correlations between patient-centred

nursing interventions based on digital technology and patient outcomes and in view of recent reviews, there are grounds for a positive assessment (Olsson et al., 2013; Penedo et al., 2020) although the area is still unripe when it comes to interdisciplinary conceptual clarity about what a patient-centred outcome is and about research methodology (Bruce et al., 2020).

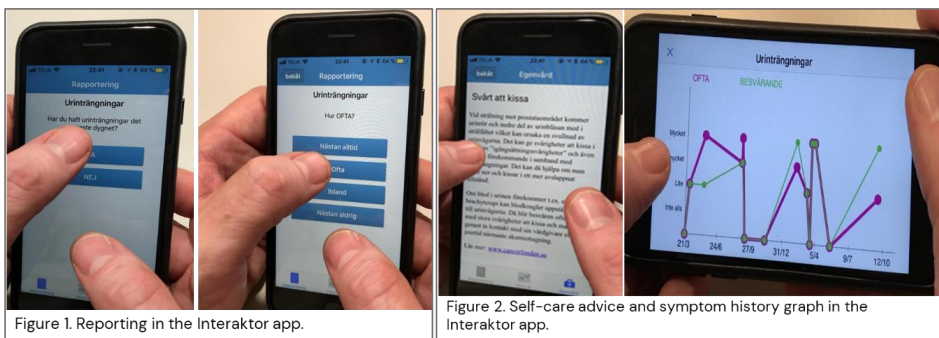
2.4 The app Interaktor – support for individualised symptom management

2.4.1 Description of Interaktor

The idea behind the app Interaktor is grounded in individualised care (Charalambous et al., 2012) and patient engagement (Higgins et al., 2017; Sahlsten et al., 2008). It encompasses a structure based on information technology to enhance patients' active care participation, providing access to health information and advice, and arranging for prompt nurse contact and support when needed. The platform includes a smartphone- or tablet- application for transmitting information via a secure server to a web interface for clinical monitoring by nurses. The nurses can view patient-reports in real time. The web-interface function also as an aid in nurse-clinician communication and as a decision aid for symptom management. Interaktor includes the following components:

- I. A symptom questionnaire for patients' daily assessment of the occurrence, frequency, and distress level of symptoms.
- II. A risk assessment model-based function that alerts the nurses in real time via text messages (SMS) when severe symptoms or concerns are reported.
- III. Symptom history graphs for patients' overview of their own symptom reports.
- IV. Information, self-care advice and links to evidence-based trustworthy webpages.

Furthermore, the app includes a free-text message function to interact with the clinicians and a daily reminder function prompting if a report has not been submitted. Interaktor also has an automated feedback function referred to as "smart advice". A tailored notice that pops up and prompts the patient to read a specific self-care advice when the patient has reported a severe level of a symptom. Patients report symptoms on a regular basis, and any time they feel unwell, via the symptom questionnaire (Figure 1). They have continuous access to evidence-based self-care advice directly related to their reported symptoms and concerns or to their own choice and can see their own symptom history in graphs (Figure 2).



The risk assessment model sends alerts to involved nurses via text messaging (SMS). This initiates an interaction between the nurse and the patient, with the patient being contacted by telephone to discuss the reported problems (Figure 3).

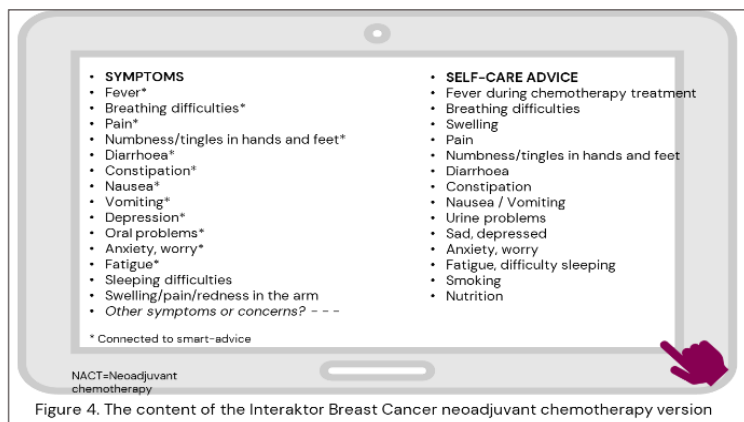


Interaktor is generic, and has been developed and tested in versions for older persons with home care (Göransson et al., 2018), patients who have undergone pancreaticoduodenectomy for pancreatic cancer (Gustavell, Langius-Eklöf, et al., 2019; Gustavell, Sundberg, et al., 2019), patients undergoing external radiotherapy for prostate cancer (Blomberg et al., 2016; Langius-Eklöf, Christiansen, et al., 2017; Sundberg et al., 2015; Sundberg et al., 2017), and patients undergoing neoadjuvant chemotherapy for breast cancer (Fjell et al., 2020). Studies have shown that patients using Interaktor during treatment for breast and prostate cancer rate less symptom burden at treatment end (Fjell et al., 2020; Sundberg et al., 2017) and similar in a group of patients with pancreatic cancer six weeks after surgery (Gustavell, Sundberg, et al., 2019).

The platform was developed, at the time of the study, in the context of formal cooperation between the research group and the company Health Navigator, which also handled the data via a secure server. Today, the app is hosted at KI and only for research purposes.

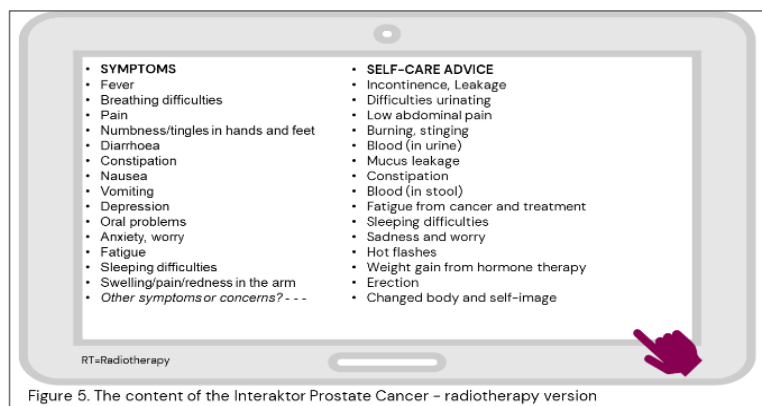
2.4.2 Interaktor Breast Cancer NACT version

The Interaktor breast cancer symptom questionnaire assesses the symptoms fever, breathing difficulties, and vomiting (triggering a red alert when reported), pain, numbness/tingling, nausea, diarrhoea, constipation, oral problems, and swelling /pain/redness in the arm (triggering a yellow alert depending on distress level), as well as depression, anxiety/worry, fatigue and sleeping difficulties (triggering a yellow alert depending on distress level). Lastly in the symptom questionnaire is an option to report other concerns via free text. The self-care advice covers respiratory and circulation, neurological, bowel and urinary, psychosocial, and lifestyle symptoms (Figure 4). The Interaktor Breast Cancer – NACT version has the “smart advice” function.



2.4.1 Interaktor Prostate Cancer RT version

The Interaktor prostate cancer symptom questionnaire assesses urinary urgency, urinary difficulties, blood in urine, diarrhoea, constipation, fatigue (triggering a yellow alert depending on frequency or distress level), blood in stool (triggering a yellow or a red alert depending on distress level), pain, sadness/depression, anxiety/worry (triggering a red alert depending on frequency or severity), flushes, mucus leakage, sleeping difficulties, and urinary leakage. Lastly in the symptom questionnaire is an option to report other concerns via free text. The selfcare advice covers urinary, bowel, hormonal, psychosocial, and sexuality-related symptoms (Figure 5). The Interaktor Prostate Cancer –RT version does not have the “smart advice” function.



3 Rationale

Generally, it can be concluded that patients undergoing neo-adjuvant chemotherapy for breast cancer and radiotherapy for prostate cancer encounter uncertainties, symptoms, reduced functions, and overall unmet needs. The individual patients' symptoms and care needs cannot be foreseen. Using ePROs in symptom management during cancer treatment has improved communication between patients and healthcare providers and decreased patients' symptom burden and even survival. Still, more evidence of the effectiveness is needed, as studies are heterogeneous regarding diagnosis and methodologies. Additionally, more knowledge that decision-makers can use to facilitate and guide implementation efforts is needed. Knowledge about how ePRO interventions impact the effective use of healthcare resources and how they impact care from the perspective of patient-centredness. Process evaluations help interpretation of the results of randomised controlled trials so that sustainable and productive interventions can be implemented more efficiently. Although frameworks for evaluating complex interventions emphasise the need to perform process evaluations, they are limited.

This thesis includes three studies conducted during two RCTs that evaluated a complex intervention for individualised symptom management support for patients during breast or prostate cancer treatment assisted by an interactive app. One RCT included patients with breast cancer and one RCT included patients with prostate cancer. In the discussion, the results of the three studies will be synthesised in frame of a process evaluation according to the three core components: implementation, impact mechanisms, and context. It also investigates cost-effectiveness, and how the intervention affected patients' health care use.

4 Research aims

The overall aim of the thesis is to contribute to the knowledge of the value of implementing ePRO in clinical practice by studies framed as a process evaluation of an intervention for individualised symptom management assisted by an interactive app. Three studies are included with the following aims:

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

Study II The aim was to evaluate perceptions of individualised care and health literacy using an interactive app (Interaktor) for symptom monitoring and self-care during curative treatment for breast or prostate cancer.

Study III The aim was to evaluate the cost-effectiveness from the healthcare provider's perspective. Secondly, the study explores the impact on the patient's healthcare utilisation and costs.

5 Methods

5.1 Design

The design of this thesis originates from two parallel randomised controlled trials (RCTs) developed and evaluated using the MRC framework for complex interventions (Craig et al., 2013; Langius-Eklöf, Crafoord, et al., 2017) (Figure 6). Within each RCT, each study participant was randomised into one of two groups: the intervention group (receiving the intervention and standard care) and the control group (receiving standard care only). The studies included in this thesis, which represent part of a process evaluation, were based on quantitative as well as qualitative data. In table 1 the overview of the studies is presented; study I used a mixed methods approach, study II used a quantitative approach and study III used a quantitative and mixed methods approach.

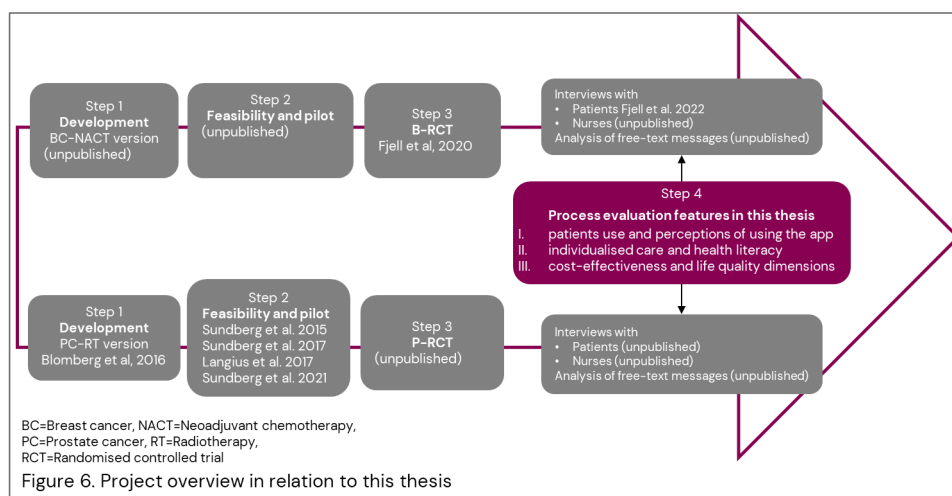


Table 1. Overview of the included studies

Study	Sample	Data sources	Data collection	Data analysis
I	B-RCT IG (n=74) P-RCT IG (n=75)	Telephone interviews Logged app data Sociodemographic data Medical records	2015-17	Descriptive statistics Chi-square test Fisher's exact test Multivariate regression Conventional content analysis.
II	B-RCT (n=140) P-RCT (n=114)	Individualised Care Scale Functional Health Literacy Scale Critical Communicative Health Literacy Scale Sociodemographic data Medical records	2015-17	Descriptive statistics Pearson correlation coefficient Student's t-test Chi-square test Multivariate regression
III	B-RCT (n=149) P-RCT (n=148)	EORTC QLQ-C30 mapped to EQ-5D-3L Register data from: Region Stockholm (VAL) Regional Cancer Centre (RCC) National Board of Health and Welfare (NBHW) Sociodemographic data Medical records	2015-17, 2020-21	Descriptive statistics Multivariate regression Cost-effectiveness analysis Conventional, Summative and Directed qualitative analysis

IG=Intervention Group

B-RCT= Breast Cancer Randomised Controlled Trial

P-RCT= Prostate Cancer Randomised Controlled Trial

5.2 Sample and setting

One RCT consisted of patients undergoing NACT with curative intent for breast cancer (B-RCT) and one RCT included patients undergoing RT with curative intent for prostate cancer (P-RCT). In both RCT 150 patients were included and randomised. In the B-RCT one patient was excluded after randomisation due to a change of treatment, hence B-RCT n=149 and P-RCT n=150 (Figure 7).

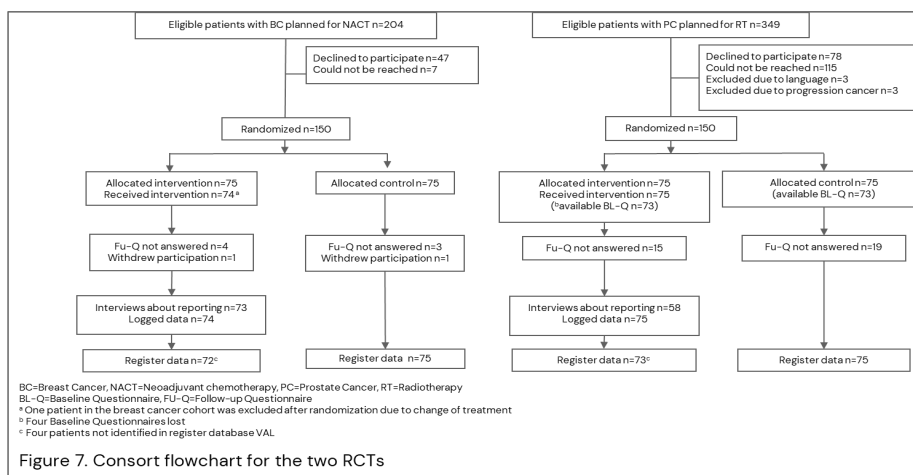


Figure 7. Consort flowchart for the two RCTs

The sample size was estimated to have an effect on symptom burden and was calculated from an effect study conducted with patients receiving RT for prostate cancer (Sundberg et al., 2017) with the primary outcome symptom distress (urinary symptoms). The effect size difference (Cohen's D) of .54 showed that for 90 % power at $P < .05$, each group needed 71 study participants.

Study I consisted of the intervention groups in each RCT. In the B-RCT, 74 patients were in the intervention group and received the intervention. In the P-RCT 75 patients were in the intervention group and received the intervention. In study I, 73 patients in the B-RCT were interviewed as one patient declined a telephone interview. In the P-RCT 58 patients were interviewed about using the intervention, mainly due to that patients were difficult to reach after their treatment had ended. Logged data from app-usage was available from all 74 (B-RCT) and 75 (P-RCT) patients.

In study II the B-RCT sample consisted of 140 patients; 1 patient in each group withdrew participation, and 4 in the intervention group and 3 in the control group did not return the follow-up questionnaire. In the P-RCT the sample consisted of 114 patients. In the intervention group 15 patients did not return their follow-up questionnaire and two were excluded as their baseline questionnaire was missing, rendering a total of 58 patients. In the control group 19 patients did not return the follow-up questionnaire (two of those also had missing baseline questionnaires) hence the control group consisted of 56 patients.

In study III the B-RCT consisted of 74 patients in the intervention group and 75 patients in the control group. The P-RCT consisted of 75 patients in the intervention group and 75 patients in the control group. Register data was missing at random for two patients in each intervention group. Two were not found due to wrong personal identification numbers, and two were likely missing since they were registered in other regions.

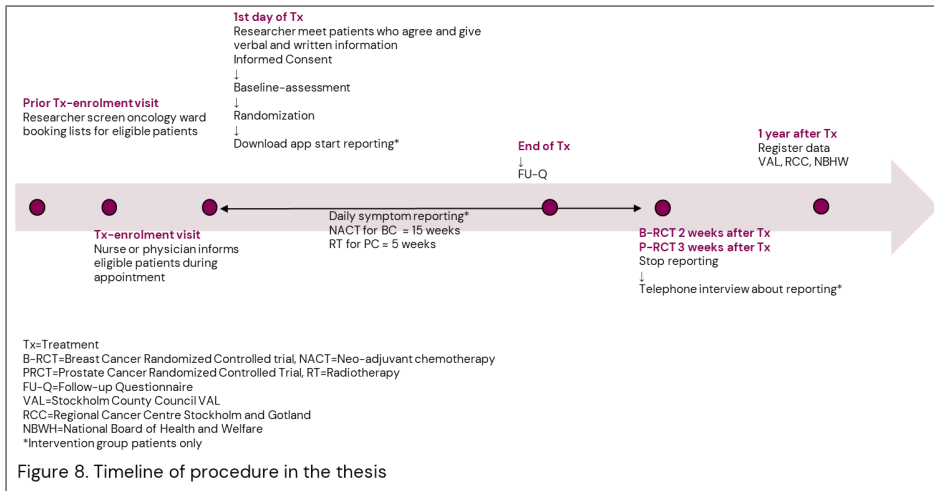
The RCTs took place in Region Stockholm (former Stockholm County) at Karolinska University Hospital and Södersjukhuset from June 2015 to August 2017.

5.3 Procedure

A researcher identified eligible patients consecutively by screening medical appointment lists at the oncological departments. Inclusion criteria were that the patients should be over the age of 18, diagnosed with non-metastatic breast or prostate cancer, and able to read and understand Swedish. Exclusion criteria were if patients had a cognitive dysfunction, documented in the medical records or according to clinical judgement by a registered nurse at the clinic. The contact nurse or physician informed eligible patients about the study, and a researcher phoned the patients who agreed to be contacted. The researcher then met with interested patients before treatment started to attain informed consent.

Patients were given verbal and written information that they would receive standard care according to the clinic's protocol, regardless of their decision on whether to be included into the study, and regardless of group allocation. Further information

contained the randomisation procedure, postal follow-up questionnaires two weeks after completing their treatment and three months after their treatment had finished – and, if they were allocated to the intervention, a telephone interview about their experiences of using the app just after the end of the reporting period. Patients were also informed verbally and in writing that medical data would be collected from their medical records. Patients who provided their written informed consent and completed the baseline questionnaire were randomised sequentially by drawing and opening an opaque sealed envelope (from a pack shuffled by an external researcher) containing the group allocation (Roberts & Torgerson, 1998) (Figure 8).



5.3.1 Intervention

The patients in the intervention group downloaded the app Interaktor (described in detailed in the Background section) onto their smartphone or tablet. If a patient did not own a smartphone or tablet, they were lent a smartphone during the intervention. Two patients per RCT borrowed a smartphone. The researchers instructed the patients verbally and in writing about using the app for reporting symptoms, viewing self-care advice, and the symptom history graphs. The patients were asked to report their symptoms every day during treatment (office hours) until two weeks after the end of NACT in the B-RCT and three weeks after the RT in the P-RCT. The researcher informed the patients that nurses at the oncological clinic would respond to alerts triggered via the app between 8:00 AM and 4:00 PM. The patients received the researchers' contact information for technical support, questions about the app or the study.

The nurses at the radiotherapy ward and the oncological departments received training and individual instructions of the app and training on using the web interface to monitor the patients' reports and alerts. They received written information and practical training with a researcher by managing simulated patient reports. Training and information sessions with nurses took place before the trial started and on an ongoing basis as new nurses started to work at the clinics. Nurses at the clinic also had contact information for the researcher and were encouraged to contact the researcher for technical support or other questions.

5.3.2 Standard care

The standard care for patients undergoing NACT for breast cancer was that patients met a physician before each treatment to assess health status and tumour response. They received treatment every week or third week at the clinic and remained at home in between (RCC, 2022). The standard care for patients undergoing RT for prostate cancer was that the patients met a physician before the treatment course started. They received treatment every working day for the entire treatment duration and had a physician visit three months after the end of treatment to assess tumour response and health status (RCC, 2021a).

According to the Swedish National Guidelines (RCC, 2021b), all patients who receive a cancer diagnosis should be assigned a contact nurse working at the clinics whom the patient can contact during office hours. The contact nurse guides the patient through the investigation, treatment, and rehabilitation by providing information about the treatment, symptoms that may occur and how to manage these. The contact nurse also gives information about psychosocial support and social services. Generally, patients are recommended "1177 Region Stockholm", a web- and mobile-based app for health services, advice, and health care contact, and 112 or the ED for life-threatening situations.

5.4 Data collection

5.4.1 Sociodemographic and medical data

Sociodemographic and medical data were included in all three studies. The patients self-reported their date of birth (converted to years at inclusion), marital status, occupational status and educational level in the baseline questionnaire. For marital status the available answer options were a) single, b) living apart; a couple – two households, and c) married/cohabiting with partner. For occupational status, the answer options were a) working, b) unemployed, c) student, d) retired, e) sick leave, f) other ____. For educational level, the answer options were a) primary education b) secondary school education, and c) university or college. Data concerning comorbid disease at the time of treatment start, medical treatment and tumour histopathology was collected from the patients' medical records. Comorbidity was calculated using the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). The CCI is based on the presence of heart, cerebrovascular, liver, kidney and lung diseases, dementia, cancer, diabetes, and AIDS. The scores are totalled and range from 0–37, with a higher value corresponding to greater comorbidity and increased relative risk of dying within 1 year.

5.4.2 Study I

5.4.2.1 Logged data from app-usage

The patient's app data was logged and stored at a server hosted by the company that developed and maintained the app during the studies. A staff member extracted and assembled the data in Microsoft Excel 2013 files. The files included the time, number and content of study participants' reports, alerts, self-care advice views and free-text messages sent. The Excel file did not contain data about use of links or graphs. The files were emailed encrypted to the researchers, and a code was sent separately by SMS.

5.4.2.2 Telephone interviews about using the app

The patients were interviewed individually by telephone close to the end of their reporting time. The interviews were conducted between November 2015 and August 2017. The interviews followed a semi-structured interview guide. The purpose of the interviews was to collect data about perceptions of using the app. Examples of questions included “*What was it like to report in the app?*”, “*How have you experienced that the technology worked?*” and “*How did you experience being called by a nurse after an alert?*”. The researcher made notes of the patients’ answers in an interview template. Five patients with prostate cancer were interviewed face-to-face, following the same interview guide. Those interviews were recorded and transcribed verbatim.

5.4.3 Study II

5.4.3.1 Questionnaires about individualised care and health literacy

The Individualised Care Scale (ICS) was used to measure perceived individualisation in care (Suhonen et al., 2000). The ICS consists of two sub-scales and assesses patients’ perceptions of individualised support through specific nursing interventions (ICS-A) and individuality in the care delivered (ICS-B). Items are rated on a five-point Likert scale by response alternatives ranging from strongly disagree to strongly agree. ICS-A and ICS-B each contain 17 items covering the domains clinical situation (seven items), personal life situation (four items), and decision control over care (six items). Higher scores imply that the care is perceived as more individualised. The questionnaire was developed in Finland for hospitalised patients (Charalambous et al., 2016; Suhonen, Papastavrou, et al., 2012). Content and construct validity and reliability has been demonstrated (Suhonen et al., 2005; Suhonen et al., 2007), also in the Swedish context (Suhonen et al., 2010). In the current study, the Cronbach alpha for the subscales (ClinA/B, PersA/B, DecA/B) and the total scales (ICS-A and ICS-B) was above .7 (range .784–.939).

The Swedish Functional Health Literacy Scale (FHL Scale) was used to measure functional health literacy (Wångdahl & Mårtensson, 2015). The FHL scale measures basic health information skills such as reading, using five items that are rated on a five-point Likert-scale ranging from never to always. Higher scores mean lower FHL. The Swedish Communicative and Critical Health Literacy Scale (CCHL Scale) was used to measure the ability to manage and communicate health information to improve one’s health (Wångdahl & Mårtensson, 2014). The CCHL scale has five items that are rated on a five-point Likert scale ranging from strongly disagree to strongly agree. Higher scores mean higher CCHL. The FHL and CCHL scales were initially developed in Japan (Ishikawa et al., 2008), but have been translated to Swedish and psychometrically tested in the Swedish context (Wångdahl & Mårtensson, 2014, 2015). In the current study, the Cronbach’s Alpha for the FHL total scale was .795 and for the CCHL the score was .857.

5.4.4 Study III

5.4.4.1 Questionnaire Health-Related Quality of Life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3.0 was used to assess health-related quality of life (HRQL) and in this study converted to EQ-5D 3L. The EORTC QLQ-C30 is a core

measure for all cancer diagnoses and include five subscales assess functioning, and three subscales and single items assess symptoms (Aaronson et al., 1993). There are also single items that assess global HRQL, overall health and perceived financial impact of illness.

5.4.4.2 Register data about healthcare utilisation, costs, and mortality

Data regarding each patient's healthcare utilisation from the start of treatment and six months forward was collected from the Region Stockholm administrative databases for inpatient care (VAL-SLV) and for outpatient care (VAL-OVR). The VAL register data included the date and type of visit (acute=yes/no), up to ten International Statistical Classification of Diseases and Related Health Problems (ICD) codes (DHHS, 2015), and up to ten classification of care measure codes (KVÅ) (Socialstyrelsen, 2018), the care facility, and costs (the variable Totkost) for each visit. Further, an additional variable to estimate the cost for each patient's health care visits (SIMKOST) that is not included in the VAL-OVR or VAL-SLV was provided.

The rationale for SIMKOST is that the degree to which Totkost captures Region Stockholm's real costs depends, among other things, on the reimbursement models applied for the different types of assignments included in each branch of care. The best conformity to actual costs is for branch acute somatic care, where Totkost is based on diagnosis-related groups (NordDRG). NordDRG is a system for classifying somatic and psychiatric inpatient, outpatient, and primary care contacts into diagnosis-related groups (DRG) (Socialstyrelsen, 2019). NordDRG is in turn based on cost per patient (KPP). KPP is a system for patient-related cost accounting (SKR, 2023).

To calculate SIMKOST, the region's costs for private specialists on national rates or care agreements according to the paid private practices database (ARV) are deducted from the profit and loss account, and per economic care branch. The summed Totkost in OVR and SLV per economic branch of care is compared against Region Stockholm's income statement per branch of care. SIMKOST is then produced by recalculating and adding to the existing Totkost to agree more with the amounts in the profit and loss accounts. The costs reported in the income statement for private care and medicines in open care are not included due to a lack of distribution keys. SIMKOST reflects roughly 90 % of outpatient care costs, and 99 % of inpatient care costs (personal communication, Region Stockholm Healthcare Administration).

The date(s) for each patient's cancer diagnosis or diagnoses and death date was collected from the Regional Cancer Centre cancer register (Regionalt Cancer Centrum Stockholm-Gotland). Data about cause of death regarding the deceased patients was obtained from the National Cause of Death register managed by The National Board of Health and Welfare (NBHW).

5.4.4.3 Intervention costs

The company that developed and maintained the app provided an economic approximation that was used to estimate intervention costs. The approximation included an assumption of 5 nurses per 100 patients. The costs were expressed as a

one-time implementation/startup cost of 50,000 SEK and weekly licensing costs per capita for nurses 1500 SEK and for patients 85 SEK.

5.5 Data analysis

The IBM Statistical Package for Social Science (SPSS) version 24–27, Microsoft Excel 2013–2016 with the add-on XLSTAT, and STATA 16 (Stata Corp. LP, College Station, TX, USA) were used for statistical analysis. A P -value $<.05$ was considered as statistically significant. Effect size was calculated for the mean difference to estimate the strength of the effect regarding significant P -values according to the formula (intervention group mean–control group mean/ SD_{Pooled}) and interpreted as $<.5$ =small, $.5$ – $.8$ medium, and $\geq .8$ large (Cohen, 1988).

5.5.1 Sociodemographic data

In regression analyses marital status was dichotomised into single/living apart or married/cohabitating, educational level into primary/secondary school or college/university, and occupation into working full-time or not working full-time.

In study I, differences in sociodemographic data were analysed between the respective RCTs' intervention group patients. In study II–III, differences in sociodemographic and clinical data were analysed between intervention and control groups within each RCT. Between-group analyses were performed by Student's t -test for continuous variables, and Mann–Whitney U, Fisher's Exact and Chi-square were used for categorical variables and non-normally distributed continuous variables.

5.5.2 Study I

5.5.2.1 Logged data

Patients' usage of the app within each RCT was analysed with descriptive statistics and presented by numbers, median and interquartile range (IQR). Each patient's total number of triggered alerts, self-care advice viewed, and free-text messages sent during their respective reporting period were entered as continuous variables in SPSS and log-transformed using natural log transformation (\log^e).

Adherence was calculated as each patient's total number of submitted reports during their respective reporting time (only counting one report per weekday), divided by the total number of that study participant's reporting weekdays, producing a percentage. To control for variance in app-usage, multiple regression analysis was performed with the sociodemographic and medical variables used as independent variables and the app-usage variables as dependent variables.

5.5.2.2 Telephone interviews

The telephone interviews were analysed inductively by conventional content analysis (Hsieh & Shannon, 2005). Notes and transcripts were firstly read several times to get an overview of and familiarisation with the data. All data was compiled into one dataset which was reviewed and systematically coded. Similar codes were grouped and

arranged into sub- and overarching categories. The authors discussed and continuously reviewed the analyses together to achieve consensus.

5.5.3 Study II

5.5.3.1 Questionnaires

For all three questionnaires (ICS, FHL Scale and CCHL Scale), single missing items were imputed by linear interpolation (Saunders et al., 2006). The percentage of imputed items for each item were less than 10%.

The ICS-A and ICS-B sum scores were calculated by summing the item scores for each domain (Clin-A/B, Pers-A and Dec-A/B respectively) and dividing by the subscales' total number of items. A total sum score for each subscale ICS-A/B was also calculated by summing all item scores and dividing by the total number of items (Suhonen et al., 2005). Student's *t*-test for independent and paired samples was used to analyse between- and within-group differences before and after treatment within each RCT.

The FHL and CCHL scale scores were first trichotomised according to their respective manual (Wångdahl & Mårtensson, 2017a, 2017b). Item responses in the FHL scale were coded as "Never" and "Seldom" = 1, "Sometimes" = 100, and "Often" and "Always" = 1000. CCHL scale item responses were coded as "Strongly disagree" and "Disagree to some extent" = 1000, "Neither agree nor disagree" = 100 and "Agree to some extent" and "Strongly agree" = 1. All item responses were summed, and scores of ≤ 100 were categorised as sufficient, scores $\geq 101 - <1000$ were categorised as problematic, and ≥ 1000 was categorised as inadequate. Between- and within-group differences were analysed with the Chi-square test. Between- and within-group differences of the mean total score for each FHL and CCHL scale items were analysed by Student's *t*-test for independent and paired samples.

The variables group (intervention/control), age, comorbidity, educational level, marital and occupational status were entered in stepwise multiple regression analysis to control for variance in the dependent variables ICS, FHL Scale, and CCHL Scale. The Pearson correlation coefficient was used to investigate the relationship between the outcome variables ICS, FHL Scale, and CCHL Scale and the app-usage variables adherence, the number of self-care advice views, the number of free-text messages sent, and the number of alerts triggered.

5.5.4 Study III

5.5.4.1 EORTC QLQ C-30 to QALYs

NICE acknowledges that EQ-5D data may not always be available and suggests incorporating data from other measures of health using 'mapping' (NICE, 2013, p. 45). Mapping is a method by which values obtained from GPBMs can be predicted from other measures or indicators of health. A response mapping algorithm (Longworth et al., 2014) was used to map EORTC QLQ C30 onto EQ-5D 3L (Rabin & Charro, 2001) and gain health state utilities. The British utility weights (Dolan et al., 1995) in the algorithm were exchanged for Swedish utility weights (Burström et al., 2013). The mean predicted EQ-5D 3L value (EQ-5D 3LP) before treatment minus the value after treatment was used to

measure effectiveness. A lesser reduction in mean EQ-5D(P) 3L was better. An intention-to-treat (ITT) (McCoy, 2017) approach was undertaken; missing values were imputed as the mean per group and time. To reflect a gradual change in life quality during treatment, QALYs were linearly calculated with the formula [(EQ-5D(P) 3L after treatment minus EQ-5D(P) 3L before treatment) x (individual treatment duration in weeks /52) /2].

5.5.4.2 Costs

All costs were converted to Euro by an exchange rate of 10.3257 SEK=€1. Costs for the intervention were estimated by dividing the overall startup cost by the total number of patients with the respective diagnosis, treated with the respective treatment regime in Region Stockholm and the Gotland Region for three years 2016, 2017 and 2018 (518 patients with breast cancer treated with NACT and 683 patients with prostate cancer treated with RT) (RCC, 2020b). The estimate included an assumption of five nurses per 100 patients. No additional costs for the nurses to handle symptom alert phone calls were collected. Hence, based on each patient's number of weeks in treatment (wt), the study participant's intervention costs were calculated with the formulas B-RCT; $(5212/518) + ((39 \times 5 / 100) \times (wt)) + (2.25 \times wt)$ and P-RCT; $(5212/683) + ((39 \times 5 / 100) \times (wt)) + (2.25 \times wt)$.

5.5.4.3 Cost-effectiveness analysis (CEA)

A stochastic (O'Brien et al., 1994) CEA per RCT (B-RCT / P-RCT) from the payer perspective (Region Stockholm) was conducted. Three ICERs were calculated. To calculate ICERa, the intervention group's interventions costs plus all health care costs minus all of the control group's health care costs were divided with the intervention group's change in QALY minus the control group's change in QALY. ICERb was calculated as above but excluded non-acute health care costs, and ICERc was calculated by dividing the intervention group's intervention costs minus the control group's intervention costs with the change in QALY for the intervention group minus the change in QALY for the control group. To explore sample uncertainty concerning the mean ICERs, non-parametric bootstrapping (1,000 replications) were used (Briggs et al., 1997).

For a visual representation, the bootstrap values of the incremental intervention costs and incremental QALYs were plotted in cost-effectiveness planes. Health care utilisation costs were classified as acute/non-acute based on the VAL-variable AKUT. The analysis was based on the study participant's treatment duration (< 1 year); therefore, no discounting of costs or results was made.

5.5.4.4 Exploration of healthcare utilisation and costs

Cost variables were produced within each RCT. Within each dataset (VAL-OVR and VAL-SLV) total and acute cost variables were produced by summing each participant's total costs and acute costs. In the P-RCT, external radiotherapy and internal (brachytherapy) costs were removed as they were similar across the groups due to the standardised treatment.

Secondly, cost variables for healthcare utilisation associated with the respective cancer treatment in each RCT were produced based on a qualitative analysis of ICD codes. The approach for the qualitative analysis was both conventional and summative (Hsieh & Shannon, 2005). According to Shieh and Shannon (2005) a conventional content analysis starts with observation and identifying what is in the content, while a summative content analysis begins with keywords identified based on interest or research literature. For the current study, all ICD diagnosis codes within each RCT were gathered in Excel sheets (one for acute outpatient and one for acute inpatient health care), and the occurrence of all unique codes was counted. In the current study, keywords were identified about reasons for acute health care use during treatment with chemotherapy and radiotherapy (for prostate cancer) in the research literature and from the most frequent diagnosis codes in the existing data sets (Excel sheets). Duplicate diagnosis codes were removed, and diagnosis codes were grouped into categories based on similarities.

In the B-RCT the ICD codes D709C, R502, R508 and R509 were categorised as fever/neutropenia, K521 and A047 were categorised as gastroenteritis/colitis, D649 was categorised as anaemia, and N390 was categorised as urinary tract infection. In the P-RCT R339, N390, R301, N390X, N304, N109, T830, R391, R319 and N300 were categorised as urinary problems. Lastly, each patient's number of visits and costs according to the categories within each RCT was calculated to create dependent visit and cost variables of acute outpatient and inpatient costs associated with the respective cancer treatment (Appendix). ‘

Table 2. Conventional and summative analysis of ICD codes in the trials B_RCT and P-RCT

Trial and focus	Key words	Diagnosis codes	Category
B-RCT neo-adjuvant chemotherapy for breast cancer	Fever	D709C, R502, R508 R509	Fever/Neutropenia*
	Gastrointestinal problems	K521 and A047	Gastroenteritis, colitis
	Anaemia	D649	Anaemia
		N390	Urinary tract infection**
P-RCT radiotherapy for prostate cancer	Urinary problems	R301, R339, R391, R319 N390, N390X, N304, N109, T830, and N300	Urinary problems**

B-RCT=Breast cancer trial

P-RCT=Prostate cancer trial

ICD= International Classification of Diseases

* Predefined code

**Code derived based on content

The cost variables were analysed descriptively and in inferential statistics by multivariate regression analysis. Visual inspection and preparatory analysis suggested that the assumption of multicollinearity was met (tolerance between .371-.956). Depending on the level of overdispersion, Poisson or negative binomial models using log

link functions were fitted to continuous variables (Abu Bakar et al., 2022). The variable Group was coded as Control= 0, Intervention =1. The continuous variables Age at inclusion, Charlson Comorbidity Score, and Baseline EQ-5D(P) 3L score were entered as covariates. The reference category was ascending (=1). In the B-RCT, the patient's number of NACT were also included as an independent variable, since there were rather significant variations among the patients.

5.5.4.5 Medical data

Based on the treating physician's documentation in the patients' medical records prior to treatment start, the patients' history of medical conditions was analysed by directed qualitative analysis (Hsieh & Shannon, 2005). According to Shieh and Shannon, directed qualitative analysis is deductive and starts with pre-defined codes. The pre-defined codes in the current study were Cardiovascular, Respiratory, Joint, Diabetes, Gastrointestinal, Cancer, Renal or Urological, Neurological, Thyroid, and Mental Health (Conditions). First, all text about the patients' pre-existing health problems were extracted onto an Excel sheet. Duplicates were removed and health problems associated with the pre-defined codes were coded. Each patients' codes were subsequently noted to produce dichotomous variables (yes/no).

Table 3. Examples of directed qualitative analysis of patients' histories of medical conditions according to physician notes before cancer treatment.

B-RCT	Physician notes in medical records	Code
Pat 1	Depressive symptoms	Mental Health
	Malignant melanoma	Cancer
Pat 2	Cholecystitis	Gastrointestinal
	Post-traumatic stress syndrome	Mental Health
Pat 3	Myocardial infarction	Cardiovascular
	Diabetes, diet-treated	Diabetes
Pat 4	Colon cancer	Cancer
P-RCT		
Pat 1	Multiple Sclerosis	Neurological
	Kidney cancer	Cancer
Pat 2	COPD	Respiratory
	Diabetes, insulin-treated	Diabetes
	Mild depressive symptoms	Mental Health
Pat 3	Testicular lymphoma	Cancer
	Tuberculosis	Respiratory
Pat 4	Arthritis	Joint problems
	Atrial fibrillation	Cardiovascular
	Diverticulitis	Gastrointestinal

For anonymity reasons the examples have been somewhat adjusted by changing the combinations.

5.5.4.6 Life Quality dimensions

To gain deeper insight into how the changes in life quality as measured with the EORTC QLQ-C30 were distributed across the five EQ-5D(P) 3L dimensions, a quantitative analysis of change within each dimension of the EQ-5D(P) 3L was performed by calculating the number and percentage of patients that reported any problems (level 2 or 3) before and after treatment. The severity coding was as follows: Level 1= No

problems, Level 2= Some problems, Level 3= Unable to, or confined to bed, or Extreme pain (depending on item). First, the number of patients in the intervention group that reported some problems (Level 2+3) at baseline was counted and deducted from the number of patients that reported some problems at follow-up. This number was converted to a percentage change. The same was calculated for the control group and after the intervention group percentage change in the intervention group was subtracted from the percentage change in the control group. The percentage change within each dimension can indicate within which dimension the difference is more pronounced. By adding the total number of dimensions difference in change a total percentage for difference in change is also produced (EuroQoL Research Foundation, 2023).

6 Ethical Considerations

The ethical standards of the Helsinki declaration guided the performance of all studies included in this thesis project (World Medical Association, 2013), and the Stockholm Regional Ethics Board approved the research project plan (permit numbers 2013/1652-31/2 and 2017/2519-32). There was no harmful content in the apps, and all medical advice adhered strictly to the current evidence. To ensure the patients' information privacy, confidentiality, and integrity, they received an anonymous user-id and a password for logging into the app. The participants were encouraged to keep this information separate to prevent unauthorised access to personal data in the app if the phone was stolen or lost. The personal information was handled confidentially. Paper and pen questionnaire data was handled in an anonymised manner through codes, and the code key list was stored in a locked cabinet only accessed by the researcher working with the data. During data management, study participants were assigned unique codes, and the code lists were kept locked in a cabinet accessed only by research group members.

One possible risk that was calculated from the beginning was about cyber security. When the trial began, the GDPR legislation had not been implemented, but there was an active debate about protecting personal data within general society and the research society. The server that hosted the patients' self-reported data had a high level of security against data breach by firewalls, which was technologically advanced during that time. App-data was logged and stored at a server approved by The Swedish Data Protection Authority. Precautions were taken during data extraction and handling; only one assigned staff member at the company that developed and maintained the app had access to the web interface for technical support. The web interface was only accessible to research group members recruiting study participants, nurses at the oncology ward involved directly in the patients' care and the assigned staff member.

All logged server data has been erased and log data files are stored according to Swedish law and in adherence to KI guidelines. Few patients in the intervention groups expressed concerns about security, but as we do not have data about reasons for patients that declined to participate, non-responders or those who dropped out we do not know if this issue somehow affected the studies.

Prior to the current study, the app had been pilot-tested in a sample (n=18) of elderly persons > 65 in municipal care, mean age 70, indicating user-friendliness. In the current thesis, individuals who did not own a smartphone were offered to borrow one during the study. For those patients that did, the researcher demonstrated how to use it, tried to ensure that the patient was comfortable handling it, and encouraged them to contact the researcher if they needed support. Another possible risk identified before the trial began was that patients who were randomised to the control group would feel that their care was suboptimal since they did not get access to the app during their treatment. At the time, that risk was accepted when weighed against the benefit of gaining new and important knowledge. The patients were offered to be informed about the outcome and study results.

7 Results

7.1 Patient characteristics

In the P-RCT, two baseline questionnaires per group went missing and four patients (two in each group) did not report marital status, occupational status and educational level, which was treated as missing. There were no statistically significant differences regarding sociodemographic and clinical characteristics between the intervention and control groups within each RCT. There were several statistically significant differences between the two RCTs regarding sociodemographic characteristics. Patients with breast cancer were on average younger (range 27–77) compared to patients with prostate cancer (range 43–82). A higher proportion of patients with breast cancer had university education and worked full-time. Patients with breast cancer also had a lower comorbidity score compared to patients with prostate cancer (Study II) (Table 4).

Table 4. Patients' sociodemographic and clinical characteristics

		B-RCT			P-RCT			
		IG n=74	CG n=75	p ^a	IG n=75	CG n=75	P ^a	P ^b
Age (in years)	M (SD)	48 (11)	50 (12)	.134 ^c	70 (7)	70 (6)	.957 ^c	<.001 ^c
Marital status n (%)	Married / Cohabiting	61 (82)	57 (76)	.222 ^d	54	55	1.00 ^d	.672 ^d
	Single/Living alone	13 (18)	18 (24)		17	16		
	Missing	0	0		4	4		
Occupation n (%)	Working full-time	57 (77)	48 (64)	.106 ^d	14	8	.246 ^d	<.001 ^d
	Not working full-time	17 (23)	27 (36)		57	63		
	Missing	0	0		4	4		
Educational level n (%)	University	50 (68)	44 (59)	.309 ^d	30	24	.388 ^d	<.001 ^d
	Not university	24 (32)	31 (41)		41	47		
	Missing				4	4		
CCI	M (SD)	1 (1.1)	1 (1.2)	.486 ^c	3	4	.391 ^c	.001 ^c
Treatments n*	M (SD)	7 (2)	7 (3)	1.00 ^d	27 (2)	27 (2)	1.00 ^d	n/a

B-RCT=Breast cancer trial, P-RCT=Prostate cancer trial

IG=Intervention group, CG=Control group

M=Mean, SD=Standard Deviation

P= P value ^a=between groups ^b= between trials ^c=Student's t-test, ^d=Fisher's Exact Test

CCI=Charlson Comorbidity Index

* Neoadjuvant chemotherapy for breast cancer and radiotherapy for prostate cancer

Most patients with breast cancer had sufficient health literacy levels at baseline and most patients with prostate cancer had problematic health literacy levels at baseline (Study II). A stepwise multiple regression analysis showed that a significant level of variance in patients' health literacy levels before treatment was explained by educational level. In both RCTs, patients with a university education had better health literacy (FHL and CCHL scales) than patients without a university education (Table 5).

Table 5. Univariate regression analyses of baseline health literacy levels

	B	95% CI for B		β	t	P	Adj R2
		Lower	Upper				
B-RCT (N=149)							
DV FHL							
IV educational level*	-1.405	-2.438	-.373	-.217	-2.690	.008	.040
DV CCHL							
IV educational level*	1.238	.281	2.196	.206	2.556	.012	.036
P-RCT (N=142)							
DV FHL							
IV educational level*	-1.526	-2.439	-.614	-.269	-3.307	.001	.066
DV CCHL							
IV educational level*	1.523	.511	2.535	.245	2.975	.003	.053

B-RCT=Breast cancer trial, P-RCT=Prostate cancer trial

* 1=Primary/Secondary education, 2=University/College,

DV=Dependent Variable, IV=Independent Variable

FHL=Functional Health Literacy, CCHL=Critical and Communicative Health Literacy

B = unstandardised coefficient, CI=Confidence Interval

β = Beta, standardised coefficient

t= t-statistic

P = P value for the independent variable

Adj R2 = Adjusted R-Square for the multiple regression model

The patients' medical records showed that 83 % (62/75) of the patients with prostate cancer in both groups had at least one medical condition documented by their physician at their cancer treatment enrolment visit. In the B-RCT the corresponding figure for the intervention group participants was 51 % (38/74) and in the control group 52 % (39/75) (Table 6). Among patients with breast cancer, a higher proportion had a medical history of thyroid problems compared to patients with prostate cancer. Among the patients with prostate cancer, a higher proportion of patients had a medical history of cardiovascular, respiratory, renal/urological, joint problems or diabetes, compared to patients with breast cancer.

Table 6. Patients' history of medical conditions

Medical conditions n (%)	B-RCT		p^a	P-RCT		P^a	P^b
	IG n=74	CG n=75		IG n=75	CG n=75		
Cardiovascular	2 (3)	0 (0)	.497 ^a	9 (12)	18 (24)	.088 ^a	<.001 ^b
Respiratory	2 (3)	3 (4)	1.00 ^a	16 (21)	9 (12)	.188 ^a	<.001 ^b
Joint problems	9 (12)	5 (7)	.401 ^a	19 (25)	9 (12)	.020 ^a	.030 ^b
Diabetes	1 (1)	0 (0)	1.00 ^a	10 (13)	10 (13)	1.00 ^a	<.001 ^b
Gastrointestinal	12 (16)	7 (9)	.472 ^a	10 (13)	6 (8)	.428 ^a	.595 ^b
Cancer	6 (8)	5 (7)	1.00 ^a	13 (17)	8 (11)	.347 ^a	.091 ^b
Renal or urological	0 (0)	1 (1)	1.00 ^a	6 (8)	7 (9)	1.00 ^a	.001 ^b
Neurological	4 (5)	8 (11)	1.00 ^a	3 (4)	3 (4)	1.00 ^a	.61 ^b
Thyroid problems	6 (8)	7 (9)	1.00 ^a	3 (4)	1 (1)	.620 ^a	.043 ^b
Mental health	2 (3)	3 (4)	1.00 ^a	2 (3)	1 (1)	1.00 ^a	.723 ^b

B-RCT=Breast cancer trial, P-RCT=Prostate cancer trial

IG=Intervention group, CG=Control group

P^a = P value Fisher's Exact Test between groups (intervention group / control group)

P^b = P value independent samples t-test

Study I

7.1.1 Adherence

The median adherence to report symptoms daily was 83% in both RCTs. There was a trend towards a decrease in adherence towards the end of the treatment that could be seen in both RCTs. In the B-RCT the adherence reached 70 % at day 73, but then remained under 70 % until day 97. In the P-RCT the adherence level reached 70 % at day 45, but then remained under 70 % until day 55. Among patients with breast cancer, adherence levels were not associated with any of the variables examined (age, marital status, educational level and comorbidity) but among patients with prostate cancer those who were married, or cohabitating had a higher adherence compared to patients who were single or lived alone.

Nearly all patients with breast cancer triggered at least one alert during the time of the trial (96 %), and most alerts were yellow (86 %). In the P-RCT 72 % of the patients triggered an alert during the time of the trial, and most alerts (90 %) were yellow. When counting adherence, the number of reports made during the weekend was excluded, but many patients also reported during the weekend. In the breast cancer group 263/1126 (23 %) of the total number of alerts were made during weekends. For the prostate cancer group, this figure was 29 % (163/570).

7.1.2 Acceptability

In the interviews the patients in both trials voiced that daily symptom reporting felt like being in regular contact with health care, safeguarded and observed. Some patients described that symptom reporting was more meaningful earlier in the treatment phase when symptoms were new and not always necessary when symptoms were more familiar. The patients appreciated that the nurse called after alerts and thought that alerts should be responded to around the clock. Overall technical problems or usability were not considered a barrier to daily symptom reporting. In both RCTs, patients spoke of memory impairment and the treatment's cognitive side effects as a hindrance to remembering to report in the app daily. Remembrance was assisted if the reporting became routine, so the automatic reminders in form of push notifications were much appreciated, but some wanted to adjust the timing of this to fit better with own daily routines. Patients that had comorbid diseases commented that reported concerns in the app were not always related to their cancer treatment, making it challenging to report by the available responses.

Daily symptom reporting felt like diary-keeping for some patients, but it could also be a disease reminder on days when a patient felt well. Symptom reporting encouraged reflections on one's wellbeing and increased awareness of symptoms, with regard to what was normal and expected and to what one should be observant of. Some patients in the B-RCT voiced that it was challenging to report when they felt extraordinarily sick, and a few worried that their alerts annoyed the nurses. In the interviews a couple of patients in both RCT described that on occasions they were not contacted by a nurse following an alert.

7.1.3 Engagement

From the logged data it could be seen that most of the patients used the app-components self-care advice and free-text messages. Patients with breast cancer viewed a self-care advice 15 times on average (SD 12) and 95 % viewed the selfcare advice at least two times. Most views were about oral problems ($\approx 20\%$) followed by nausea (12 %) and pain (10 %). Approximately one third of the selfcare advice-views followed a prompt (smart advice). Patients with prostate cancer viewed a self-care advice notice 9 times on average (SD 13) and 67 % made two views, 20 % were about urinary urgency followed by difficulties urinating (13 %) and weight gain (8 %). According to the interviews, the content in the symptom questionnaire and self-care advice was regarded as relevant and covered most symptoms, but participants voiced that the app should contain more self-care advice information about psychological symptoms and diet. As for the symptom reporting, the patients perceived that the self-care advice were particularly helpful in the beginning of treatment or when a symptom first occurred.

Most patients wrote free-text messages at some point but there was considerable variation between patients regarding how many. Among patients with breast cancer 93 % wrote at least one and 75 % of the patients with prostate cancer. The mean number of free-text messages sent for patients with breast cancer was 15 (SD 16), for patients with prostate cancer it was 7 (SD 9). The message content was not analysed in-depth, but common topics were symptoms not in the symptom questionnaire, as well as requests for or declines of contact.

In the interviews the patients described the history graphs as being a helpful feature. Some patients with breast cancer used the graphs to compare symptoms over time and to detect symptom patterns relating to the treatment intervals. Some patients with prostate cancer said the graphs were useful as they displayed when symptoms increased or decreased. More often compared to patients with breast cancer, those with prostate cancer commented that they didn't use the links or graphs since their symptoms were mild or did not bother them.

Multivariate regression showed that among patient with breast cancer, older patients sent less free-text messages. Among the patients with prostate cancer, those who were older, and those who had a higher level of education made more self-care advice views while patients with more comorbidities, made fewer self-care advice views.

7.2 Study II

7.2.1 Individualised care

In the B-RCT there were no significant differences between the intervention and control group regarding perceptions of individualised care. Intervention group patients rated individualisation regarding the clinical situation lower at follow-up compared to baseline, with a decrease in the subscale Clinical situation (Clin-A) being observed ($P=.013$, effect size .4). In the P-RCT, patients in the intervention group rated individuality in the care regarding decision control (ICS-B, Dec-B) higher compared to patients in the control

group ($P=.041$, effect size .4). Intervention group patients rated individualisation in care regarding the clinical situation lower at follow-up compared to baseline, with a decrease in the subscale Clinical situation (Clin-A) being observed ($P=.03$, effect size .3). Multivariate regression analysis showed that variance in the patients' perceptions of the individualisation of care (ICS-A/ICS-B) was not statistically significantly explained by patients' usage of the app (adherence level, number of self-care advice views made, or free-text messages sent, or alerts triggered).

7.2.2 Health literacy

Neither of the RCTs demonstrated a significant change in the proportion of patients classified as having either sufficient, problematic, or inadequate levels of health literacy after the intervention. In the B-RCT there were no statistically significant differences between the intervention and control group in health literacy scores at the item level before or after the treatment. In the P-RCT, patients in the intervention group rated their ability to "...seek information from a variety of sources..." ($P=.012$, effect size .48) and "...understand and communicate the information to others..." ($P=.016$, effect size .46) as better compared to the patients in the control group after treatment.

The Pearson correlation coefficient showed that study patients with a lower level of communicative and critical health literacy triggered more alerts in the app than patients with a higher level ($r_{58} = -.368$, $P = .004$).

7.3 Study III

7.3.1 Cost-effectiveness B-RCT

Incremental QALYs (QALYs gained) was .0076 (95% CI .0074 - .0078). The mean total cost for Interaktor per patient was €92 (SD 2) (Table 7). The mean incremental cost for the intervention and all healthcare was €1,454 (95% CI 1,368 - 1,540). ICERa was €202,368 (95% CI 152,008 - 252,728). The mean incremental total cost for the intervention and acute healthcare was €353 (95% CI 311 - 395). ICERb was €49,903 (95% CI 37,049 - 62,758). Lastly, when healthcare costs were excluded from the analysis, the ICERc was €13,213 (95% CI 11,145 - 15,281).

7.3.2 Cost-effectiveness P-RCT

Incremental QALYs was .0002 (95% CI .0001 - .0002). The mean total cost for Interaktor per patient was €43 (SD .2) (Table 7). The mean incremental cost for the intervention and all healthcare €-120 (95% CI -184 - -56). The ICERa was €-1,092,136 (SD 35,155,229 95% CI -3,274,774 -1,090,502). The mean incremental cost for the intervention and acute healthcare was €417 (95% CI 376 - 458). The ICERb was €745,987 (SD 16,006,924 95% CI -247,317 - 1,739,292). Lastly, when health care costs were excluded from the analysis, the ICERc was 13,118 (SD 1,314,743 95% CI -68,468 - 94,704).

Table 7. Intervention costs €

Intervention costs €	B-RCT	P-RCT
Fixed cost (per capita)	10	8
Licensing fee patient per week	2	2
Licensing fee nurse per week per patient (assuming 5 nurses per 100 patients)	2	2
Mean total intervention cost M (SD)	92	2 43 .2

B-RCT=Breast cancer trial, P-RCT=Prostate cancer trial

M=Mean, SD=Standard Deviation

7.3.3 Healthcare utilisation and costs B-RCT

In both groups, 2 % of the outpatient costs represented acute care. In the intervention group, 18 % of the patients had a total of 34 acute outpatient visits for fever. In the control group, the corresponding figure was 12 %; 21 visits. In the intervention group, 9 % had an unplanned admission from outpatient to inpatient care; 37 unplanned admissions. In the control group, 8 % had an unplanned admission from outpatient to inpatient care; 29 unplanned admissions.

About a third of all inpatient care was acute in both groups (intervention group 31.8 %, control group 29.3 %). The most common conditions in both groups were fever, gastroenteritis/ colitis, anaemia, and urinary tract infection. There were no significant relations between the groups regarding the number of visits or costs (outpatient and inpatient, acute or total). The only significant relations were that older age ($P=.002$), higher health-related quality of life at baseline ($P<.001$), and less comorbidity ($P=.024$) significantly predicted lower outpatient healthcare costs.

7.3.4 Healthcare utilisation and costs P-RCT

Nearly 6 % of the outpatient cost represented acute care in the intervention group, and in the control group the corresponding figure was 5 %. In both groups, 33% of the patients had an acute outpatient care visit. In the intervention group, 7 % of the patients had an acute outpatient visit for urological problems; 7 visits. In the control group, the corresponding figure was 8 %; 14 visits. Acute outpatient visits for urological problems that led to an unplanned admission from outpatient to inpatient care happened to one patient in the intervention group (1 time) and two patients in the control group (3 times).

Most inpatient care was acute (80%) in the intervention group, the corresponding figure for the control group was 65 %. Acute inpatient care episodes were mostly by reason of dyspnoea (4 times) and acute subendocardial infarction (3 times) in the intervention group and urinary tract infection, (3 times) and anaemia (2 times) in the control group.

There were no significant relations between the groups regarding the number of visits or costs (outpatient and inpatient, acute or total). The only significant relations were that patients with higher health-related quality of life before treatment had less outpatient care visits ($P=.002$), were less likely to have an acute outpatient care visit for urological problems ($P=.018$) and were less likely to have an inpatient care visit ($P=.039$).

7.3.5 Life Quality dimensions B-RCT

The mean EQ-5D(P) 3L before treatment was .86 in the intervention group and .87 in the control group. After treatment the mean EQ-5D(P) 3L was .84 in the intervention group and .80 in the control group ($P=.036$, effect size .099) (Table 8). The differences in change were Mobility, -5%; Self-care, -5%; Usual activities, -10%; Pain/Discomfort, -8%; and Anxiety/Depression, -11%.

7.3.6 Life Quality dimensions P-RCT

The mean EQ-5D(P) 3L before treatment was .88 in the intervention group and .89 in the control group. After treatment the mean EQ-5D(P) 3L was .87 in the intervention group and .88 in the control group. The values did not differ statistically significantly in between the groups at either time points (Table 8). The differences in change within each dimension were: Mobility, 1%; Self-care, -1%; Usual activities, 1%; Pain/Discomfort, -4%; and Anxiety/Depression, -3%.

Table 8. Patients EQ-5D(P) 3L scores before and after treatment

B-RCT						P-RCT											
IG	CG					95 % CI	IG	CG				95 % CI					
M	(SD	M	(SD	df	t	P	Lower	Upper	M	(SD	M	(SD	df	t	P	Lower	Upper
BL	.86(.09)	.87(.08)	147	-41	.681		-.033	.022	.88(.08)	.89(.07)	148	-.72	.472	-.033	.015		
FU	.84(.09)	.80(.11)	147	2.12	.036	*099.002	.066		.87(.08)	.88(.07)	148	-.66	.510	-.032	.016		

EQ-5D(P) 3L=Predicted EQ-5D 3L according to Longworth et al. (2014)

B-RCT=Breast cancer trial, P-RCT=Prostate cancer trial

BL=Baseline, FU=Follow-up

IG=Intervention group, CG=Control group

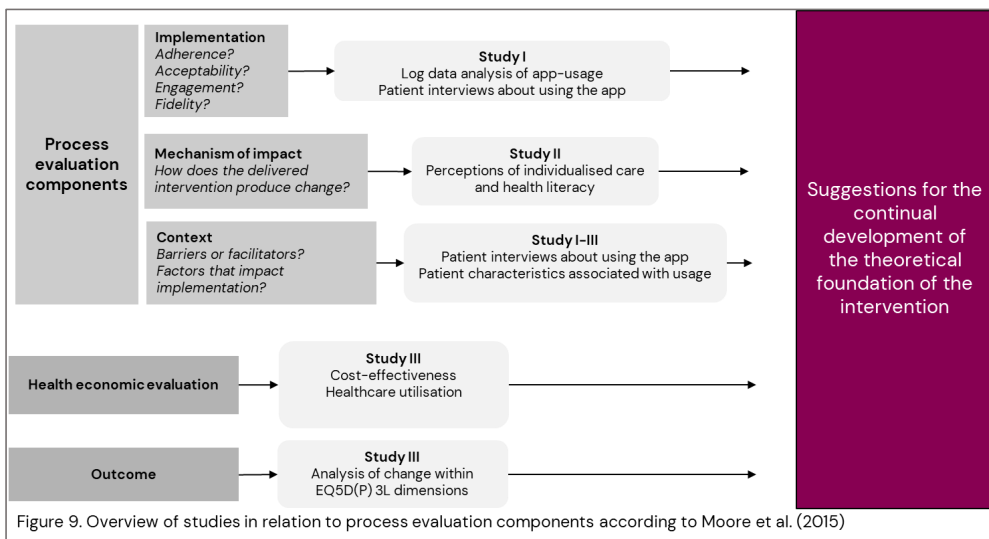
M=Mean, SD=Standard Deviation

* =Cohen's *D* Independent samples

Df=Degrees of freedom

8 Discussion

I will discuss applicable findings from studies I-III under headings related to the components of process evaluation (Figure 9). The findings from study III that relate to the cost-effectiveness of the intervention and impact on healthcare utilisation will be addressed separately. Afterwards I will make suggestions for the continual development of the theoretical foundation for the intervention.



8.1 Implementation

8.1.1 Adherence

The adherence levels reported in the current thesis (83 %) appear favourable, given the levels reported in the research literature (Cho et al., 2021). Higher levels have been reported – however, it is essential to consider how adherence has been operationalised when comparing studies. In a systematic review of electronic systems for patients with cancer to report symptoms from home (Cho et al., 2021), the studies that used a similar method to measure adherence as was used in the current thesis (dividing the number of expected symptom reports by the number of reports submitted) reported mean adherence percentages that ranged from 45 to 90 %. Higher mean percentage rates were reported in the studies that measured adherence by dividing the number of patients who had reported with the number of enrolled patients (70–92 %). Studies have also measured usage by dividing the average number of log-ins per day or the average number per trial period but not reported if patients always reported during the log-ins. The way adherence was analysed in this thesis is in line with the suggestion by Sieverink et al. (2017); hence the high levels can be taken to validate that patients did use the app as intended, indicating frequent and continuous contact with their healthcare professionals during their cancer treatment was valuable.

8.1.2 Acceptability and engagement

In the current thesis, patients generally felt symptom reporting was easy and fast. Overall, the app was described as a convenient means of support. The present thesis's interviews indicate that time influences patients' app use. Daily symptom reporting was experienced as especially meaningful when symptoms were unfamiliar, but as the patient's experience and familiarity grew, there was a lower desire and tendency to report symptoms daily. In the research literature, two longitudinal use patterns among studies that assess usage over time have been identified (Cho et al., 2021). One involves a gradual increase from the beginning to the mid-point and then a gradual decrease. The second is a gradual decrease from beginning to end and fits well with those discovered in the current thesis. A gradual decline may signify more independence in self-management and a patient with confidence in their experience-based knowledge and expertise regarding their symptoms and self-management. However, a qualitative study with women undergoing NACT (Beaver et al., 2016) found that the women expressed increased needs for support towards the end of treatment because of more symptoms. This has also been observed for patients undergoing radiotherapy for prostate cancer; for example, Dickinson et al. (2021) observed that cognitive fatigue peaks during treatment completion. In line with prior research (McCann et al., 2009), the current thesis shows that with time and experience, patients acquired general knowledge about the disease and treatment and desired more individualised and in-depth information than what the app contained. This is in line with a review of telehealth experiences among women with breast cancer that found interventions with a stationary format were perceived as less pleasant to use (Meneses et al., 2023).

The interview results in the present thesis show that patients experience remote symptom monitoring as mainly positive, which harmonises with results from other qualitative studies (Darley et al., 2023; Leonardsen et al., 2022). When patients with cancer were asked about the positive or negative aspects of remote monitoring during the Covid-19 pandemic, they emphasised saving time and feeling less ill not having to visit the hospital (Leonardsen et al., 2022). Although most were not reluctant to discuss sensitive topics during remote consultations with clinicians (telephone or videoconferencing), losing body language and real-life eye contact could create a feeling of distance. Therefore, participants stressed that remote monitoring could only partially substitute for physical visits. Participants experienced remote monitoring more positively as time passed (Leonardsen et al., 2022).

Regarding the intervention in the present thesis, the self-care advice and free-text functions were intended to correspond to the individual patient's needs, so there were no recommended usage levels. The qualitative results demonstrated that patients appreciated these functions – for example, patients with comorbidities described clarifying when a reported symptom was related to a previous condition by free text. Logged data confirmed that patients did use the free-text and self-care advice functions. It has already been shown that patients want to contextualise reported symptoms, like pain, with information about location, intensity compared to previous reports and self-care performed (McCann et al., 2009). Patients generally are positive

towards asynchronous communication with healthcare professionals via email or SMS (Conroy et al., 2023; Kristiansen et al., 2023; Zanaboni & Fagerlund, 2020). However, clinicians are more reluctant towards such communication and prefer physical visits due to safety concerns and fear that simplified communication will increase their workload (Antoun, 2015; Clark et al., 2023; Conroy et al., 2023). Clinical benefits from electronic asynchronous free-text communication to clinicians have yet to be thoroughly researched (Goyder et al., 2015; Voruganti et al., 2017). Conroy et al. (2023) reported a positive association between using a message function and two-year survival and chemotherapy-related hospitalisations among patients with breast cancer. Causality could not be concluded, and of the patients who used the function, a higher proportion had private healthcare insurance and higher median income.

8.1.3 Fidelity

As Moore et al. (2015) state, qualitative data can indicate if the delivery of an intervention has high fidelity to how it was intended (Saarijarvi et al., 2022). In the interviews, patients described that, on occasion, they were not phoned by a nurse, although their report had triggered an alert, but we do not know the entire situation surrounding these events. The logged data shows that the patients reported (and triggered alerts) also during the weekends, so some of these instances may have occurred during weekends. Still, if a patient triggered an alert during a weekend but had forgotten that the nurse would not respond or lost track of which day it was, this may have negatively affected the patients' trust in the intervention. Several patients also asserted that the nurses should monitor and respond to alerts around the clock or during weekends. This was initially how the intervention was intended.

8.2 Mechanisms of impact

8.2.1 Individualised care and health literacy

For patients with breast cancer, the underlying mechanisms of impact contributing to the positive effects on symptom burden demonstrated by Fjell et al. (2020) are less elucidated by the current thesis results. No effects were shown regarding individualised care perceptions; a decrease was seen in the clinical dimension. Furthermore, patients did not improve their health literacy levels, although these were relatively high at baseline. Perceptions of individualised care as measured with the ICS, have also been observed to correlate negatively with perceived health status; patients with lower health status perceive their care as less individualised, which may explain why the patients rated their care as less individualised after their cancer treatment (Suhonen, 2006).

Some findings regarding hypothesised mechanisms of impact were observed among patients with prostate cancer, which may help elucidate the results of the effect study yet to be published. The intervention group patients rated the support from nurses to have decision control as more individualised. Further, intervention group patients regarded their critical health literacy skills as higher than those in the control group after using the app – this is positive since most had problematic levels to begin with. The current thesis also shows that health literacy was significantly associated with

education level. Both findings align with another study, including patients with prostate cancer who improved their health literacy after using Interaktor (Sundberg et al., 2020). It is also interesting to note that patients with lower health literacy triggered more alerts in the app compared to patients with higher levels – this harmonises with empirical evidence showing that patients with low health literacy have more reported symptoms (Clarke et al., 2021; Halverson et al., 2015; Husson et al., 2015; Nilsen et al., 2020; Song et al., 2012). These results are encouraging from a health care equity perspective if we take them to mean that patients with low health literacy can improve critical health literacy skills and that patients with low health literacy, more reported symptoms, and more triggered alerts also receive more nurse support (Lawler et al., 2021).

8.3 Context

8.3.1 Barriers or facilitators

Qualitative results in the current thesis indicate that internet access is not a barrier to using Interaktor. This is not surprising since internet access in Sweden is high, even though the proportion of people who lack internet access is somewhat higher among elderly persons (SCB, 2020). On a global level, though, internet access can still be a barrier for patients with cancer to report their symptoms from home, although not on a significant scale (Cho et al., 2021), and this is likely a transient phenomenon. The current thesis results indicate that interpersonal factors like health status influenced the use of Interaktor. For example, patients described that reporting symptoms was extra valuable when feeling ill, but when patients were feeling very unwell, reporting was also challenging due to a lack of energy. Memorising could also be a barrier.

In the early days of e-health research, Eysenbach (2005) asserted in a seminal paper the need to understand patients' e-health usage and suggested that usage metrics analysis should be combined with systems theory and patient demographics to predict use. Christensen and Mackinnon (2006) commented that patient characteristics, such as the severity of the patient's health problem and individual preferences, were likely to impact patients' usage and also needed to be analysed by correlation or predictive techniques. Both qualitative and quantitative empirical evidence has since shown that patients' health can be a barrier to reporting symptoms from home (Cho et al., 2021)—for example, fatigue, memory loss, poor hand strength, and visual impairment. Nevertheless, not all studies show that health status impacts patients' usage. For example, studies with patients in the survivorship/follow-up phase (van der Hout, van Uden-Kraan, et al., 2021), less frequent or optional reporting rates (Borosund et al., 2013; Judson et al., 2013; van der Hout, van Uden-Kraan, et al., 2021) and participants recruited through the general media (Borosund et al., 2013). It should be noted that patient health also impacts recruitment to research studies of ePRO interventions. One mobile phone-based ePRO system study reported that 42 % (41/97) of the invited patients declined to participate – often due to health reasons, such as being in too much pain or too worried (Bielli et al., 2004).

There are features of e-health applications that can help patients – for instance, in the research for the present thesis, the interviews showed that patients felt that reminders

were helpful. Prior evidence shows that reminders are effective (Cruz et al., 2019; Kelders et al., 2012). For example, a systematic review (Cruz et al., 2019) about mobile self-management apps for patients undergoing breast cancer treatment found that participants who used reminders had higher app usage rates during the intervention and better outcomes than patients who did not. Providing shorter symptom questionnaire alternatives or allowing patients to skip selected symptom questions may help fatigued patients.

The current thesis research showed that some patients with breast cancer wanted responsibility for contacting the nurse themselves. But some also described worries that their alerts would annoy the nurses. It needs to be investigated whether these findings signify that patients have an excessive consideration for the nurses or that patients sincerely want increased control of nurse contact. Previous studies have demonstrated that female, younger, and highly educated patients prefer a more active role in care (Florin et al., 2008; Kolovos et al., 2016). Nevertheless, the alert function initiating nurse contact for patients with severe symptoms is a fundamental aspect of the Interaktor intervention. Even though patients are responsible for self-management, nurses can reinforce patients' self-management abilities through support and guidance (Cuthbert et al., 2019; Encarnacao et al., 2018).

8.3.2 Factors that impact implementation

The current thesis interview findings show that patients with breast and prostate cancer described using graphs differently – to detect a symptom pattern and aid activity planning (breast cancer) or as visualising symptom improvement or deterioration (prostate cancer). To an extent, this likely mirrors differences in the chemotherapy and radiotherapy symptom profiles. However, it may also reflect that the patients with breast cancer were younger (and may have had more caring responsibilities) and that they, to a higher degree, were working full-time.

Among patients with prostate cancer, those older, those less educated, and those with comorbid disease used the self-care advice less. Further, having comorbid conditions was mentioned as something that could make symptom reporting in the app less straightforward. Correspondingly, Borosund et al. (2013) reported that comorbidities were associated with decreased use of a cancer self-management system. The literature has highlighted that healthcare digitalisation may cause inequalities for older patients and those with multimorbidity. Such disparities can be constituted by a lack of relevant and accessible information (Kristiansen et al., 2023; Verma et al., 2022). It has been shown that the situation of older persons who experience comorbid diseases complicates cancer self-management. Patients have expressed uncertainty about using websites and web-based information and feel safer listening to their health care professionals (Haase et al., 2021). In Sweden, almost a third (28 %) of persons over 65 have multimorbidity (having at least two chronic conditions); in European countries, the average is higher (37 %) (OECD, 2020). To an extent, the thesis samples probably reflect the clinical landscape on patients' levels of multimorbidity, except that patients with severe cognitive problems were excluded. In the future, it may be valuable to investigate

whether patients with cognitive impairments also benefit from the intervention, although with the help of a carer or relative. Anecdotally, it did emerge that a spouse on occasions had reported symptoms on behalf of a patient.

The results can also indicate a need for more training in using the app or reveal that navigating back and forth between features in the app is challenging. Nearly all patients (in both trials) used their device (most often a smart phone), but even if a person owns a smart phone, they may have limited experience using apps. Studies have shown that using a larger mobile tablet instead of a smartphone can increase adherence rates to remote health measurement interventions (Simblett et al., 2018). It may be beneficial to collaborate cross-disciplinarily so that usability aspects are analysed even further. For example, occupational therapists could weigh in on making apps more inclusive for patients with impairments, and designers could show how to make navigating between different app functions easier. Such collaboration could produce digital tools that are as inclusive as possible. To ascertain that patients can navigate the app, it could be beneficial to make a follow-up telephone call to patients one week into using the intervention and ask if they feel confident about using all the components.

Among patients with breast cancer, older age was associated with less use of free-text messages. Still, older age was also associated with fewer acute visits for treatment-related symptoms. Hence, older patients with breast cancer may have sent fewer free-text messages because they experienced milder or fewer symptoms. Conclusions cannot be drawn about causality, but a previous study (Göransson et al., 2018) showed that elderly patients described Interaktor as easy and intuitive. Also, other studies have undermined stereotypical assumptions about elderly patients' ability to use digital tools (Beatty et al., 2017).

The symptom management process for patients undergoing cancer treatment has been conceptualised as dynamic since symptoms' occurrence, frequency, and intensity change throughout treatment phases and due to interactions with family and health care providers (Brant et al., 2016). The factors affecting the use of Interaktor during the RCTs can be divided into environmental, individual, and intervention factors, as in the model by Short et al. (2015) describing factors influencing user engagement. External factors like internet access do not appear to be a limiting factor; instead, it seems essential to consider the dynamic intertwinement of individual and intervention factors, like patients' health status, desire to control healthcare contacts and experience-based knowledge about symptoms. Since these factors vary, researchers may also need to adjust their premisses regarding how the intervention is intended to work.

8.4 Health economic evaluation

8.4.1 Cost-effectiveness

The intervention cost was below €10 per week/patient in both RCTs. The intervention decreased the patient's loss of HRQOL during treatment. However, the effect was small and only significant for patients with breast cancer. Since the difference in HRQOL was slight and the time frame was relatively short, the number of QALYs gained was also

small. Moreover, when patients' health care costs were included in the analysis, the large variation in health care costs resulted in such considerable insecurity regarding the cost-effectiveness estimates that they are of limited value for decision-makers. Few studies exist to compare our results with, but a recent report describes a health economic evaluation of a similar intervention, eRAPID (Velikova et al., 2022). Cost-effectiveness was evaluated both from a healthcare and a societal perspective. In this analysis, development costs were not included, but costs for the training material for patients and nurses and maintenance of the software were. The authors found that when costs for time out of work, patient travel and non-prescription medications were included, the costs for the intervention group were less than for usual care. Still, the difference was not enough to reach cost-effectiveness, according to NICE, since the differences in QALYs were small and not significant. A CEA of the Onko-Compass showed a small positive effect on HRQOL when measured with EQ-5D and no significant differences in direct or non-direct medical costs from a healthcare or societal perspective (van der Hout, Jansen, et al., 2021). An essential difference with the current thesis research is the care context; the study included long-term survivorship patients.

In the current thesis research, the ICER for patients with breast cancer surpassed the Swedish NBHW threshold when all healthcare costs were included but was only slightly above the NBWH low cost per QALY definition when non-acute care was excluded. For patients with prostate cancer the ICER was surpassed when non-acute care costs were excluded but considerable cost savings were demonstrated when all healthcare costs were considered. These results are rather challenging to interpret, but the results do not indicate considerable cost-savings from less or changed healthcare utilisation. Still, more factors impact when subsidy decisions are made and a tendency to accept a higher cost per QALY in cancer care has been detected (Dakin et al., 2015).

Even though direct cancer costs more than doubled between 1995–2018, the cancer proportion of total healthcare costs has increased by less than a percentage point, and production loss from morbidity and premature mortality stands for the highest societal costs for cancer (Hofmarcher et al., 2020). In Europe, non-healthcare costs are similar to healthcare system costs for cancer (Hofmarcher et al., 2020); therefore, health economic evaluations from a societal perspective are needed. The MRC process evaluation guidelines also recommend taking a societal perspective since failing to consider the societal perspective can limit decision-makers ability to make the best decision regarding resource allocation (Moore et al., 2015). Further, it is vital to examine the cost-effectiveness of digital health from a societal perspective since when care is transferred from inpatient to outpatient settings, healthcare costs can be shifted to patients and informal caregivers (Collins et al., 2017), hence reliance on informal care as a substitute for and complementing health services can generate inequalities.

Considering the current thesis research, and existing prior evidence, it is becoming increasingly conceivable that ePRO, rather than lowering direct medical costs from less healthcare use, can create societal savings due to increased survival (Caminiti et al., 2022; Lu et al., 2023). Hypothetically, if patients, due to lesser decreased HRQOL, can

continue to work during their treatment to a greater extent, this may also generate societal savings. For breast cancer, the costs for production losses represent more than half (54 %) of the total cost, so bringing down these costs can yield considerable benefits. In comparison, the corresponding proportion for prostate cancer is about a third (31 %), probably as a higher proportion of the patients are retired (Lundqvist et al., 2016). It needs to be investigated whether societal cost savings can be generated with ePRO through increased acute and planned care costs if patients with symptoms are “caught” more efficiently. However, studying and estimating morbidity-caused productivity loss (sickness absence and inability to work) can be challenging since data which can generate robust estimates are lacking (Hofmarcher et al., 2019). A cost-effectiveness analysis from a healthcare perspective still has value, as it can guide local decision-makers and be a first step toward a more encompassing evaluation (Drummond et al., 2015).

8.4.2 Healthcare utilisation

The current thesis showed that for the patients receiving treatment for breast cancer the intervention group made more visits for neutropenia/fever compared to patients in the control group. As aggressive infections can have such rapid progress in patients undergoing chemotherapy, healthcare (intravenous antibiotics) is often required even if the patient has not yet started to experience other symptoms (apart from a temperature rise) (Koenig et al., 2020). Also, in the evaluation of eRAPID, more visits for fever were observed in the intervention group (Absolom et al., 2021). This finding can be interpreted as validation that patients with breast cancer who reported their symptoms via Interaktor received a timelier and prompt symptom management as a result of the alerts triggered when reports of fever were made. However, for the patients treated for prostate cancer the results were reverse, patients in the intervention group had fewer acute visits for urological problems. Similar to prior research (Jairam et al., 2019), this thesis showed that neutropenia, gastrointestinal symptoms and anaemia were common reasons for patients’ acute hospitalisations. However, in the current thesis, the proportion of acute care visits for treatment-related symptoms was small compared to the patient’s total visits.

Researchers have tried to predict acute care use based on demographic and clinical variables, but it has been shown that the phenomenon is very complex (Henry et al., 2021; Prince et al., 2019). In the current thesis group membership (intervention/control) was not associated with the number of acute care visits but that HRQOL before treatment was. Evidence suggests that several socioeconomic, demographic and clinical factors affect hospitalisations and emergency department visits during systemic anticancer treatment (Prince et al., 2019). Henry et al. (2021) observed a positive impact on avoidable ED visits from a 24-hour nurse–telephone support system with triage. Still, the researcher found that other unidentified significant factors also explained much variability. Comorbidities generally did not predict avoidable ED visits, but a history of congestive heart failure did. Half of the patients with congestive heart failure had avoidable ED visits during the study period. The author noted that the patient

population with congestive heart failure is complex, and this group has more frequent hospital admissions and readmissions. The researchers recommended intensified monitoring of these patients when adding agents to or changing patients' regimens (Henry et al., 2021). Several studies suggest that treatment-related factors strongly impact hospitalisations (Prince et al., 2019), and ED visits are much more common following the first treatment cycle following treatment regimen changes and with more cytotoxic agents. Other factors impacting hospitalisation include cancer type and reduced performance status (Henry et al., 2021; Prince et al., 2019).

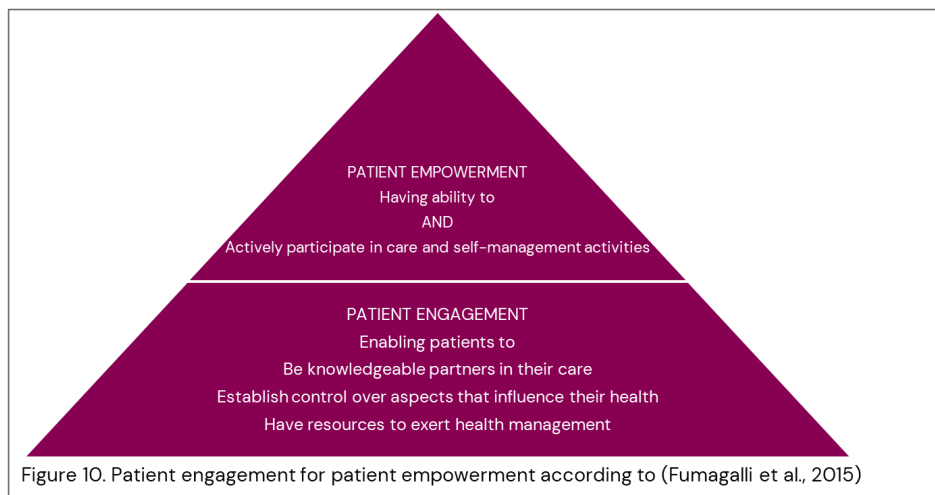
8.5 Enhancing operationalisation of individualised care and developing the theoretical foundation

Given the current thesis results and in view of previous studies of patients using Interaktor (Fjell et al., 2022; Gustavell et al., 2017; Langius-Eklof, Christiansen, et al., 2017; Sundberg et al., 2020) I will here suggest how operationalisation of the theoretical underpinning of the intervention can be more enhanced and propose a way forward to develop the theoretical foundation for the intervention.

Radiotherapy for prostate cancer is considerably more standardised compared with neoadjuvant chemotherapy for breast cancer, although the total dose, number of treatments and anti-hormonal therapy may vary (RCC, 2021a; Mottet, et al. 2021). As a result, the app version is more fitted to the individual patient since most receive a similar treatment. But for patients with breast cancer, tumours are categorised, defined and treated significantly differently, so, there are substantial variations within the group of patients receiving NACT for breast cancer (RCC, 2022). For example, most but not all patients have a surgically created access port to a central vein where chemotherapy is administered. The number of cytotoxic agents used, how often the treatment is given, and the length of treatment varies and affects symptoms a lot. Patients with a dose-dense regimen and patients given more cytotoxic agents have more severe symptoms. Therefore, the app for patients with breast cancer may need to be more tailored. In the future, enhanced individual adaptation of app settings, and recommendations for reporting frequency, can be a way to strengthen the operationalisation of individualised care.

Empirical contributions to Suhonen's work to develop and describe the theoretical concept of individualised care (Suhonen et al., 2002) are based on studies with hospitalised patients, mainly during their discharge process. The measurement of the concept emphasises the nurses' actions to adapt the nursing care according to the patient's wishes – and the underlying notion is that the nurse practically performs or partakes in the nursing care procedures. However, unlike hospitalised patients, patients still living at home perform much of the care independently as self-care. Then the nurse's role becomes more to individually support the patient to care for himself based on the patient's needs. Therefore, the theory may need to be developed by emphasising these aspects more, and I suggest using the concept of empowerment (Calvillo et al., 2015; Fumagalli et al., 2015; Risling et al., 2017) to describe, explain and justify the results from the Interaktor studies.

Patient empowerment is the goal for patient engagement (Barello et al., 2016; Fumagalli et al., 2015; Risling et al., 2017; WHO, 2016). Patient empowerment comprises patients' active care participation through self-care activities, which at an individual level, in direct care, can be achieved by enabling patients to be knowledgeable partners in their care, to establish control over aspects that influence their health and to have resources for exerting health management (Calvillo et al., 2015; Fumagalli et al., 2015; Risling et al., 2017) (Figure 10). In theory, simplifying patient-healthcare provider communication and accessing information and support are essential for patient engagement and empowerment (Calvillo et al., 2015; Eskildsen et al., 2017; Fumagalli et al., 2015).



The notion that using Interaktor may promote patient empowerment fits with other empirical evidence. Several qualitative studies about digital health experiences for chronic disease management (including cancer) include descriptions of empowerment. For example, patients have pronounced that accessing information and performing tasks like measuring vital signs increased their self-efficacy and readiness to engage during physical clinic appointments (Taylor et al., 2022). An essential outcome of patient empowerment is reduced anxiety and emotional distress (Calvillo et al., 2015; Eskildsen et al., 2017). Therefore, it is interesting to note that the life quality dimensions that most differed between intervention and control groups in the Interaktor study were related to emotional distress and disease/treatment-related symptoms. Fjell et al. (Fjell et al., 2022) interviewed 40 patients with breast cancer (from the sample for the current thesis) in individual interviews about their experiences of care. The results showed that the app increased their care participation as they were supported in accounting for their symptom experience between the treatments in a more accurate way since they had reported the symptoms regularly.

Among the patients with prostate cancer, those in the intervention group rated their individualised care perceptions as higher regarding decision control - they also had improved self-rated ability to understand and communicate important health information. Dahl and Eagle (Dahl & Eagle, 2016) suggest that policymakers' expectations

of patients' active care participation and empowerment are problematic due to assumptions about patients' health literacy. Their analysis of the readability of online health information and patient leaflets about chronic medical conditions showed that much was written in too complicated language for many in the general public. The authors reasoned that challenges associated with patients' health literacy need to be recognised. An implication of lower health literacy among patients undergoing cancer treatment can be that an approach built on continuous assessment of symptoms may be more suitable compared to a method that relies heavily on verbal and written information given before the treatment starts. It has been shown that patients value ongoing dialogue and collaboration via patient-clinician interactions that recognise interdependency and responsibility-taking for both the patient and the provider, but that patients may not always want responsibility; instead, depending on the context, they may want a more passive role when feeling pain or anxiety (Bastemeijer et al., 2016).

Patient empowerment has been interchangeably used with other concepts, and more consensus is needed on operationalising and measuring patient empowerment through supportive e-health solutions (Eskildsen et al., 2017; Pekonen et al., 2020; Risling et al., 2017). A systematic review of instruments used to measure patient empowerment in cancer patients (Eskildsen et al., 2017) outlined four essential components: firstly, an intrapersonal aspect, or feelings of self-control/efficacy; secondly, an interactional component, such as the ability to understand the health care system (resembling, and related to health literacy), and thirdly, a behavioural part, namely the actions a person takes. Lastly, the authors added a relational component to capture the concept, called "enablement" (p 157). Enablement accounts for the patient/provider balance, as a patient can only be empowered if the health professional enables this. This assumption aligns with individualised care in that nurses' actions determine the level of individualisation in the patients' care (Charalambous et al., 2012). As we advance, I propose that future studies examine patient testimonies and use of Interaktor through the lens of patient empowerment, suggestibly with focus on the element's enablement and emotional distress. Furthermore, using a quantitative instrument that include these domains can also be used in evaluation (Eskildsen et al., 2017). It is interesting to note that patients expressed that the app should contain more information about psychological symptoms and diet, and these requests can be taken to indicate that patients want the healthcare to pay increased attention to support and enable patients to self-manage their mental well-being and lifestyle.

8.5.1 Limitations

The pandemic has not considerably affected this research. The patients had completed their reporting and responded to follow-ups. Two register data withdrawals were performed when persons were recommended to work from home, but assistance was swift and helpful.

8.5.1.1 Transferability

We can only compare the results from the two trials to a limited extent, as the two samples were of different sex and diagnoses. However, interesting reflections on the use of the app can be made regarding both similarities and differences based on age and diagnosis.

Caution should be taken when extrapolating the current thesis findings, as the samples do not wholly reflect the general population of patients with breast or prostate cancer. For example, due to the exclusion criterion of having a documented cognitive decline or being judged by a nurse as unable to report symptoms daily via an app. This may be more significant regarding patients with prostate cancer as they are older and more prone to cognitive decline. Relying on nurses' judgement of patients' fitness to be included in a study can make the thesis results somewhat vulnerable to a bias caused by informal gatekeeping- if nurses, due to paternalistic or undue consideration, acted to protect for example, patients with mental health problems. There are descriptions in the literature that clinicians can experience conflict when they discuss clinical trials with a patient (Whicher et al., 2015). For example, they can feel that the patient is vulnerable and does not understand what participation entail, or they think that discussing the research takes time from other patients. A fear that the patient will stop trusting the clinician and suspect that the clinician's loyalty lies elsewhere may also be an issue.

For patients with breast cancer, it needs to be pointed out that neoadjuvant chemotherapy was given to larger (>5 cm) and more aggressive tumours at the time of this study. In general, the patients who receive NACT are younger, although the indication to treat patients with breast tumours by NACT has increased during the writing of this thesis (Cain et al., 2017). During NACT, the patient still has a tumour in the breast, which may cause extra anxiety (Hay & Pascoe, 2020). However, due to positive evidence of the benefits of NACT, it will likely be used for a more significant proportion of patients with breast cancer ahead (Montemurro et al., 2020). Hence, the results in the present thesis are not transferable as the population receiving NACT hereafter differ in demographics and tumour characteristics.

Another issue regarding the transferability of the thesis results is that the studies were performed in an urban setting. One of the hopes for digital health is that it will reduce care inequalities as rural dwellers have been demonstrated to have less access to care (WHO, 2011). The patients in the current thesis may have utilised care more during their treatment since care may be easier accessible in Stockholm than in other regions in Sweden (Region Stockholm, 2022). Patients who live rurally may rely more on self-management and self-care due to having a longer distance to the hospital. They may be more inclined to try an e-health solution and value the intervention more (Nelson et al., 2021).

8.5.1.2 Missing data

A source of uncertainty is the number of missing questionnaires from patients with prostate cancer. The dropout rate was rather large: 20 % in the intervention group

(15/75) and 25 % (19/75) in the control group. Due to the significant dropout rate, the applicable study results may have lacked statistical power to detect significant differences, and the risk is also increased that statistically significant results are false (Dumas-Mallet et al., 2017). According to Fewtrell et al. (2008), less than 5% dropout is not a problem, but levels of 20 % are a severe risk. Among patients with breast cancer, the dropout rate was lower; 7 % (5/74) in the intervention group and 5 % (4/75) in the control group. Three reminders were sent to the patients who did not return their follow-up questionnaires. However, the logged data showed that the patients in the intervention group used the app despite not responding to their questionnaires. In the current thesis, the four patients with missing baseline questionnaires were random, but the significant non-response rates of follow-up questionnaires are impossible to conclude. Non-response regarding the follow-up questionnaires can be due to several factors, such as respondent fatigue, weak design, or that the questionnaire is perceived as irrelevant to the responder.

The ICS has previously been used for patients with cancer (Kousoulou et al., 2019), but to the author's knowledge, it has not been used in an outpatient context. There were items in the individualised care scale that patients in text comments and verbally noted as irrelevant for them. For example, the item "My daily habits have been considered during the hospital stay (e.g. personal hygiene)? Furthermore, "I have decided what time I take care of my hygiene". There is a balance between using a questionnaire as intended because conclusions about validity and reliability depend on how the questionnaire has been psychometrically tested. For patients with prostate cancer that did not undergo internal radiotherapy (brachytherapy), hospitalisations were not part of the treatment regime. In this thesis, the internal consistency of the Individualised Care Scale was good. The individualised care scale has demonstrated both ceiling and floor effects in another study (Rodríguez-Martín et al., 2018); however, in the current thesis, this was not a big issue, except for a tendency of ceiling effect regarding the intervention group patients with breast cancer; at follow-up in the subscale for the clinical dimension, and for both groups with breast cancer regarding ICS-B decision control at follow-up which may impact the interpretation of the lack of significant results in this cohort.

Although most researchers agree that the preferred solution to handle missing data is to prevent it - imputation can be a way to handle missing data (Lodder, 2014; Saunders et al., 2006). All imputation methods can lead to biased conclusions depending on assumptions regarding why the data is missing and the imputation method chosen. The reason for imputing data is not to know how the patient would have responded but to estimate the underlying distribution of the data and thereby provide accurate estimates of means, variances and correlations without losing too much power (Lodder, 2014). Imputation was used for missing items in Study II and missing questionnaires and registered data (visits/costs) in Study III. In study II, missing items were assumed to be missing at random and imputed by linear interpolation. A disadvantage of linear interpolation is that it is not highly precise (Saunders et al., 2006). However, this influenced little in the study as there were few missing items. In

study III, missing data was imputed as mean per group and time point. Imputing a mean is one of the easiest methods for imputation (Lodder, 2014). A negative aspect of imputing means is that it decreases the variation, which affects the hypothesis testing assumptions. However, if less than 10% is imputed by mean, this probably does not cause problems. A more conservative method would be to impute the control group's mean per time point. Another method that could have been used would be to impute the median value, as the median is less sensitive to outliers. However, this is generally not recommended (Lodder, 2014).

There is some evidence for actions that can increase retention rates. These include monetary incentives, providing a pen with a postal survey, and electronic reminders (Gillies et al., 2021). However, more research is needed, and the evidence is not highly graded. Regarding postal surveys, it has been observed that longer questionnaires (more than seven pages) have lower response rates than shorter ones and that health status or age does not significantly impact the response rate (Iglesias et al., 2000). A sample of 346 women who had undergone mastectomy for breast cancer achieved a postal response rate above 70 % for a nine-page questionnaire using a method which included sending a reminder one week after the first survey and sending a pack with the complete survey at week 3 and 7 (Kazzazi et al., 2018). However, the researchers received feedback that the reminder was a negative reminder of having been hospitalised, illustrating the need to reflect on ethical issues around how many reminders can be sent.

As Eysenbach (2005) points out in the seminal paper about the law of attrition, a common phenomenon in e-health research is that patients drop out of the studies (do not respond to questionnaires) before they stop using the intervention. This was also true in the current thesis, particularly in the sample of patients with prostate cancer. While patients in the intervention group did not return their follow-up questionnaires, several patients continued to use the app after their reporting time was due to end. When only dropout is considered as opposed to attrition, which is about when users stop using the application, the efficacy of the intervention can be underestimated.

8.5.1.3 Randomisation and reporting bias

According to the Cochrane risk of bias tool (Sterne et al., 2019), the risk of bias does not differ between different randomisation processes, for example, unrestricted randomisation versus blocked (to prevent unbalanced ratios), and regarding all demographic and most clinical variables, the control and intervention groups were balanced. Another source of bias concern the risk that only positive results are reported (selection bias). In the current thesis, a study protocol was published before the data collection had ended and data analysis had begun. However, some deviations from the study protocol have occurred. For example, in the study protocol and original research plan, it was stated that biomarkers and data about mortality would be collected and analysed. Data about mortality was collected and analysed, but biomarkers were not collected due to changed regulations in data protection concerning GDPR. In both studies II and III, minor differences were demonstrated;

however, it is still vital that the results are published transparently and publicly available.

8.5.1.4 Interviews

A critical aspect of achieving credibility in qualitative research is the researchers pre-understanding because the researcher is the instrument (Graneheim & Lundman, 2004). Regarding the analysis of the interviews in Study I, shared first authorship benefited the process, and the two co-authors' competence complemented each other. The first author (Fjell) had worked with developing the intervention from the beginning, had long clinical experience in oncology nursing and managed the recruitment and inclusion process regarding patients with breast cancer. The current thesis's author was peripheral in the sense of not being involved in developing the intervention and was native to oncology. This complemented the analysis with fresh eyes and a novel and curious outlook. Moore et al. (2015) state that the relationship between the researchers that perform the process evaluation and intervention developers must be functional so that the researcher can have a critical outlook and, for example, Question if the intervention is used differently from how it was intended. The strength of the current thesis results is that quantitative results from transparent analysis methods complement and, in study I, qualitative and quantitative results were triangulated and, therefore, extra robust (Leech & Onwuegbuzie, 2007).

The telephone interviews were brief and did not probe the patients' experiences profoundly. Also, they were not audio-recorded, but the researcher noted answers in a template. However, nearly all findings have been described previously and harmonise with other qualitative studies. For example, patients experience remote symptom monitoring as mainly positive (Darley et al., 2023; Leonardsen et al., 2022), fatigue and remembrance can be a barrier, and reminders are perceived as helpful. It can thus validate the current thesis results that previous authors have reported most qualitative findings and that some have also been described in reviews. Logged data was not available to corroborate the findings about the patients' use of symptom graphs, which is a limitation.

8.6 Own reflections from writing the thesis

Since I began my work with this thesis, global events have added perspectives to the results. During COVID-19, healthcare was reorganised to protect patients with cancer as they were at greater risk of infection due to impaired immune systems (Murphy et al., 2022). Healthcare increased the use of previously implemented telehealth services and developed new ones—like combinations of phone consultations, video calls and texts. Satisfaction rates were high, and patients described improved convenience and lower costs for work absence, fuel and parking. But there were also downsides, such as concern for privacy (for example, having a private space at home when discussing sensitive topics with healthcare professionals), increased isolation, lack of training and access to equipment. Research indicates that patients prefer blended services, but informing patients about the outcome of treatment or prognosis and performing examinations via telehealth appears to be less accepted among patients (Murphy et al.,

2022). Patients and healthcare providers may be more inclined towards digital solutions like Interaktor after the pandemic, and the results may have been somewhat different if the study had been performed today.

Another development that adds perspective to the thesis involves artificial intelligence (AI). Two applications of AI which are increasingly being used today within cancer care research are modelling to predict short-term mortality or survival for patients treated for cancer and text screening to identify keywords or phrases from patient notes to support advanced care planning, determine symptom severity or monitor online support groups (Reddy et al., 2023). It is not difficult to imagine how an application like Interaktor could fit in a context where AI is used with patient-reported data, helping clinicians interpret and respond to free-text messages and symptom reports and gaining knowledge about patients' symptom experiences.

I have discovered that there are many more stakeholders within digital health, in addition to patients, researchers, and clinicians; for example, manufacturers and developers of devices, apps, and related services (Ekman, 2018). Many of which are driven by the desire to earn money rather than altruism (Isakadze & Martin, 2020). Developments within digital healthcare solutions are partly catalysed by promises of healthcare savings (Cederberg, 2016), as an increasingly elderly population is forecasted to increase healthcare costs (Lundqvist et al., 2016). Methods to estimate cost-effectiveness thresholds can involve estimating the value lost when other healthcare is cancelled to fund new healthcare, or alternatively, it can include assessing what individuals are willing to give up in consumption, in order to gain additional QALYs. If resource distribution reflects societal preferences, these estimates should correspond; otherwise, health care may be under or over-funded (Henriksson et al., 2018). According to Henriksson et al. (2018), cost-effectiveness comparisons indicate that healthcare may be underfunded. In light of this, it might be that in order to provide cancer care that is perceived as acceptable to individuals with cancer and their families, policymakers' hopes that digital health will lower healthcare costs are too optimistic.

Other factors also indicate that healthcare spending needs to increase rather than decrease. Hofmarcher et al. (2020) argue that until recently, rising costs from new cancer drugs were mainly compensated by reductions in the costs for inpatient care, but considering that the process of shifting cancer care to an outpatient setting has progressed far, continued measures here will produce less savings in the future. Then it will become increasingly difficult to finance further investments in new treatments without an increase in the share of health expenditures devoted to cancer care.

8.7 Future research

A natural progression of this work is to analyse the experiences of the clinical nursing staff that worked with the patients during the two trials by monitoring reports and responding to alerts. The issue of the patients' use of free text is intriguing and could produce interesting findings if explored in future research. A greater focus on how the app fits with the patient's treatment trajectory from early days in treatment onwards by qualitative and quantitative follow-ups would also be a fruitful area to gain knowledge about how the app can be adjusted to the progressive needs of the patient. An important issue for further research is to investigate if the app affects the costs of patients' sick leave and out-of-pocket expenses. Lastly to gain a fuller picture by evaluations of real-world implementation on a larger scale are needed.

8.8 Recommendations for policy

Continued efforts are needed to make the symptom management support for patients with cancer timelier and more efficient using ePRO in clinical practice. A key policy priority should therefore be to plan for the necessary investments to ensure implementation of appropriate systems, services and support. Provision of systems for using ePRO in clinical practice will enhance patients' ability to participate in their own care and may be a way to promote patient empowerment.

9 Conclusions

From the thesis results we can conclude that patients with breast and prostate cancer used the app and valued the intervention as a way to promote participation in care and gain assurance through continuous contact with healthcare professionals. This corresponds well with the concept of empowerment and how this can be achieved through structures for patient engagement. Using the app can positively affect individualisation in care and health literacy for patients with prostate cancer undergoing radiotherapy. Making the app more individual, for example, by adjusting features more according to the patient's clinical situation and preferred settings may benefit patients with breast cancer undergoing chemotherapy.

It was not entirely proven that the intervention saved healthcare costs neither was it shown that healthcare costs would be considerably higher. The knowledge gained in this thesis will be helpful to interpret the effects on symptom burden and quality of life and, in the long run, support stakeholders in deciding realisation in clinical practice.

10 Popular science summary of the thesis

Worldwide, every third person gets cancer. Breast and prostate cancer are the most common among women and men. They are treated and often cured by surgery, chemotherapy, and radiotherapy, often followed by hormonal therapy. Patients can experience many different symptoms from the disease and treatment –most can be eased, but if symptoms are too severe, treatment must pause, reducing the likelihood for cure. Patients with cancer who report their symptoms to healthcare via trustworthy electronic solutions such as mobile apps (m-health) can be helped faster, leading to less symptom burden. Still, those who decide about implementation, need proof that patients will use and value the app and regard their care as improved by using it. It should also be shown that using the app during cancer treatment is cost-effective.

The app described in the current thesis was developed for patients to report their symptoms and concerns to healthcare professionals and receive advice rapidly. It includes the components: 1) daily reporting of symptoms and concerns, 2) alerts to nurses when patients report symptoms with urgent risks, 3) graphs so patients can see their symptom history 4) self-care advice. A nurse monitors the patient's reports and contacts patients with severe symptoms by phone. The app was tested in patients with breast cancer during chemotherapy (N=149) and with prostate cancer during radiotherapy (N=150). This thesis aims to investigate the value of implementing the app in clinical practice from both the patient's and a health economic perspective.

Study 1 shows that most patients used the app to report their symptoms daily and read self-care advice. Patients considered the app easy to use and felt safe since a nurse called if they had severe symptoms. Patients' usage differed; among women with breast cancer, older women used the free-text function less. Among patients with prostate cancer, those having a lower educational level or those with other illnesses than cancer read the self-care advice less. **Study 2** showed no differences between those who used the app and the control group among women with breast cancer on how individualised their care was or how they felt about using health information. Among patients with prostate cancer, those using the app regarded the support from nurses for making decisions about their care as more individualised than the control group. They also felt more confident about using important health information (health literacy). **Study 3** shows that all patients' life quality decreased during treatment but less for those using the app. The change in the patient's quality of life with regards to their time in treatment was used to calculate quality-adjusted life years (QALY). Patients who used the app gained QALYs compared to the control group but at a cost. Since the care costs varied greatly, a more extensive study is needed to determine if using the app influences care costs. Compared to the control, patients with breast cancer who used the app had more acute visits for fever, and patients with prostate cancer who used the app made fewer visits for urological problems.

From the results, we can conclude that patients with breast and prostate cancer used the app and valued the intervention as a way to promote care participation and gain assurance through continuous contact with healthcare professionals. Using the app can positively affect individualisation in care and health literacy for patients with prostate cancer undergoing radiotherapy. More individualised settings may benefit patients with breast cancer. It was not completely demonstrated if the intervention decreased or increased healthcare costs. The knowledge gained will be helpful to interpret the effects on symptom burden and quality of life and, in the long run, support stakeholders in deciding realisation in clinical practice.

11 Acknowledgements

This thesis would not have been possible without some persons who I want to acknowledge.

I could not have undertaken this journey without **my supervisors** who sustained my learning and development;

My main supervisor **Professor Ann Langius-Eklöf** – with your excellent scientific knowledge and your viewpoint solidly anchored in the discipline you escorted me through the research with advice, discussions, and constructive comments. But you have also been very generous by giving me freedom to explore. I am sincerely grateful for all the help I received from you, and I really feel that your comments improved my texts.

Associate Professor Kay Sundberg – you have always been accessible and approachable with help and support. You contributed with practical perspectives and genuine consideration for my learning.

Dr Marie Nilsson – you were always generous with practical and professional knowledge in research matters and compassionate emotional support.

I would also like to express my deep gratitude to **Ann Langius-Eklöf** and **Kay Sundberg** for conceiving the idea, planning, and conducting the research project and allowing me to participate.

I am greatly indebted to **Per Ekstrand** Head of the Division of Nursing at NVS KI, for really supporting me practically so I could finish this dissertation. **Lena-Marie Petersson** my unit manager at the Division of Nursing, you have also contributed so much to me finishing this thesis, and I am very grateful for your support.

Thank you also **Karolinska Institutet** and the **Doctoral School in Health Care Sciences** for all the valuable opportunities for learning, networking and be inspired that have been arranged and facilitated during my doctoral education.

My deepest and most sincere gratitude to **all the patients** who participated in the studies and **all the nurses** who monitored and responded to the alerts for their time and commitment to improving cancer care.

I also want to thank my excellent mentor **Sofi von Laskowski**, thank you for sharing life after graduate school insights, showed opportunities and kickstarted me in Excel.

I would also like to express my deepest gratitude to my former co-doctoral student, inspiration, chaperon in Barcelona, **Maria Fjell** who co-authored the first study in this thesis. Having your support made all the difference – you made things so much easier. From both Maria and me a big thank you to **Professor Molassiotis** for helpful input on the discussion section of study I.

I also wish to express my gratitude to **Joakim Ekstrand**. Thank you for a very pedagogical introduction to the exciting topic of Health Economy which I received as a student in your introductory course at Kristianstad University. I am so grateful that you

agreed to be part of and co-author the third thesis study which would not have been possible without your expertise.

I want to express a very special thanks to all my former and current **ICare research group colleagues** who have been indispensable for my learning and development by tirelessly providing me with feedback. Your comments always made my texts and presentations so much better! You have been one of my most valuable resources throughout this journey; **Maria Fjell, Mats Christiansen, Veronica Lindström, Tina Gustavell, Nazmije Kelmendi, Kristina Rooth, Lena-Marie Petersson, Åsa Craftman, Linda Gellerstedt and Tina (Druvan) Grape.**

I want to thank **all my teacher and doctoral student colleagues at the Division of nursing**, and particularly mention **Johanna Wangmar**, the most caring work colleague and (room) mate. Further, **Annica Karlsson, Catarina Cleveson, Gunnar Crivér, Alfred Nyeko, Martin Lindström, and Lina Adham.** **Maria Arman's** seminar series and theoretical course in caring science developed me personally and my understanding of the discipline.

I am grateful to all who at some points have been co-doctoral student with me at the Division of Nursing for camaraderie, fun doctoral student lunches and for being so generous with constructive feedback on my texts in forskarforum. **Sharon Kagwa** and **Anahita Amarpour**, a special thanks for your valuable comments during my KAPPA seminar. Thank you also **Professor Lars Eriksson** and **Liselotte Rydström** for conducting my KAPPA seminar and for all the helpful comments you provided on my early draft of this KAPPA.

For financial support I would also like to acknowledge **Riddarhuset** for personal study grants and the project and doctoral education financiers **Karolinska Institutet, the Swedish Research Council, Radiumhemmet's Research Funds, Forte Research Council for Health, Working Life and Welfare and the Kamprad Family Foundation.**

Lastly, I want to thank my family. My mother, **Anette Carlsson**, for emotional and financial support, and domestic assistance, **Carl Crafoord** for pliant shared parenthood, stimulating discussions and being my critical friend who commented texts from an outside perspective, and my son **Oscar Crafoord** for the patience you have had with my work hours and for keeping my spirits up by providing meaning.

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APPENDIX

International Classification of Diseases (ICD) codes

B-RCT	Swedish	English	
D709C	Neutropeni UNS	Neutropenia UNS	Fever/Neutropenia
R502	Läkemedelsutlöst feber	Drug-induced fever	
R508	Annan specificerad feber	Other specified fever	
R509	Feber, ospecificerad	Fever, unspecified	
K521	Toxisk gastroenterit och kolit	Toxic gastroenteritis and colitis	Gastroenteritis, colitis
A047	Enterokolit orsakad av Clostridium difficile	Enterocolitis caused by Clostridium difficile	
D649	Anemi, ospecificerad	Anaemia, unspecified	Anaemia
N390	Urinvägsinfektion, utan angiven lokalisering	Urinary tract infection, unspecified location	Urinary tract infection
P-RCT			
R339	Urinretention (urinstämma)	Urinary retention (urinary incontinence)	Urinary problems
N390	Urinvägsinfektion, utan angiven lokalisering	Urinary tract infection, unspecified location	
R301	Tenesmer i urinblåsan	Tenesmus in the bladder	
N390X	Urinvägsinfektion, utan angiven lokalisering	Urinary tract infection, unspecified location	
N304	Strålcystit	Radiation cystitis	
N300	Akut cystit	Acute cystitis	
R391	Andra miktionssvårigheter	Other micturition difficulties	
N109	Akut tubulo-interstitiell nefrit	Acute tubulo-interstitial nephritis	
T830	Mekanisk komplikation av kvarkateter	Mechanical complication of quaternary catheter	
R319	Ospecificerad hematuri	Unspecified hematuria	

B-RCT= Breast cancer trial

P-RCT=Prostate cancer trial

