# Innovations in patient-centered breast cancer research

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# Innovations in patient-centered breast cancer research

Innovaties op het gebied van patiëntgericht borstkanker onderzoek
(met een samenvatting in het Nederlands)

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**Danny Aschwin Young-Afat**

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te Rotterdam

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This thesis is dedicated to three strong, inspiring women
who fought hard to stay with us as long as they could,
and who have touched my life in significant ways:

**Marie Karg-Jessurun**

**Monique Malmberg**

&

**Mireille Hofwijk**

*"I only ask to be free. The butterflies are free."*

(Charles Dickens)

# CONTENTS

## Part 2 Innovations in patient-reported outcome (PRO) utilization

# 1

# Introduction and thesis outline

# BREAST CANCER

Nowadays, when a woman notices a lump in her breast, the thought of breast cancer immediately comes to mind. This association is due to the high incidence of breast cancer worldwide (1.7 million newly diagnosed women each year), and a high lifetime risk of developing breast cancer (12-14% in Western European countries).[1,2] Incidence of breast cancer is rising, but breast cancer survival is also improving. In the Netherlands, the ten-year survival rate has improved from 61% to 79% since 1981.[3] This is the result of detection of tumors in an earlier stage (i.e. screening programs, more accurate imaging) and better treatment options, allowing for better curative treatment.[4]

Treatment has become less invasive and less mutilating. A mastectomy is nowadays only indicated in selected cases, as most women are eligible to undergo breast-conserving surgery followed by radiotherapy.[5] Radiotherapy has become more precise with less damage to healthy tissue, and systemic therapy has become more targeted with less severe side effects. Selected patients with large tumors are now also eligible for breast-conserving surgery due to the advent of neoadjuvant systemic therapy and oncoplastic surgery.[6,7] Although many of these innovations have improved breast cancer prognosis, breast cancer treatment still impacts health-related quality of life (HR-QoL) and the cosmetic outcome. For example, 25% of patients who underwent axillary lymph node dissection for regional metastases experience chronic, invalidating arm morbidity five years after treatment[8], and up to 90% of patients treated with chemotherapy experience some form of cognitive impairment.[9,10] Thus, there is still much progress to be made to improve life after breast cancer treatment.

# CHALLENGES IN BREAST CANCER RESEARCH

For breast cancer patients, many experimental interventions are being developed in multiple fields (e.g. surgery, radiotherapy, lifestyle interventions) aiming to improve oncological outcomes, to reduce treatment toxicity, and to optimize quality of life after treatment. For instance, in the UMC Utrecht alone, several ablative image-guided interventions are being developed such as MRI-guided high

intensity focused ultrasound (MR-HIFU) and pre-operative single-dose ablative radiotherapy[11,12], all aimed at the same patient population. These interventions became available for formal testing at the same time, and many more interventions are rapidly arising. This rapid rate of development and the large amount of novel interventions makes it challenging to evaluate each intervention in an RCT (i.e. the gold standard to evaluate effectiveness of interventions). Furthermore, comparing results between RCTs is difficult, as each trial often uses different outcomes and different follow-up schedules. Failing to test all these novel interventions in RCTs prevents effective treatments from being implemented, but may also allow for implementation of ineffective interventions when proper evaluation was omitted.

Another challenge in RCTs is that novel interventions are often appealing, as their expected theoretical advantages sound promising. Although it is explained to patients that the intervention may turn out to be less effective than the standard of care, patients often show disappointment when allocated to the standard of care arm. Their disappointment leads to biased results in the control group or patients withdrawing from the trial.[13] As a result, many RCTs fail to recruit their targeted sample size, and 40% of cancer trials are being terminated prematurely.[14] Also, RCTs often include highly selected patients that do not resemble the average patient that is sitting in front of the physician on a daily base. For example, elderly patients are often not included in trials, as they are considered to be more fragile and less ideal to test interventions.[15] Even when elderly are eligible for inclusion, physicians often will not ask elderly to participate, not wanting to impose a burden onto patients that are considered fragile. Therefore, trial results are often not generalizable to the entire population of interest, which hampers implementation of innovations in clinical care.

All these challenges may lead to a waste of funding, time and effort, and delayed implementation and identification of innovations that are beneficial for patients. Therefore, novel ways to enable randomized evaluation are highly needed.

## NOVEL METHODS FOR OUTCOME EVALUATION

The cohort multiple randomized controlled trial (cmRCT) design was created to overcome some of the before mentioned challenges in pragmatic trials, and may be a promising alternative to the classic RCT design.[16] This novel pragmatic trial design combines strengths from longitudinal cohort studies with randomized evaluations of interventions. The cohort multiple randomized controlled trial consists of a longitudinal cohort where all patients receive the standard of care upon enrollment. Outcomes are collected regularly for the entire cohort, which ideally includes easily available outcomes, such as routine care data and patient-reported outcomes (e.g. HR-QoL). When experimental interventions become available for randomized evaluation, the cohort is used as a sampling pool. Patients who are randomly selected for the intervention are given the option to undergo this intervention, whereas those who were not selected continue receiving standard of care and their observational data are used in comparison.[16] Outcomes of those randomly offered an intervention are compared with outcomes of those receiving standard of care. These outcomes need to be available for the entire cohort, as control patients are not contacted during trials for extra measurements. Therefore, when setting up a cmRCT cohort, it should be carefully considered which outcomes to collect, as this determines which endpoints will become available for future trials. Patient-reported outcomes cover a wide range of relevant outcomes (e.g. quality of life, fatigue, cognitive functioning, pain), and can therefore serve as valuable endpoints for cmRCT-based trials.

## PATIENT-REPORTED OUTCOMES

Patient-reported outcomes (PROs) evaluate questions and outcomes meaningful to patients. PROs allow us to look at health care through the eyes of patients thus ensuring that their concerns are being captured and addressed.[17] PROs can only be assessed from the patient's perspective, which is usually done using specifically designed questionnaires that enable self-reporting, i.e. PRO-instruments.[18] With PRO-instruments we can evaluate how symptoms interfere with, for example, daily physical functioning, sexual functioning, emotional functioning and psychosocial functioning.

Although PROs have been used in many observational breast cancer studies, comparing study results is challenging due to differences in PRO-instruments and data collection schedules.[18] The International Consortium for Health Outcomes Measurement (ICHOM) has proposed a standard set for breast cancer aiming to standardize data collection and to increase uptake of PROs.[19] This standard set includes specific domains to be measured for all breast cancer patients, at fixed moments in time while using only validated PRO-instruments. These PRO-instruments include the cancer specific EORTC QLQ-C30 for general HR-QoL after cancer treatment[20], the breast cancer specific EORTC BR23 for breast cancer related symptoms[21], and the BREAST-Q for HR-QoL and patient satisfaction after breast cancer surgery.[22] This standard set for breast cancer may increase uptake of PROs in routine care, and therefore eventually also increase use of PROs as endpoints in pragmatic RCTs. In cancer trials, hard outcomes such as survival and cancer recurrence often serve as primary outcomes. Although such objective outcomes are essential to evaluate, they may not always cover all that matters to patients when treatment decisions have to be made. For example, a certain treatment may reduce the probability of cancer recurrence but if this treatment is associated with chronic nausea and daily breast pain, this may not be what every patient would opt for.

Measuring PROs in routine care, and providing feedback to patients is associated with better patient-physician dialogues, improved HR-QoL and even associated with better survival of cancer patients.[23] These proven benefits, combined with the simple tools provided by ICHOM to measure PROs in routine care, may be the trigger for routine care cohort studies to become standard of care. The next step would then be to design those routine care cohorts in such a way that data may be used for randomized evaluations. This is where cmRCT may further prove its worth, and could further attract interest of the research community.

# AIM & OUTLINE THESIS



## PART 1 - The cohort multiple randomized controlled trial design (cmRCT)

The main objective of part 1 of this thesis (Chapter 2 – 5) was to implement and evaluate the novel cmRCT design in a clinical breast cancer setting. In Chapter 2 the cmRCT design is explained, and ethical pros and cons of cmRCT are evaluated with reference to ethical guidelines (e.g. Declaration of Helsinki, Belmont Report). A staged-informed consent procedure is proposed to avoid the identified ethical challenges. Chapter 3 describes the implementation of the UMBRELLA cohort – the first cmRCT cohort in a clinical breast cancer setting. Chapter 4 presents survey results evaluating patients' understanding of the cmRCT design. This study was conducted among participants in the three ongoing cmRCT cohorts with embedded trials in our hospital in the field of breast cancer, bone metastases and colorectal cancer. Chapter 5 shows results from an observational study conducted within UMBRELLA with routine care data and patient-reported outcomes (PROs). This study aimed to assess prevalence, and determinants of breast edema in patients treated with breast-conserving therapy, and its effect on QoL.

## PART 2 - Innovations in patient-reported outcome (PRO) utilization

In part 2 (Chapter 6 – 8), the aim was to evaluate novel methods to improve PRO utilization. Chapter 6 explores potential advantages of using a supportive breast cancer app in clinical practice, including its potential to collect PROs. In Chapter 7, results are presented from the first RCT (i.e. BRIOS trial) where the PRO-instrument 'BREAST-Q' was used as the primary outcome. The BRIOS trial was a pragmatic RCT comparing cosmetic satisfaction and HR-QoL after a novel one-stage implant-based breast reconstruction technique using an acellular dermal matrix (ADM), and the standard of care two-stage procedure using tissue expanders followed by a definitive breast implant later in time. Chapter 8 describes the development and evaluation of the short and individualized version of the BREAST-Q by applying computerized adaptive testing (CAT), a method with potential to reduce the length of PRO-instruments. Chapter 9 provides an overall summary, and this thesis concludes with a general discussion and future perspectives on patient-centered breast cancer research (Chapter 10).

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# Part 1

The cohort multiple randomized controlled trial design (cmRCT)

2

# Staged-informed consent in the cohort multiple randomized controlled trial design

*Epidemiology*, 2016

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# ABSTRACT

The 'cohort multiple randomized controlled trial', a new design for pragmatic trials, embeds multiple trials within a cohort. The cohort multiple RCT is an attractive alternative to conventional RCTs in fields where recruitment is slow, multiple new (competing) interventions for the same condition have to be tested, new interventions are highly preferred by patients and doctors, and the risk of disappointment bias, cross-over, and contamination is considerable. In order to prevent these unwanted effects, the cohort multiple RCT provides information on randomization to the intervention group/arm only, and only after randomization (i.e. pre-randomization). To some, especially in a clinical setting, this is not ethically acceptable.

In this paper, we argue that pre-randomization in the cohort multiple RCT can be avoided by adopting a staged-informed consent procedure. In the first stage, at entry into the cohort, all potential participants are asked for their informed consent to participate in a cohort study and broad consent to be either randomly selected to be approached for experimental interventions or to serve as control without further notice during participation in the cohort. In a second stage, at the initiation of an RCT within the cohort, informed consent to receive the intervention is then only sought in those randomly selected for the intervention arm. At the third stage, after completion of each RCT, all cohort participants receive aggregate disclosure of trial results.

This staged-informed consent procedure avoids pre-randomization in cmRCT and aims to keep participants actively engaged in the research process.

# INTRODUCTION



In 2010, Relton and colleagues introduced the "cohort multiple randomized controlled trial (cmRCT) design" for pragmatic trials.[1] The cohort multiple RCT is expected to be particularly useful in fields where multiple interventions for the same condition are being developed (e.g. oncology), where recruitment is slow, and for interventions that are highly desired by patients and doctors.[1,2]

The cohort multiple RCT was introduced in the setting of obesity management and treatment of post-menopausal symptoms.[3,4] In 2013, we introduced the design into the clinical oncology practice. The patient-centered informed consent process, as originally proposed[1], led to intensive discussion with the Research Ethics Committee of the University Medical Center Utrecht, the Netherlands.

In the original cohort multiple RCT design, all prospective participants with the condition of interest are asked informed consent for participation in a cohort study (Figure 1). They thereby agree to standardized collection of clinical and/or patient reported outcomes. When an experimental intervention is ready for comparison with the standard treatment, all participants, eligible to undergo this intervention, are identified from the cohort and aggregated into a 'subcohort of eligible participants'. From this 'subcohort' a number of participants are randomly selected and asked to "try" the experimental intervention.[1,2] If they decline, they receive care as usual.

Eligible participants in the 'subcohort' who are not randomly selected for the intervention, will receive standard treatment, are not informed about the intervention, and will serve as controls. [1,2]

By informing participants in this way, the authors aimed for the informed consent procedure to more closely resemble routine clinical practice, where people are usually not told about treatments they will not receive, nor that their treatment will be allocated by chance.[1] Furthermore, avoiding – from a patient's perspective – the complicated process of randomization might result in increased recruitment rates and prevent cross-over and disappointment bias.[1,2]

At the same time, the patient-centered informed consent model in the cohort multiple RCT harbors controversial aspects of pre-randomization (i.e. participants are randomized without prior consent and are unaware they could serve as a controls). Although some trials use pre-randomization (e.g. Zelen design), [5,6] one important objection is people might lose trust in doctors if they learn that they have been used as research subjects without their explicit consent.[7]

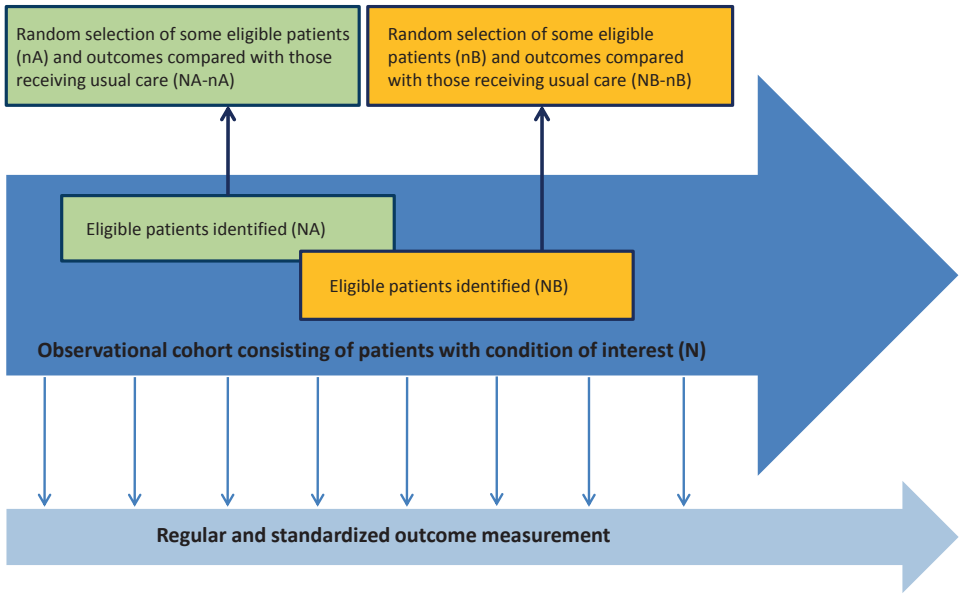


**Figure 1. The cmRCT design**

In the cohort multiple RCT, a prospective observational cohort is created, consisting of people with a specific disease, condition or a certain exposure (N). For each patient within the cohort, baseline and follow-up data are collected prospectively at regular intervals. In addition, the cohort serves as a facility for multiple RCTs. For each experimental intervention to be tested, information from the cohort is used to identify a 'subcohort of all eligible participants' (NA). From this subcohort, a random sample (nA) is selected for the intervention (which they can accept or refuse). Their outcomes will be compared with those who have not been selected and who continue to receive care as usual (NA – nA). This process can be repeated when another intervention becomes available for formal testing in an RCT (for example, NB).

In this paper, we propose a staged-informed consent procedure (Figure 2) to avoid pre-randomization in cohort multiple RCTs and to keep participants actively engaged and informed about research that is being conducted with their data.



# METHODS

## Staged-informed consent for cohort multiple RCTs

The cohort multiple RCT embeds RCTs in a longitudinal observational cohort. Informed consent requirements are similar to regular cohort studies, as set out in main ethical and legal guidelines for the conduct of research with human subjects (e.g the WMA's Declaration of Helsinki, CIOMS guidelines).[8,9] Our staged-informed consent model may be regarded as a further specification of those guidelines for studies with a cohort multiple RCT design.

In the first stage, before entry in the cohort, participants are asked for their informed consent for standard outcome measurements. At the same time, but in a separate question, patients are asked for their broad consent for treatment allocation to be decided by chance (i.e. randomization) when experimental interventions become available to be tested in RCTs within the cohort. Participants are informed that they will be re-contacted when selected for the intervention arm to provide informed consent for receiving the experimental intervention, and that, if selected as controls, they will not be re-contacted, nor receive information about interventions administered to the intervention arm.

Participants who do not want to be randomly assigned to interventions in the (near) future cannot participate in RCTs conducted within the cohort. Their data can, however, be used for observational studies (e.g. prediction studies, non-randomized comparative studies). Furthermore, their data provide information on to what extent RCT participants represent the full cohort, which may be useful to assess the generalizability of results from RCTs that have been performed within the cohort.

By giving broad consent *before* the actual randomization, participants are no longer randomly assigned without prior consent. This procedure resembles broad

consent approaches used in biobank research, in which participants consent to collection and storage of their bodily material without knowing specific aims of future studies conducted with their donated material.[10]

In a second stage, only those participants who are randomly selected for the intervention are informed about the experimental intervention, and asked to give informed consent to undergo the intervention. They will sign a second informed consent, including all conventional requirements for human subjects who participate in RCTs, such as the study aim and information about risks and potential benefits of the specific intervention.[8,9]

Controls will not be informed about the actual randomization. By avoiding disclosure at this moment in time, participants in the control arm are not aware of the RCT, which prevents disappointment bias, cross-over, and contamination during ongoing trials. Since these patients will receive care as usual and they already gave broad consent for randomization (stage 1), it is reasonable to argue that their autonomy is not being infringed.

In stage 3, after completion of each RCT, all cohort participants receive *aggregate* disclosure of trial results, if they opt in to receive this information. We will not inform controls on an *individual* level that they have served as controls, as this only seems to serve the purpose of full disclosure, without providing the patient with any benefits compared to receiving results at a group level.

Providing aggregate disclosure is in line with the recently proposed moral framework for a learning health care system. Here, patients "contribute to the common purpose of improving the quality and value of clinical care and health care systems".[11] Cohort multiple RCTs neatly fit into the learning health care system, which embeds research into clinical practice in order to continuously improve clinical care.[12,13] We think that patients in a learning health care system should be treated as "scientific citizens"[14], meaning that researchers actively engage patients in the research process. This is only possible by informing participants, before entry into the observational cohort (stage 1), what participation in this cohort with a cohort multiple RCT design entails, and inform them that in certain medical disciplines pragmatic trials with a cohort multiple RCT design are the preferred

way to improve knowledge in that specific medical field. By giving participants the opportunity to receive aggregated results from RCTs and observational studies within the cohort, their broad consent for RCTs within the cohort will eventually lead to their being well informed about what has happened at a group level with the data they have provided.



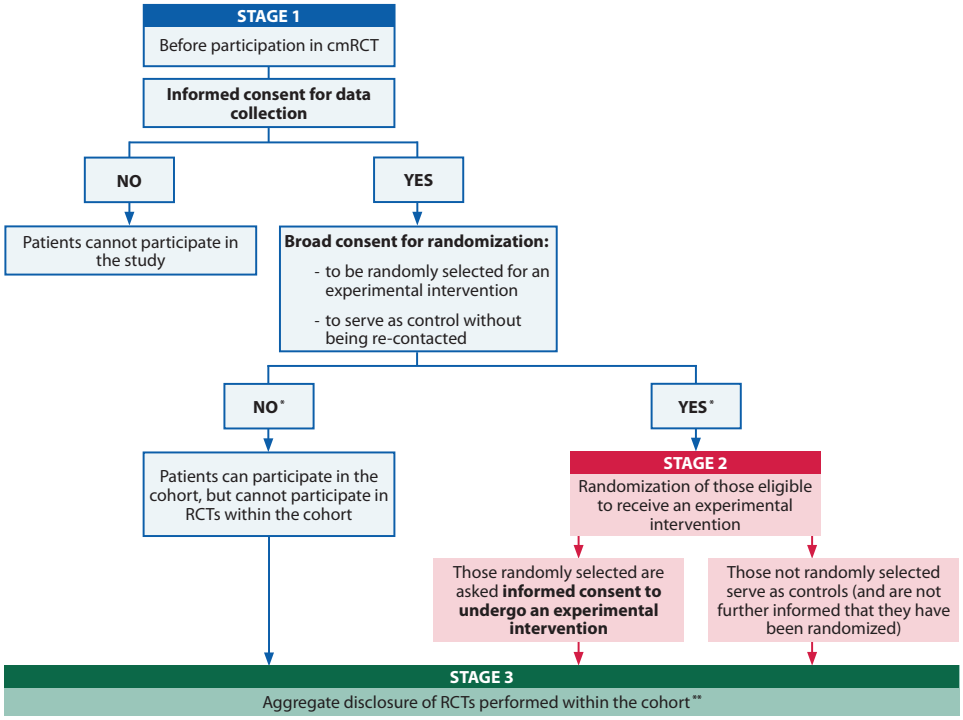


**Figure 2. Staged-informed consent model for cmRCT**

*Dynamic informed consent model which enables participants to change their previous ' yes or no' preference at any moment in time

**Provided after each completed RCT, but only to those who opted-in for aggregrate disclosure (asked in stage 1).

Aggregate disclosure may sometimes lead to patients realizing that they were either not eligible to participate, or have served as controls for interventions they might have desired. This may be disappointing, but this disappointment will not have introduced bias during the RCT. However, in longitudinal cohorts, patients may be randomly selected for interventions many years after cohort entry, when

they no longer remember, or even regret, their broad consent. Therefore, we emphasize that our proposed staged-consent model is a *dynamic informed consent model*, in which participants are regularly updated and re-contacted to opt-in for future research projects.[15] If there are multiple opportunities to rethink the broad consent for randomization, people remain actively engaged which may enhance their willingness to continued participation.

Modern information techniques, such as websites and digital newsletters, provide easy ways to register whether or not participants opt in for aggregate post-trial information, and may enable easy changes in patients' preferences for broad randomization over time.

# DISCUSSION

The staged-informed consent model for cohort multiple RCTs provides a solution to the ethically challenging pre-randomization, while preserving methodological advantages of this study design (e.g. avoiding disappointment bias) and improved generalizability of trial results.

In some cases participants will enter a cohort multiple RCT cohort when (multiple) RCTs are already ongoing or new RCTs are planned. Some may argue that, in those cases, broad consent is unfair, since the purposes of the first studies are known. However, upon entry into the cohort (stage 1) it is often not yet known whether a participant will be eligible for an ongoing RCT, so providing specific information in stage 1 is not necessary and could lead to unwanted effects, which the cohort multiple RCT aims to prevent (e.g. disappointment bias, drop-out).

The staged-informed consent model separates three questions ('Do you want to participate in research?', 'Do you agree that your treatment is to be decided by chance?' and 'Do you actually want to receive this particular experimental intervention?'). This provides patients with the opportunity to think about each question separately, while in classic RCTs these questions are all asked at the same time. Separating these questions gives more insight into which patients refuse any type of research (stage 1), which patients only refuse intervention research (stage

1), and which patients only refuse a particular intervention (stage 2). High refusal rates for certain interventions provide valuable information on acceptability for a particular intervention by patients in clinical practice.



While non-disclosure of randomization in the original cohort multiple RCT might potentially lead to improved recruitment rates[1], we found that the staged-informed consent procedure also leads to high recruitment rates. At our hospital, in three ongoing cohorts following this design including patients with rectal cancer (PICNIC, n=370), bone metastases (PRESENT, n=495) and breast cancer (UMBRELLA, n=820), 85%-90% of all patients who were asked to participate were enrolled by using the staged-informed consent model. Additional broad consent to be randomized was given by 80%-90% of all cohort participants. These numbers show that the staged-informed consent model works well in a clinical oncology setting, where patient recruitment is notoriously challenging.[16]

# CONCLUSION

In the cohort multiple RCT design, a staged-informed consent procedure avoids pre-randomization and actively engages participants in the research process during cohort participation.

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# 3

# The Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA): objectives, design and baseline results

*Breast Cancer Research and Treatment*, 2017

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# ABSTRACT


## Purpose

In oncology, RCTs are often beset by slow recruitment, limited generalizability and strong preferences for interventions by patients and physicians. The cohort multiple randomized controlled trial (cmRCT) is an innovative design with the potential to overcome those challenges. In cmRCT, a prospective cohort serves as an infrastructure for multiple RCTs. We implemented cmRCT in a clinical breast cancer setting by creating UMBRELLA – a large prospective cohort of breast cancer and DCIS patients/survivors.

## Methods

For all participants, clinical data and patient-reported outcomes (PROs - i.e. quality of life, fatigue, anxiety and depression, physical activity, work ability and cosmetic satisfaction) are being collected at regular time-intervals for a period of 10 years. These data are being used both for observational and randomized studies. For each intervention to be tested against standard care, a subcohort of eligible patients is identified within UMBRELLA. From this subcohort, a random sample of patients is offered the intervention. Their outcomes are compared to outcomes of patients receiving standard care.

## Results

So far, between October 2013 and July 2016, we have recruited 1308 participants. In this period, 1308/1486 (88%) patients who were invited for participation in UMBRELLA consented to cohort participation. Of those, 1138 (87%) gave broad consent for randomization to future interventions. Return rate for PROs at baseline were 80%, and varied from 67% to 74% during follow-up. Several observational studies – and the first randomized intervention study – are currently ongoing.

## Conclusions

Results from UMBRELLA show that this novel study design is feasible and acceptable to patients in a clinical breast cancer setting. We invite researchers who are interested in conducting randomized or observational studies within the UMBRELLA cohort to contact the UMBRELLA scientific advisory board.

# INTRODUCTION

With a lifetime risk of one in seven, breast cancer is an important public health concern among women in the Western world.[1,2] Due to earlier detection and better treatment, breast cancer survival has improved substantially.[1-3] However, current treatment is associated with substantial morbidity, including lymphedema, breast deformities, (chronic) pain and fatigue. Therefore, new breast cancer treatments should not only focus on further improving (progression-free) survival, but should also aim for good quality of life (QoL), functional outcomes and satisfying cosmetic results.[4]



Interventions aiming to achieve these purposes include minimally invasive treatment of the primary tumor (e.g. axillary irradiation instead of surgery), as well as lifestyle interventions (e.g. dietary interventions, exercise programs, supportive health apps).[5-7] Before implementation in routine care, these interventions would ideally be evaluated in randomized controlled trials (RCTs) to confirm whether theoretical benefits translate into actual benefits for patients.

RCTs are the gold standard in comparative research, but often face many challenges. RCTs often are beset by slow recruitment, leading to 40% of cancer trials ending prematurely[8], which is unethical with regards to patients unnecessarily being exposed to potentially harmful or inferior interventions, as well as a waste of time and resources. In the field of breast cancer, the large amount of new interventions entering the market makes it virtually impossible to adequately evaluate each intervention in a separate RCT. It is also complicated to directly compare different interventions tested in separate trials, due to differences in inclusion criteria, outcome measures and follow-up schemes.[9] RCTs often suffer from limited generalizability due to strict inclusion criteria and selective participation.[10] When highly desired interventions are being evaluated, patients are often disappointed when allocated to the control arm, which may result in drop-out, cross-over and/or disappointment bias.[11] And lastly, for physicians, the informed consent procedure is cumbersome, as they have to explain (at least) two treatment options that they cannot both with certainty offer to their patients.

In order to deal with these challenges, the cohort multiple randomized controlled trial (cmRCT) design was proposed.[12] In this design, a prospective cohort serves as an infrastructure for multiple RCTs. Advantages of the cmRCT design have been described previously, and include efficient use of control patients, improved comparison between different trialed interventions, enhanced generalizability, and reduced disappointment bias.[12,13]

Clinical and methodological experts in the field of breast cancer combined their knowledge to create a cohort of breast cancer patients according to the cmRCT design – 'Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion' (UMBRELLA). With UMBRELLA we aim to:

- Generate short and long-term data on clinical and patient-reported outcomes during and after breast cancer treatment.
- Provide an infrastructure for multiple randomized evaluations of interventions for breast cancer patients and survivors.

In this paper, we describe UMBRELLA's study design and clinical experiences after 30 months of active recruitment. This paper will serve as the basis for all future observational studies and RCTs using the UMBRELLA cohort.

# MATERIALS AND METHODS

## Enrollment

Patients are recruited at the University Medical Center Utrecht (UMC Utrecht), the Netherlands. All patients with invasive breast cancer and ductal carcinoma *in situ* (DCIS), who are referred to the department of Radiation Oncology, are eligible for participation in UMBRELLA. Patients with limited understanding of the Dutch language and patients under the age of 18 years are ineligible. Since the UMC Utrecht is the regional center for radiation treatment, UMBRELLA includes patients from secondary and tertiary hospitals. Each year, approximately 575 eligible patients visit the UMC Utrecht for adjuvant radiation treatment of the breast (and axilla).

Before their first visit to the department of radiation oncology, all patients with breast cancer or DCIS receive detailed written information about UMBRELLA. They are scheduled to visit a researcher/research assistant 30 minutes prior to their first appointment with the radiation oncologist. During this research consultation, the researcher/research assistant explains the study in detail, and written informed consent is obtained from those who agree to participate. The study protocol for UMBRELLA was approved by the Institutional Review and Ethics Board of the University Medical Center Utrecht, the Netherlands.



## Staged-informed consent

UMBRELLA serves as a facility for multiple trials and follows the cmRCT design. In this context, informed consent is obtained through a staged procedure.[14] Before entering the cohort, all patients give written informed consent for collection and use of clinical data. Patient reported outcomes (PROs) are collected at baseline and at fixed intervals during follow-up.

In addition, patients may give broad consent to be randomly allocated to experimental interventions in the (near) future. Only those randomly allocated to the intervention arm are offered the experimental intervention (which they can accept or refuse). If they accept, additional written informed consent to undergo the experimental intervention will be obtained. Patients who refuse the intervention receive standard care. Patients who are randomly allocated to the control arm also receive standard care, and are not informed about being in the control arm.

Data from all patients may be used for observational studies in UMBRELLA, but only those who provide broad consent for randomization are eligible for participation in RCTs within UMBRELLA. After completion of an RCT within UMBRELLA, all patients – irrespective of participation in the specific study – receive aggregated results.

## Clinical data

Within UMBRELLA, various clinical data are prospectively collected including demographics, tumor characteristics, treatment and toxicity, and imaging data (e.g. mammography, radiotherapy planning computed tomography (CT) scans). Clinical data are captured from electronic medical records, referral letters and annual reports from the national cancer registry.[2] Socio-demographic data include gender, date of birth, age at diagnosis, highest level of education, postal code (to estimate socio-economic status), body mass index (BMI) and WHO performance status.

Disease characteristics include method of detection (symptomatic, screening), date of diagnosis, laterality, localization within the breast, classification according to Breast Imaging-Reporting and Data System (BIRADS)[15,16], tumor size, nodal status, clinical and pathological stage (classified as American Joint Committee on Cancer c/pTNM classification), multifocality and multicentricity, histologic type, invasiveness, Bloom-Richardson grade, hormone receptor status and HER-2 status.

Treatment characteristics comprise type of surgery of primary tumor (breast conserving surgery or mastectomy) and regional lymph nodes (sentinel node biopsy, axillary lymph node dissection and/or regional radiotherapy), type and timing of reconstructive surgery, surgical margin status (radical, focally irradical, irradical), (neo)adjuvant systemic therapy, radiotherapy parameters (e.g. irradiated volumes, prescribed dose), (surgical) complications, re-admission and center of surgical treatment. Toxicity is captured according to the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE). Information on recurrence and survival is collected annually by means of (self-reported) questionnaires, the national pathology database (PALGA) and the Central Bureau of Statistics (CBS).

The principal investigators and delegates are responsible for daily cohort management. Data quality is checked periodically. All data are stored and handled according to Dutch privacy law regulations.

## Patient-reported outcomes

We collect PROs by means of validated questionnaires designed to quantify health-related QoL from the patient's perspective. These questionnaires are sent to patients upon entry into the cohort (baseline), at 3 and 6 months and every 6 months thereafter with a total follow-up of at least 10 years. It takes approximately 20 minutes to fill out the set of questionnaires at each time point.



Patient-reported information is collected on QoL, fatigue, anxiety and depression, physical activity, work ability and cosmetic satisfaction through the following questionnaires:

- Quality of Life: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, including breast cancer specific module BR23[17]
- Fatigue: Multidimensional Fatigue Inventory-20[18]
- Anxiety and Depression: Hospital Anxiety and Depression Scale (HADS)[19]
- Physical activity: QUestionnaire to ASses Health enhancing physical activity (SQUASH)[20]
- Work ability: Work Ability Index (WAI)[21]
- Cosmetic outcome: Cosmetic Evaluation[22]

# RESULTS

So far, between October 2013 and July 2016, we have recruited 1308 participants. In this period, 1308 out of 1486 (88%) patients who were invited for participation in UMBRELLA consented to cohort participation (Table 1). Of those, 1138 (87%) gave broad consent for randomization to future interventions.

The mean age of cohort participants was 59 years (27-95), 86% were treated with breast conserving surgery (BCS) and 14% underwent mastectomy. Those who did not provide broad consent for random allocation were slightly older (60 years versus 57 years). Moreover, other differences between patients who provided broad consent for random allocation and those who did not were also marginal (Table 2).

Return rates for questionnaires at baseline were 80%, and varied from 67% to 74% during follow-up (Table 1). Sixty percent of patients chose to fill out PROs online, while 40% opted for paper questionnaires.

**Table 1. UMBRELLA participation rates and questionnaire return rates between October 2013 and July 2016**

| | % (n / N) |
|---|---|
| Eligible patients | 1486 |
| Cohort participation | 88% (1308/1486) |
| - *broad consent for randomization* | 87% (1138/1308) |
| **Questionnaire return rates *** | |
| Baseline | 80% (1041/1308) |
| 3 months | 74% (868/1178) |
| 6 months | 73% (750/1027) |
| 12 months | 69% (537/773) |
| 18 months | 68% (339/498) |
| 24 months | 67% (146/217) |

* Because this is an ongoing, actively recruiting cohort the denominator decreases

Descriptive baseline results already provide some insight into patients' perspectives during and after treatment. Baseline scores for health-related QoL domains are shown in Table 2. Compared to patients who returned the baseline questionnaires, non-responders were slightly younger (54 years versus 58 years), and a higher proportion of non-responders were treated with mastectomy (23% versus 15%) and loco-regional radiotherapy (19% versus 13%).

Within the cohort, several longitudinal observational studies are investigating PROs in relation to patient, tumor and treatment characteristics. Studies in progress include, for example, a study on lymphedema of the breast after breast-conserving treatment (incidence, determinants and the effect of edema on health-related QoL). In another study the association between cardiovascular events and presence of coronary artery calcium on radiotherapy planning CT scans was investigated.[23] This study showed that one in four breast cancer patients planned for radiotherapy have coronary artery calcium, which is known to be a strong risk factor for cardiovascular disease. Within UMBRELLA, Knuttel et al. assessed preferences of breast cancer patients and healthy women regarding new non- and minimally invasive breast

cancer treatment options, compared to conventional surgical treatments. These results may be helpful to guide the development of innovative breast cancer therapies and randomized studies to evaluate these novel techniques.[24] Also, the first randomized comparison within UMBRELLA is currently ongoing (FIT trial). The FIT trial evaluates the effect of an exercise program on QoL in breast cancer survivors with low levels of physical activity 12 to 18 months after diagnosis.[25]



## Strengths of UMBRELLA

The major strengths of UMBRELLA are that we systematically invite all eligible patients to participate in UMBRELLA, the high participation rate, the longitudinal capturing of PROs, and the ability to foster multiple trials within a longitudinal cohort. By systematically inviting all eligible patients, and by keeping the physician out of the informed consent procedure, selection is minimized. Due to the high participation rate, UMBRELLA provides a representative study sample.

In UMBRELLA, a wide range of PROs are systematically collected. PROs are becoming increasingly important endpoints to better understand patients' symptoms, experiences, health-related QoL and side effects of treatment.[4] Such outcomes will be important when determining which new treatments will be implemented in routine care and will provide valuable input for the process of shared decision-making.

UMBRELLA follows the cmRCT design, which is associated with several advantages. It has the unique ability to facilitate multiple randomized evaluations of (experimental) interventions. Patients may participate in several cmRCTs simultaneously (which may sometimes require stratified randomization if interactions between interventions is to be expected). Direct comparison between interventions is possible, because all trials are conducted within the same study population, making use of the same follow-up scheme and available outcomes.[12] Patients who are not selected for an intervention (the controls) are not informed about interventions under study, which reduces the risk of disappointment bias and contamination compared to classic RCTs. Furthermore, physicians and researchers only explain an intervention that they can *actually* offer to the patient. This reduces the workload of physicians participating in trials, as they only have to explain experimental interventions to patients in the intervention arm.

**Table 2. Characteristics of UMBRELLA participants between October 2013 and July 2016**

| Characteristics | Full cohort | Consent for future random allocation | No consent for future random allocation | Returned baseline questionnaire | Did not return baseline questionnaire |
|---|---|---|---|---|---|
| Number of participants | 1047* | 910 | 137 | 838 | 209 |
| Age at recruitment | | | | | |
| Mean (range) | 58 (27-83) | 57 (27-83) | 60 (28-82) | 58 (26-83) | 54 (23-82) |
| **Surgery** | | | | | |
| Breast conserving | 82% (858/1047) | 82% (742/910) | 83% (114/137) | 84% (700/838) | 76% (158/209) |
| Mastectomy | 17% (176/1047) | 17% (157/910) | 14% (19/137) | 15% (128/838) | 23% (48/209) |
| ALND only | <0.5% (3/1047) | <0.5% (3/910) | 0% | <0.5% (1/838) | 1% (2/209) |
| No surgery | 0.5% (6/1047) | <0.5% (4/910) | 1.5% (2/137) | 0.5% (6/838) | 0% |
| Unknown | <0.5% (4/1047) | <0.5% (4/910) | <0.5% (1/137) | <0.5% (3/838) | 0.5% (1/209) |
| **Radiotherapy**** | | | | | |
| Local | 83% (680/815) | 83% (584/700) | 83% (94/113) | 84% (561/666) | 80% (119/149) |
| Loco-regional | 14% (116/815) | 14% (99/700) | 15% (17/113) | 13% (88/666) | 19% (28/149) |
| Regional only | 1.5% (12/815) | 1% (10/700) | 2% (2/113) | 1.5% (11/666) | 0.5% (1/149) |
| None | <0.5% (3/815) | <0.5% (3/700) | 0% | <0.5% (2/666) | 0.5% (1/149) |
| Unknown | 0.5% (4/815) | 0.5% (4/700) | 0% | 0.5% (4/666) | 0% |
| **Tumor histology***** | | | | | |
| Ductal | 82% (734/899) | 81% (634/781) | 85% (98/116) | 82% (599/731) | 80% (135/168) |
| Lobular | 11% (100/899) | 11% (89/781) | 10% (11/116) | 11% (78/731) | 13% (22/168) |
| Ductolobular | 3% (27/899) | 3% (24/781) | 3% (3/116) | 3% (25/731) | 1% (2/168) |
| Other | 4% (35/899) | 4% (31/781) | 3% (4/116) | 3% (24/731) | 5% (8/168) |
| Unknown | <0.5% (3/899) | <0.5% (3/781) | 0% | 0.5% (5/731) | 0.5% (1/168) |

**Table 2. Characteristics of UMBRELLA participants between October 2013 and July 2016** *(Continued)*

| Characteristics | Full cohort | Consent for future random allocation | No consent for future random allocation | Returned baseline questionnaire | Did not return baseline questionnaire |
|---|---|---|---|---|---|
| **pT-stage** | | | | | |
| in situ | 12% (109/902) | 12% (94/780) | 13% (15/120) | 13% (93/729) | 9% (16/173) |
| 1 | 58% (542/902) | 59% (459/780) | 55% (66/120) | 59% (427/729) | 57% (99/173) |
| 2 | 20% (180/902) | 20% (153/780) | 23% (27/120) | 20% (142/729) | 22% (38/173) |
| ≥3 | 3% (26/902) | 3% (21/780) | 4% (5/120) | 3% (21/729) | 3% (5/173) |
| X/0 | 7% (61/902) | 7% (53/780) | 6% (7/120) | 6% (46/729) | 9% (15/173) |
| **Screen-detected** | | | | | |
| Yes | 47% (302/638) | 47% (253/543) | 48% (45/93) | 48% (257/531) | 42% (45/107) |
| No | 50% (321/638) | 51% (276/543) | 51% (47/93) | 50% (264/531) | 53% (57/107) |
| Unknown | 2% (15/638) | 3% (14/543) | 1% (1/93) | 2% (10/531) | 5% (5/107) |
| EORTC Global health status / QoL (baseline) | 74 (18) | 74 (18) | 75 (17) | 74 (17) | 75 (19) |
| EORTC Physical functioning (baseline) | 85 (16) | 85 (16) | 85 (15) | 84 (16) | 84 (15) |
| EORTC Fatigue (baseline) | 71 (22) | 71 (22) | 72 (22) | 71 (23) | 70 (22) |

NOTE: Percentages may not add up to exactly 100% as a result of rounding.
* These numbers are based on data after linkage with the Dutch Cancer Registry files. Since this process happens annually, not all clinical data for the entire cohort have been obtained. The total amount of collected data may vary per variable as a result of available information at the time of linkage.
** Loco-regional includes radiation on axillary and/or peri-clavicular lymph nodes
*** Tumor histology 'other type' comprises mucinous, medullary and metaplastic carcinoma.
EORTC scores: Scores range from 0-100 and higher scores represent a better health status. Abbreviations: ALND - axillary lymph node dissection; pT - pathological tumor size according to TNM classification.

By adopting a staged-informed consent procedure, we separated consent for cohort participation from consent for accepting interventions after being randomly selected. Instead of receiving a large amount of study information at once, UMBRELLA participants only receive the essential information they need, at the time they need it to make a well-informed decision. This resembles the way information is shared in routine care, thus potentially increasing generalizability to a clinical setting and potentially increasing patients' ability to process and understand the informed consent procedure.

## Limitations of UMBRELLA

One of the limitations of UMBRELLA is that we only include patients referred for radiotherapy. As a result, around 60% of all invasive breast cancer and DCIS patients are eligible.[2] We have recently obtained ethical approval to expand our cohort to patients without an indication for radiotherapy. Clinical data collected in this cohort are generated in routine care, and are therefore rather pragmatic. Endpoints for trials within UMBRELLA need to be part of the pre-defined outcomes being measured for all patients. However, it is possible to collect additional data for specific studies if required. Since cmRCT is a rather new design, several aspects still need further exploration. For instance, an in-depth evaluation of statistical approaches when running multiple trials with potential for interaction between treatments has not yet been performed. Finally, the questionnaire return rates slowly decrease over time. This is a problem that many other prospective cohort studies encounter. In our cohort we are actively informing patients about results of studies conducted with cohort data in the hopes of keeping participants actively involved and motivated to return the questionnaires.

## Collaborations

International collaborations are essential to improve the breast oncology field. We invite researchers who are interested in conducting randomized or observational studies within the UMBRELLA cohort to contact the UMBRELLA scientific advisory board, led by Dr. H.M. Verkooijen (h.m.verkooijen@umcutrecht.nl).

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# 4

# Patients' understanding of the cohort multiple randomized controlled trial design

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# ABSTRACT


## Purpose

The 'cohort multiple Randomized Controlled Trial (cmRCT)' design aims to overcome challenges hampering pragmatic trials (e.g. slow recruitment, contamination of control arm, disappointment bias) by only informing those randomized to the intervention arm. We previously introduced staged-informed consent, including broad informed consent for randomization, to avoid ethical concerns surrounding this approach. We explored participants' understanding of this novel design and its informed consent procedure in a clinical oncology setting.

## Methods

We surveyed 579 patients with cancer, who were participating in three ongoing cmRCT cohorts, including 396 consecutive patients shortly after agreeing (n=312) or declining cohort participation (n=84), 121 consecutive patients who had been randomized to an experimental intervention, and a random sample of 62 cohort participants who had not been invited for interventions. We assessed 1. Reasons for cohort and intervention (non) participation, 2. Recollection of broad consent for randomization, and 3. Understanding of – and perspectives on – randomization procedures.

## Results

1. Altruism was the main reason (95%, 296/312) to participate in a cmRCT cohort study; 2. Two weeks after providing broad consent for randomization (n=249), 76% remembered their broad consent decision correctly (i.e. same answer as on signed informed consent form). In the random sample of patients not offered interventions 1-6 months after providing broad consent (n=62), 41% remembered their broad consent correctly. In the group randomized to an intervention (n=121), 79% understood that being selected was related to previously providing broad consent for randomization; 3. In the group randomized to an intervention (n=121), 39% understood they were selected based on chance, while 44% indicated not being interested in understanding selection procedures. The idea of not being selected for an intervention while your data were being used in comparison with those receiving experimental interventions, felt neutral (88%), reassuring (10%) or negative (2%) to the random cohort participants (n=62) who had not been selected for experimental interventions.

## Conclusions

Patients' recollection of broad consent, and their understanding of randomization was adequate shortly after enrollment, and also after being selected for an intervention, but more frequent reminders are necessary to also keep those who were not approached for interventions well informed and aware of broad consent throughout cohort participation.

# INTRODUCTION

Randomized controlled trials (RCTs) are essential to evaluate effectiveness of novel treatments, but are often beset by slow recruitment, limited generalizability, contamination of the control arm, and disappointment bias. Especially in oncology, 40% percent of cancer trials end prematurely.[1] The cohort multiple Randomized Controlled Trial (cmRCT) design is an alternative method to conduct pragmatic RCTs and was designed to reduce those challenges.[2]



In cmRCT, patients consent to longitudinal data collection in the context of a cohort or registry study. From this cohort, patients may be randomly allocated to experimental interventions.[2] Only those randomly allocated to an intervention will be notified, while control patients continue receiving standard of care without further notice.

In 2013, we introduced cmRCT in a clinical oncology setting and created a staged-informed consent procedure.[3] In this staged-informed consent procedure, at cohort entry, patients provide broad informed consent for randomization to future interventions. They are informed that they may serve as controls without further notice when not randomly selected for the intervention(s).[3] After randomization, a second informed consent is obtained from those allocated to an intervention. Finally, after trials are completed, aggregated results will be shared with all cohort participants.

At our hospital, we have been applying cmRCT and this staged-informed consent procedure to three separate cohorts for patients with colorectal cancer, bone metastases and breast cancer.[4-6] In these cohorts, several trials are currently running.[7-10] So far, participation rates have been high in all three cohorts, indicating feasibility and patient acceptability of the design in a clinical oncology setting.[3,4,6] However, it is also important to evaluate whether patients participating in these studies are well informed from a clinical trial standpoint; do patients understand the cmRCT design and the random selection process, and do they remember providing broad consent?

We explored patients' understanding of the cmRCT design among participants of our hospital-based cohorts and embedded trials, by assessing 1. Reasons for (non)participation, 2. Recollection and perspectives of broad consent and 3. Understanding of – and perspectives on – randomization procedures.

# METHODS

Between October 2015 and April 2018, we conducted a survey among participants and patients eligible to participate in cmRCT cohort studies at the department of Radiation Oncology. The survey explored patients' perspectives on the cmRCT design at several stages of cohort and trial participation, by assessing 1. Patients' reasons for cohort and intervention (non-)participation, 2. Patients' recollection of broad informed consent, 3. Patients' understanding of – and perspectives on – randomization procedures, and 4. Patients' perspectives on receiving aggregated results of trials completed within the cohort was explored. Since no validated questionnaires were available for these purposes, questionnaires were developed by our team of researchers, clinicians and ethicists.

Five groups of patients received questionnaires (Figure 1):

- Group 1. Patients who consented to cohort participation (surveyed within two weeks after agreeing)
- Group 2. Patients who declined cohort participation (surveyed within two weeks after declining)
- Group 3. Patients randomized to an experimental intervention who accepted the intervention (surveyed after being approached for the intervention)
- Group 4 Patients randomized to an experimental intervention who declined the intervention (surveyed after being approached for the intervention)
- Group 5. Random sample of cohort participants who had not been selected for an intervention arm of ongoing trials at the moment of surveying (surveyed 1 to 6 months after cohort enrollment).

To explore patients' recollection of broad consent for randomization, we asked the question "Did you provide consent to receive invitations for future experimental interventions?" (i.e. asked in all groups except for group 2). Patients' responses

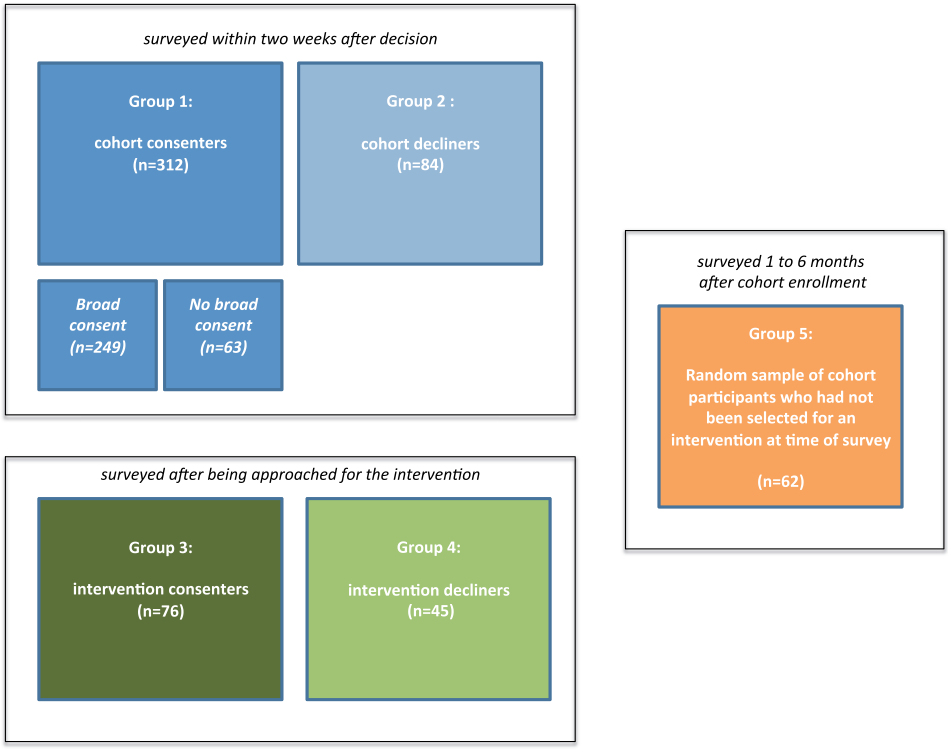
were compared to their signed informed consent forms to calculate the percentage of patients remembering their decision correctly.

To explore perspectives of patients who were not selected for an intervention, but who's data may be (or have been) used in comparison (i.e. group 4), the following scenario was presented "In this cohort, you could theoretically be/have been selected for experimental interventions. How would you feel if you were not selected for an intervention, but your data would be used in comparison with patients receiving such an intervention?".



Most questions in this survey study allowed for simultaneous endorsement of more than one response option, thus answers may add up to more than 100%. The study was exempted from full ethical review by the Institutional Review Board of the University Medical Center Utrecht, and adhered to the Declaration of Helsinki.

**Figure 1. Overview of surveyed groups**



# RESULTS

In total, 579 patients responded to the survey (estimated response rate of approximately 70%). This study population consisted of 81 patients with rectal cancer, 147 patients with bone metastases and 351 patients with breast cancer.

The survey that evaluated perspectives after agreeing to cohort participation was completed by 312 patients (i.e. group 1, Table 1). The survey after declining cohort participation was completed by 84 patients (i.e. group 2, Table 1).

The survey that evaluated perspectives of patients randomized to the intervention arm was completed by 121 patients (i.e. group 3, Table 2), of which 84 accepted the offered intervention and 45 declined. This sample consisted of 103 patients randomized to an intervention within the breast cancer cohort (i.e. UMBRELLA FIT trial), 9 randomized to an intervention in the colorectal cohort (i.e. Rectal BOOST trial), and 9 patients in the bone metastases cohort (i.e. VERTICAL trial).[7-9] In total, The survey after declining the intervention was completed by 45 patients (i.e. group 4).

The questionnaire that was sent to a random sample of cohort participants who had not been selected for an intervention arm of ongoing trials at the moment of surveying (i.e. group 5, Table 3) was completed by 62 patients.

## Patients' reasons for cohort and intervention (non-) participation

***Group 1***

The two most common reasons for cohort participation were 'hoping to help future patients' (95%, 296/312) and 'hoping for personal gain' (18%, 56/312).
Within this first group, 249 patients (80%) provided broad consent for potential future randomization, of which 28% (n=69/249) hoped to receive an invitation for an experimental intervention within the first two weeks.
Of those who did not provide broad consent for randomization (n=63), the two most selected reasons were 'not interested in experimental interventions' (32%, 20/63) and 'too much of a burden' (33%, 21/63).

***Group 2***

Patients who declined cohort participation (n=84), had the following reasons: 58% felt emotionally or physically unable to participate (49/84), 31% did not want to be confronted with the disease more than necessary (26/84), and 19% (16/84) had no desire to participate in research in general.

***Group 3***

After accepting the offered intervention (n=76), 84% (64/76) were 'hoping for direct benefit', 79% (59/76) accepted the intervention to help gain knowledge for future patients, and 4% (3/76) felt obligated to accept the intervention.



***Group 4***

Patients who were offered an intervention after randomization, but who declined this offer, were asked for their reasons for declining the intervention (n=45). Reasons for declining an intervention were either that they did not expect direct benefit from participating (16%, 7/45) or reasons directly related to the offered intervention (e.g. no time for the physical activity intervention, physical burden of the physical activity intervention) in 84% (38/45).

## Patients' recollection of broad informed consent

***Group 1***

Within 2 weeks after enrollment, in the group that provided broad consent (n=249), 76% (188/249) remembered their broad consent decision correctly (i.e. same answer as on signed informed consent form), 16% (40/249) recalled a decision different than the one selected on their informed consent form, and 8% (21/249) selected 'I do not remember'. In the group that did not provide broad consent for randomization (n=63), 79% (50/63) remembered their prior choice correctly, 16% (10/63) recalled a different decision than the one selected on their informed consent form, and 5% (3/63) answered not remembering what they had decided upon enrollment.

***Group 3 + 4***

After having been selected and approached for an intervention, 42% of patients (51/121) understood that this was due to their prior broad consent for randomization, 37% (45/121) understood that this was due to their prior broad

consent but had forgotten about it until they were approached and 15% (18/121) could not remember providing broad consent for randomization.

They were also asked how often the thought of possibly being approached for experimental interventions had crossed their minds, 56% (68/121) stated never to have thought about it again although being aware that it would be possible, and only one patient thought about it frequently.

***Group 5***

In the random sample of cohort participants who had not been selected for an intervention arm of ongoing trials at the moment of surveying (n=62), 29% (n=18/62) did not remember whether they had agreed to future randomization, 30% (n=19/62) recalled a decision different than the one selected on their informed consent form and 40% (n=25/62) provided the same answer as they had selected on their informed consent form.

## Patients' understanding of – and perspectives on – randomization procedures

***Group 3 + 4***

After being random selected for the intervention (n=121), when asked "Do you know how you have been selected for the experimental intervention", 44% (53/121) answered not to care, 39% (47/121) correctly answered that this was based on chance, 12% (15/121) thought it was based on reasons other than chance, and 5% (6/121) selected not knowing how they were selected but would liked to have known this.

Sixty-three percent (76/121) felt neutral about being randomly selected, 26% (31/121) felt lucky or special, 7% (9/121) felt insecure, worried or anxious.

***Group 3***

Patients who accepted the intervention (n=76) were also asked how they would feel if their data were being used in comparison with patients offered the experimental intervention, if they would not have been selected, after which 92% (70/76) stated they would feel neutral, 5% (4/76) would feel reassured, 3% (2/76) would feel angry.

***Group 5***

The 62 patients from the random cohort sample were also asked how they would feel if their data were being used in comparison with those of patients who had been offered an experimental intervention. Of those, 88% (54/62) indicated they would feel 'neutral', six patients would feel reassured (10%), one patient would feel angry, and one patient would feel insecure.

## Patients' perspectives on receiving aggregated results of trials completed within the cohort

***Group 3***

In the group that accepted an intervention (n=76), 89% wanted to receive trial results after completion and to 11% it did not matter whether or not they would receive results.

***Group 4***

In the group that declined the intervention (n=45), 51% wanted to receive trial results, 24% did not want to receive results and 24% selected 'it does not matter to me whether or not I receive results'.

***Group 5***

In the random sample of potential control patients (n=62), 50% (31/62) would like to receive results of trials conducted within the cohort they are participating in, 19% (12/62) did not and 31% (19/62) had no preference.

**Table 1. Reasons for participation and understanding of cmRCT in patients agreeing to cohort participation (n=312) – Group 1 and 2**

| Survey question | % | n/N |
|---|---|---|
| **Group 1: After agreeing: Why did you decide to participate in the cohort study? (n=312)**** | | |
| Hoping for personal gain | 18% | 56/312 |
| Hoping to help future patients | 95% | 296/312 |
| I feel obligated | 5% | 15/312 |
| Other reason | 4% | 11/312 |
| **Group 1: Broad consent providers: Are you hoping to receive invitations for interventions? (n=249)** | | |
| No | 14% | 35/249 |
| Don't really care | 58% | 145/249 |
| Yes, a little | 22% | 54/249 |
| Yes, a lot | 6% | 15/249 |
| **Group 2: After declining: Why did you decline participation in this cohort study? (n=84)**** | | |
| No desire to participate in research in general | 19% | 16/84 |
| I feel physically unable | 27% | 23/84 |
| I feel emotionally unable | 31% | 26/84 |
| No confrontations with my disease more than necessary | 31% | 26/84 |
| I do not think this study will provide personal gain | 8% | 7/84 |
| I don't want to commit to anything (for a longer period of time) | 0% | 0/84 |
| I am worried about my privacy and safety of my data | 7% | 6/84 |
| **Group 2: After declining broad consent: Why didn't you provide consent to receive invitations for (future) experimental interventions? (n=63)** | | |
| I am not interested in experimental interventions | 32% | 20/63 |
| I do not think I will be eligible for experimental interventions | 19% | 12/63 |
| I do not want to be burdened with extra information about new studies | 33% | 21/63 |
| Other reason | 16% | 10/63 |
| **Group 1: After agreeing to broad consent: Did you provide consent to receive invitations for (future) experimental interventions? (n=249)** | | |
| I do not remember | 8% | 21/249 |
| Correct recollection* | 76% | 188/249 |
| Incorrect recollection | 16% | 40/249 |
| **Group 1: After not agreeing to broad consent: Did you provide consent to receive invitations for (future) experimental interventions? (n=63)** | | |
| I do not remember | 5% | 3/63 |
| Correct recollection* | 79% | 50/63 |
| Incorrect recollection | 16% | 10/63 |

* Correct answer means that the patient selected the same answer as on their signed informed consent form.
** Answer may not add up to 100% due to the option to endorse more than one answers, or as a result of rounding.

**Table 2. Perspectives of patients after having been randomly selected and approached for an experimental intervention (n=121) – Group 3 and 4**

| Survey question | % | n/N |
|---|---|---|
| **Group 3: Why did you decide to participate in this experimental intervention study? (n=76)** | | |
| I think that participating will provide direct benefits for myself | 84% | 64/76 |
| I am participating to help (future) patients | 79% | 59/76 |
| I am participating because I felt obligated | 4% | 3/76 |
| Other | 0% | 0/76 |
| **Group 4: After declining an intervention: Why did you decide not to undergo this intervention? (n=45)**** | | |
| No direct benefit | 16% | 7/45 |
| Too much of a burden | 58% | 26/45 |
| I expected disadvantages from accepting this intervention | 9% | 4/45 |
| Other | 8% | 8/45 |
| **Group 3 + 4: Do you understand that you have been selected based on your prior choice to potentially receive invitations for experimental interventions? (n=121)** | | |
| No, I cannot remember this | 15% | 18/121 |
| Yes, but I had forgotten about it until being approached for the experimental intervention | 37% | 45/121 |
| Yes, I immediately realized when being approached for the experimental intervention | 42% | 51/121 |
| No answer | 6% | 7/121 |
| **Group 3 + 4: Did you ever think about the possibility of being invited to undergo an intervention? (n=121)** | | |
| No, because I could not have known this | 37% | 45/121 |
| No, never thought about it again although I was aware that it would be possible | 56% | 68/121 |
| Yes, sometimes (at least once a month) | 4% | 5/121 |
| Yes, often (at least once a week) | 1% | 1/121 |
| No answer | 2% | 2/121 |
| **Group 3 + 4: Do you know how you have been selected for the experimental intervention? (n=121)** | | |
| No, but I don't care | 44% | 53/121 |
| No, but I would have liked to know beforehand | 5% | 6/121 |
| Yes, researchers chose me from a large group of patients | 7% | 9/121 |
| Yes, I was selected based on chance from a group of patients who met criteria for this intervention | 39% | 47/121 |
| Yes, all patients in the cohort will be offered this intervention | 5% | 6/121 |

**Answers may not add up to 100% due to the option to endorse more than one answers, or as a result of rounding.

**Table 2. Perspectives of patients after having been randomly selected and approached for an experimental intervention (n=121) – Group 3 and 4** (Continued)

| Survey question | % | n/N |
|---|---|---|
| **Group 3 + 4: How did you feel about the way you were selected for this intervention? (n=121)**** | | |
| Neutral | 63% | 76/121 |
| Lucky/special | 26% | 31/121 |
| Scared/anxious | 3% | 4/121 |
| Relieved | 0% | 0/121 |
| Reassured | 1% | 1/121 |
| Insecure/worried | 4% | 5/121 |
| Angry | 0% | 0/121 |
| Other | 3% | 4/121 |
| **Group 3: What if you had not been offered this experimental intervention, but your data would have been used in comparison with the experimental intervention. How would that make you feel?** | | |
| Neutral | 92% | 70/76 |
| Lucky/special | 0% | 0/76 |
| Scared/anxious | 0% | 0/76 |
| Relieved | 0% | 0/76 |
| Reassured | 5% | 4/76 |
| Insecure/worried | 0% | 0/76 |
| Angry | 3% | 2/76 |
| Other | 0% | 0/76 |
| **Group 3: After accepting an intervention: Is it important to you to receive information about the effect of this intervention after the trial is completed? (n=76)** | | |
| No, I do not want to receive results | 0% | 0/76 |
| Neutral, it does not matter to me whether or not I receive results | 11% | 8/76 |
| Yes, I would like to receive results | 89% | 68/76 |
| **Group 4: After declining an intervention: Is it important to you to receive information about the effect of this intervention after the trial is completed? (n=45)** | | |
| No, I do not want to receive results | 51% | 23/45 |
| Neutral, it does not matter to me whether or not I receive results | 24% | 11/45 |
| Yes, I would like to receive results | 24% | 11/45 |

**Answers may not add up to 100% due to the option to endorse more than one answers, or as a result of rounding.

**Table 3. Perspectives of a random sample of cohort patients who were not receiving any interventions at time of survey (n=62), one to six months after enrollment – Group 5**

| Survey question | % | n/N |
|---|---|---|
| **Group 5: Did you provide consent to receive invitations for (future) experimental interventions? (n=62)** | | |
| I do not remember | 29% | 18/62 |
| Correct answer* | 41% | 23/62 |
| Incorrect answer | 30% | 17/62 |
| **Group 5: In this cohort, you could theoretically be selected for experimental interventions. How would you feel if you were not selected for an intervention, but your data would be used in comparison with patients receiving such an intervention? (n=62)**** | | |
| Neutral | 88% | 54/62 |
| Lucky/special | 0% | 0/62 |
| Scared/anxious | 0% | 0/62 |
| Relieved | 0% | 0/62 |
| Reassured | 10% | 6/62 |
| Insecure/worried | 1% | 1/62 |
| Angry | 1% | 1/62 |
| Other | 0% | 0/62 |
| **Group 5: Is it important to you to receive information about the effect of interventions that were studied within the cohort? (n=62)** | | |
| No, I do not want to receive such results | 19% | 12/62 |
| Neutral, it does not matter to me whether or not I receive such results | 31% | 19/62 |
| Yes, I would like to receive such results | 50% | 31/62 |

* Correct answer means that the patient selected same answer as on their signed informed consent form.
**Answer may not add up to 100% due to the option to endorse more than one answers, or as a result of rounding.



# DISCUSSION

This study evaluated perspectives and understanding of the novel cmRCT design in patients with cancer who were participating in cmRCT cohorts and embedded trials. In our hospital, the reason for cohort participation indicated by almost all patients with cancer (95%) was to help gain knowledge for future patients. Recollection of their broad informed consent status for (potential) future randomization to experimental interventions was adequate within the first two

weeks after providing informed consent (>76%), and also after being approached for an intervention (79%), and dropped to 41% in the random sample of patients who had not been selected for interventions one to six months after providing informed consent. Of those randomized to an intervention, 39% understood that this was based on chance, 44% was not interested in the methods of selection, and 12% thought that selection was based on a method other than chance. Most patients (64%) felt neutral after being randomized to an intervention, and 26% felt lucky or special. Patients who were not receiving interventions were acceptant of the thought that their data were being used in comparison to those receiving an intervention (only 2% stated they would experience negative emotions).

Our study was performed at the Radiation Oncology department where cmRCT cohorts have been implemented into routine care since 2013. Jagsi et al surveyed 875 patients with cancer to evaluate their views on use of routine clinical data for (amongst others) the academic research. They found that 71% of patients felt that consent should be obtained at least once before using their data.[11] They also found that 35% patients with cancer found it necessary to obtain consent each time their data were being used for research. This study encourages the use of our staged-informed consent approach, since with this approach we obtain consent for all relevant study activities at least once upon enrollment, and additional informed consent is obtained when patients need to actively do something other than what is part of routine care.

Thirty-nine percent of patients selected for an intervention, understood that selection for being offered experimental interventions was based on chance. However, 44% stated that they were not interested in understanding these selection methods. One optimistic explanation for this answer would be that patients made a well-informed decision with a good understanding of the study design upon enrollment, and therefore no longer cared about fully understanding the design later in time. A less favorable explanation would be that these patients never fully understood the design upon enrollment, and do not want to understand the design at the current moment because it's too complex for them to understand. In general, the concept of randomization is difficult to understand for patients/ study participants. Kodish et al explored understanding of randomization in childhood leukemia classic RCTs, which showed that 50% of parents (n=68/137)

did not understand the randomization procedure shortly after enrollment.[12] In this study, despite devoting significant time to explaining informed consent, which was confirmed by videotaped interviews, understanding did not improve. An important review of available literature on empirical issues in informed research by Flory, Wendler and Emanuel showed that the majority of studies found that fewer than half of study participants understand randomization.[13] The only evidence for an intervention that improved understanding was to provide a face-to-face informed consent process, with the opportunity for a dialogue and interaction with a qualified person. There was no added benefit if this person was an investigating physician, nurse or outside educator.[13] Taking these findings into account, understanding of randomization seems to be well above average in our cohorts shortly after enrollment (>76%) and after being selected for an intervention (79%). Only in those who have never been selected for an intervention, understanding seems in line with the literature (41%). Although these results may reflect the actual situation in our cohorts, this group consisted of only 56 patients. Larger number of patients are required, and perhaps more qualitative interviews, to truly understand their understanding of randomization.



In an attempt to improve understanding of informed consent, the US federal regulations for conducting research with human subjects (i.e. The Common Rule) were updated and simplified.[14,15] This simplification was done, as perceptions were that informed consent forms are often too lengthy, too complex and patient burden needs to be reduced. The revised Common Rule states that patients should receive information that a reasonable person would want to receive. Our study serves as a starting point for exploring what type of information patients participating in cmRCT studies want to receive, in relation to what type of information is currently provided. Our results suggest that researchers using a cmRCT design should place more emphasis– prior to signing the informed consent form – on testing whether or not patients adequately understand the cmRCT design. An easy way to test understanding would be to ask patients to explain broad consent and the study selection methods after receiving all information, prior to signing the informed consent form. This allows researchers to identify where understanding is limited, which could then be addressed and improved before the patient signs informed consent. Testing understanding by asking feedback is the most successful intervention in the available informed consent literature.[13]

In our study, after being selected for an intervention (n=121), 79% of patients understood that this was due to providing broad informed consent for randomization in the past. The majority of these patients were selected from the breast cancer cohort (83%, 101/121 patients). These patients were approached 12 to 18 months after enrollment in the cohort to undergo a supervised physical activity program aimed at improving quality of life in physically inactive patients. These numbers suggest that recollection of broad informed consent is being triggered when approached for an intervention and the vast majority of patients understand that they were approached because of their prior consent. This number is in contrast to the only 41% of patients remembering correctly whether or not they agreed to future randomization, in the random sample that we approached 1 to 6 months after enrollment. This is an important finding that needs attention, as it suggests that we may need to inform patients about their broad consent status more frequently. At the moment, all three cohorts inform patients (bi)annually about aggregated study results and cohort participation rates, through meetings and newsletters. More frequent updates, including brief reminders of the broad consent concept, may be required to ensure adequate understanding of cohort participation and of what is being done with their data.

After hearing that they were randomly selected for an intervention, 27% of patients felt lucky or special. It is important for researchers to explain, prior to accepting, that the intervention may also turn out to be less effective than the current standard of care or even harmful. If patients do not understand this concept, then this may induce therapeutic misconception (i.e. failure to understand the distinction between what is part of clinical research and of ordinary care).[16] If patients accept the intervention without understanding the potential consequences from undergoing the intervention, this could mean that they did not provide meaningful consent from an ethical point of view.

In this study, understanding and perspectives of patients who declined cohort participation are underrepresented. Their perspectives are only evaluated directly after declining cohort participation, since we do not have consent to ask patients' opinions later in time. It would be relevant to evaluate whether patients regret their decision after learning what type of studies have been conducted over time in the cohort they declined to participate in. When learning about these results,

patients might decide that they would like to participate in – or contribute data to – such studies after all. Therefore, our staged-informed model was proposed as a dynamic model meaning that patients have the option to change their minds and participate in the cohort after initially declining.[3,17] To allow for this, entry into the cohorts and results of fully completed embedded trials, need to be available both to participants and non-participants of the cohort. The easiest way is by providing results from observational studies and completed embedded trials on websites of participating hospitals, including information on how to access cohorts after initially declining participation. We have provided results from observational studies on the website of our hospital, and will provide trial results as soon as the first trial is completed. This dynamic approach may have important methodological consequences, as patients who enter the cohort later in time, may differ from patients who participated at the start of radiotherapy. Patients entering the cohort later in time, will have missing baseline (and other follow-up) measurements, which could prevent them from meeting inclusion criteria for all available trials. For example, if measurements at time of radiotherapy are a part of inclusion criteria for a certain trial. Therefore, at the moment, we do not actively encourage the dynamic broad informed consent, but patients may decide to withdraw or change their broad consent status at any time, which is explained upon enrollment. So far, patients have terminated cohort or cmRCT-based trial participation, but no patients have only changed their broad consent status.

Fifty percent of patients who had not been offered an intervention indicated they do not want to receive aggregated trial results. Also, only 2% of these patients would feel negative if their data were being used in comparison with patients receiving an intervention. Only those who accepted an intervention were highly interested in receiving trial results (89%). This implies that the final stage of our staged-informed consent model, where we proposed providing aggregated trial results to the entire cohort, may only be what half of the patients prefers. To respect patients' wishes, it should be asked upon enrollment what type of feedback they would like to receive. They may also be referred to cohort websites or other sources where updated results will be made available real-time. Patients who are approached to undergo an intervention, can easily be asked again during the second informed consent whether they would like to receive final results of the trial they have been selected for.

Our study provides the first evaluation of perceptions and understanding of the cmRCT design in patients with cancer who are participating in ongoing cmRCT cohorts and embedded trials. The main motive for research participation is improving outcomes for future patients. The majority of patients randomized to experimental interventions remembered providing broad informed consent and understood the selection procedure, or were not interested in understanding this procedure. Frequent reminders of broad consent are required to keep all participants informed. Only 2% of patients not selected for interventions would feel negative about the idea of not being selected for interventions but only potentially serving as controls without further notice. Therefore, cmRCT is an attractive alternative for pragmatic RCTs in clinical oncology.

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# 5

# Breast edema following breast-conserving surgery and radiotherapy: patient-reported prevalence, determinants and effect on health-related quality of life

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# ABSTRACT

## Purpose

The association between lymphedema of the arm and impaired health-related QoL (HR-QoL) has led to significant changes in clinical practice. However, data on lymphedema of the breast (i.e. breast edema) are lacking. We prospectively evaluated prevalence and determinants of breast edema, and its effect on patient-reported HR-QoL and breast pain.

## Methods

We prospectively included 836 patients undergoing breast-conserving surgery followed by radiotherapy between October 2013 and October 2016 (UMBRELLA cohort). Patient-reported breast edema, HR-QoL and breast pain were assessed by means of EORTC-C30/BR23 before starting radiotherapy, and at 3, 6, 12 and 18-months thereafter. We assessed which patient, tumor and treatment characteristics were associated with breast edema. With mixed-effects models we assessed the impact of breast edema on patient-reported HR-QoL domains and breast pain over time, adjusting for confounders.

## Results

Within a median follow-up of 28 months (IQR 15), 207 (24.8%) patients experienced breast edema at some point in time. Prevalence of breast edema was highest at 6 months (12.4%, 95%CI 10.0-14.7). Larger tumor size, oncoplastic surgery, axillary lymph node dissection, loco-regional radiotherapy, radiotherapy boost on the tumor bed and adjuvant chemotherapy were associated with breast edema. Breast edema was independently associated with more breast pain, and with poorer QoL, physical functioning and body image.

## Conclusion

Breast edema occurs frequently within the first year after breast-conserving surgery and radiotherapy, and is independently associated with more breast pain and impaired HR-QoL. This information is important for use in clinical practice and should be incorporated in shared-decision making.

# INTRODUCTION

Due to earlier detection of breast cancer and more effective treatment, breast cancer prognosis has improved substantially over the past decades.[1-3] As such, long-term side effects of treatment and health-related quality of life (HR-QoL) are becoming increasingly relevant.[4,5]

Breast-conserving therapy (BCT) – which consists of breast-conserving surgery (BCS) followed by whole breast irradiation – has become the standard of care for early-stage breast cancer, as the oncologic outcome is similar to that of mastectomy.[1-3] With the advent of neoadjuvant systemic therapy and oncoplastic surgical techniques, BCT can nowadays also be offered to women with larger tumors.[6,7] With the increasing proportion of patients undergoing BCT, physicians more often report isolated lymphedema of the breast (i.e. breast edema), the reasons of which are still not well understood.[8]



While the association between lymphedema of the arm and impaired HR-QoL is widely acknowledged, less is known about the impact of breast edema on HR-QoL.[9] Compared to arm edema fewer studies are available, most of which have been performed retrospectively or cross-sectionally and without the use of patient-reported outcomes (PROs).[10] Breast edema is most often reported as part of physician-reported toxicity scores in studies evaluating experimental interventions for breast cancer treatment. Studies primarily aimed at assessing breast edema in routine care are rare.[8,9] Also, the effects of modern treatment options, such as oncoplastic surgery and neoadjuvant chemotherapy (with or without immunotherapy), on the risk of breast edema have not been evaluated.[10]

Evidence-based treatments for breast edema are not yet available, but a substantial amount of women are treated with long-term interventions, such as manual lymphatic drainage, taping of the breast and compression therapy following BCT. Understanding prevalence and risk factors for breast edema is important to guide clinical decision making, to adequately inform patients about its impact on QoL and to serve as a starting point for developing targeted evidence-based interventions to prevent breast edema.

The aim of this study was to evaluate the prevalence and determinants of breast edema, and to evaluate the association between breast edema and patient-reported HR-QoL and breast pain in a large prospective cohort of women undergoing BCT.

# METHODS

## Participants

This study was conducted within the prospective observational 'Utrecht cohort for multiple breast cancer intervention studies and long-term evaluation' (UMBRELLA) including women with breast cancer or ductal carcinoma in situ referred for radiation treatment at the University Medical Center Utrecht in the Netherlands.[11] All participants gave written informed consent for longitudinal collection of clinical data and PROs at regular intervals during and after treatment. The UMBRELLA study was approved by the institutional review board of the University Medical Center Utrecht, adheres to the Declaration of Helsinki and is registered on clinicaltrials.gov.[12]

We prospectively included all women, 18 years of age and older, who underwent BCS followed by whole-breast irradiation (with or without additional regional radiotherapy) between October 2013 and October 2016. All patients with at least 12 months follow-up, who had completed surgery, radiotherapy and – if applicable – adjuvant chemotherapy, and who returned at least one questionnaire assessing PROs were included in the analysis.

## Data collection

Patient, tumor and treatment characteristics were prospectively collected during routine clinical medical care and obtained from electronic patient files, self-reported questionnaires and quarterly provided data from the Netherlands Cancer Registry.

Presence of patient-reported breast edema was assessed prior to the start of radiotherapy and at 3, 6, 12 and 18 months thereafter. Breast edema was evaluated by means of EORTC QLQ-BR23 question 51 (i.e. 'During the past week; Was the area of your affected breast swollen?') on a 4-point Likert scale (i.e. 'not at all', 'a little', 'quite a bit' or 'very much').[13]

The following potential determinants were studied: age, (neo)adjuvant systematic therapy (chemotherapy, endocrine therapy, immunotherapy, alone or in combination), oncoplastic surgery, sentinel node biopsy, axillary lymph node dissection (ALND), tumor size, radiotherapy boost to the tumor bed (i.e. local radiotherapy boost), and regional lymph node irradiation (i.e. axillary and/or peri-clavicular lymph nodes). In line with Dutch guidelines, oncoplastic surgery was defined as oncological resection combined with redistribution of local breast and surrounding tissue in patients after a large proportion (generally more than 20%) of the breast had to be resected as part of BCS.[14] Simple full thickness closure was not considered as oncoplastic surgery.

For all patients, completion dates for questionnaires were registered, and the time between the dates of start of radiotherapy, chemotherapy and all other treatments were assessed. Treatment variables were assessed as potential determinants, when the start of the concerning treatment (radiotherapy, chemotherapy and all other treatments) preceded the date of completing the questionnaire. For example, for patients receiving adjuvant chemotherapy 4 months after initiation of radiotherapy (baseline), chemotherapy was not assessed as a potential determinant for breast edema at baseline and 3 month, but only at 6, 12 and 18 months.



To estimate the effects of breast edema on patient-reported QoL, physical functioning, sexual functioning, body image and breast pain, we assessed PROs (i.e. EORTC QLQ-C30 and the breast cancer specific module BR23) before the start of radiation treatment, and 3, 6, 12 and 18 months thereafter. Breast pain was assessed by means of EORTC OLQ- BR23 question 50 ('During the past week; Have you had any pain in the area of your affected breast?' on a 4-point Likert scale), while scores for the EORTC domains QoL, physical functioning, sexual functioning and body image were calculated according to EORTC QLQ-C30 and BR23 guidelines.[13,15]

## Statistical analysis

Frequencies, proportions and means with standard deviations for normally distributed variables – and medians with interquartile ranges otherwise – were used to describe clinical characteristics of study participants and prevalence of breast edema.

To identify determinants that were significantly associated with breast edema, we compared differences in the percentages of breast edema between groups for each possible determinant. This was done before the start of radiotherapy, and 3, 6, 12 and 18 months thereafter, using a t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables using complete case analysis. For this analysis, data on patient-reported breast edema (i.e. EORTC-QLQ-BR23 question 51 'During the past week; Was the area of your affected breast swollen?') were dichotomized to 'not at all or a little' versus 'quite a bit or very much'. Questionnaires returned later than 4 weeks after the planned assessment interval were excluded from the analysis.

To compare QoL-related domains (i.e. QoL, physical functioning, sexual functioning, and body image) and breast pain between patients with and without edema, we used linear mixed-effects models for repeated measures. Data from patients who returned at least two PRO measures were included. An autoregressive covariance structure was included with the assumption that measurements closer together in time are more correlated in longitudinal data than measurements further apart. Fixed effects in the model were time (time after start of radiotherapy, categorical), group (breast edema versus no breast edema), the interaction between time and group, and potential confounders (i.e. age, ALND, tumor size, local radiotherapy boost, regional lymph node irradiation, adjuvant systemic treatment). For this analysis, outcome data on patient-reported breast pain were linearly transformed into a continuous score ranging from 0 to 100, according to the EORTC manual for symptom scores (i.e. higher scores indicate more symptoms). Results were presented as estimated marginal means and mean differences (MD).

All reported p-values were two-sided, and values $<0.05$ were considered statistically significant. Statistical analyses were performed with IBM Statistical Package for Social Sciences (SPSS) software, version 24 (Armonk, NY: IBM Corp.).

# RESULTS

In total, we included 836 patients treated with BCT in this study with a median follow-up of 28 months (IQR 15). This included 724 (87%) patients with invasive breast cancer, and 112 (13%) patients with DCIS. A total of 656 (78%) patients received whole-breast irradiation only, and 180 (22%) patients received whole-breast irradiation with additional regional lymph node irradiation (i.e. loco-regional radiotherapy) (Table 1).

Within the first 18 months after cohort enrollment, 207 (25%) patients had experienced breast edema at some point in time. At baseline (i.e. prior to the start of radiotherapy) 12% (100/836) of patients reported breast edema. Prevalence of breast edema was 7% (58/819) at three months, 12% (96/777) at six months, 8% (58/709) at twelve months and 6% (33/601) at eighteen months (Table 2).



Determinants significantly associated with breast edema (Table 3) were oncoplastic surgery, axillary lymph node dissection (ALND), local radiotherapy boost, loco-regional radiotherapy and adjuvant chemotherapy. Also, women with edema had larger tumors (17mm, IQR 14) than women without breast edema (13mm, IQR 10). Variables that were not associated with breast edema were age, neoadjuvant chemotherapy with or without immunotherapy, sentinel node biopsy and adjuvant endocrine therapy.

Patients with breast edema reported significantly higher levels of breast pain than patients without edema at all time intervals (baseline, 3, 6, 12 and 18 months), also after adjusting in the mixed model for age, ALND, tumor size, local radiotherapy boost, loco-regional radiotherapy and/or adjuvant systemic treatment. Patients with breast edema reported poorer QoL, poorer physical functioning and poorer body image than patients without breast edema; statistically significant mean differences at baseline and 6 months, also after adjusting in the mixed model for age, ALND, tumor size, local radiotherapy boost, loco-regional radiotherapy and/or adjuvant systemic treatment. Figure 1 and 2 demonstrate crude results, and Table 4 presents the adjusted mixed model results.

**Table 1. Characteristics of study participants treated with breast-conserving surgery and adjuvant radiotherapy between October 2013 and October 2016, with at least 12 months follow-up (n=836)**

| Characteristic | No. of patients (%) |
|---|---|
| **Age at inclusion**, median (IQR) | 58 (16) |
| **Neo-adjuvant systemic treatment** | |
| None | 699 (83) |
| Chemotherapy | 49 (6) |
| Chemotherapy and immunotherapy | 88 (11) |
| **Oncoplastic surgery** | |
| Yes | 92 (11) |
| No | 396 (47) |
| Unknown | 348 (42) |
| **Sentinel node biopsy** | |
| Yes | 705 (84) |
| No | 131 (16) |
| **Axillary lymph node dissection** | |
| Yes | 120 (14) |
| No | 716 (86) |
| **Pathological tumor stage (pT)** | |
| Ductal carcinoma in situ (DCIS) | 102 (12) |
| T1 | 594 (71) |
| T2 | 133 (16) |
| ≥T3 | 7 (1) |
| **Radiotherapy treatment** | |
| Local radiotherapy | 656 (78) |
| Loco-regional radiotherapy * | 180 (22) |
| **Local radiotherapy boost (i.e. tumor bed)** | |
| Yes | 286 (34) |
| No | 459 (55) |
| Unknown | 91 (11) |
| **Adjuvant chemotherapy** | |
| Yes | 232 (28) |
| No | 604 (72) |
| **Adjuvant endocrine therapy** | |
| Yes | 656 (79) |
| No | 180 (21) |

* includes radiotherapy on axillary and/or periclavicular lymph nodes
IQR; interquartile range.

**Table 2. Patient-reported presence of breast edema in patients receiving breast-conserving therapy (i.e. breast-conserving surgery followed by radiotherapy)**

| | Breast edema | |
|---|---|---|
| Baseline | 12.0% (9.8-14.1) | 100/836 |
| 3 months | 7.1% (5.3-8.8) | 58/819 |
| 6 months | 12.4% (10.0-14.7) | 96/777 |
| 12 months | 8.2% (6.1-10.2) | 58/709 |
| 18 months | 5.5% (3.6-7.3) | 33/601 |

CI = confidence interval. Edema was defined by EORTC-BR23 question 50 ('No edema' consists of 'Not at all' and 'A little'; 'Edema' consists of 'quite a bit' and 'very much').
Baseline is after breast-conserving surgery but before radiotherapy; 3 months measurement is after the completion of radiotherapy (and at least 2 months after the initiation of radiotherapy). Because this is an ongoing, actively recruiting cohort the denominator decreases over time.



**Figure 1. Impact of breast edema on breast pain following breast-conserving surgery and radiotherapy (unadjusted scores)**

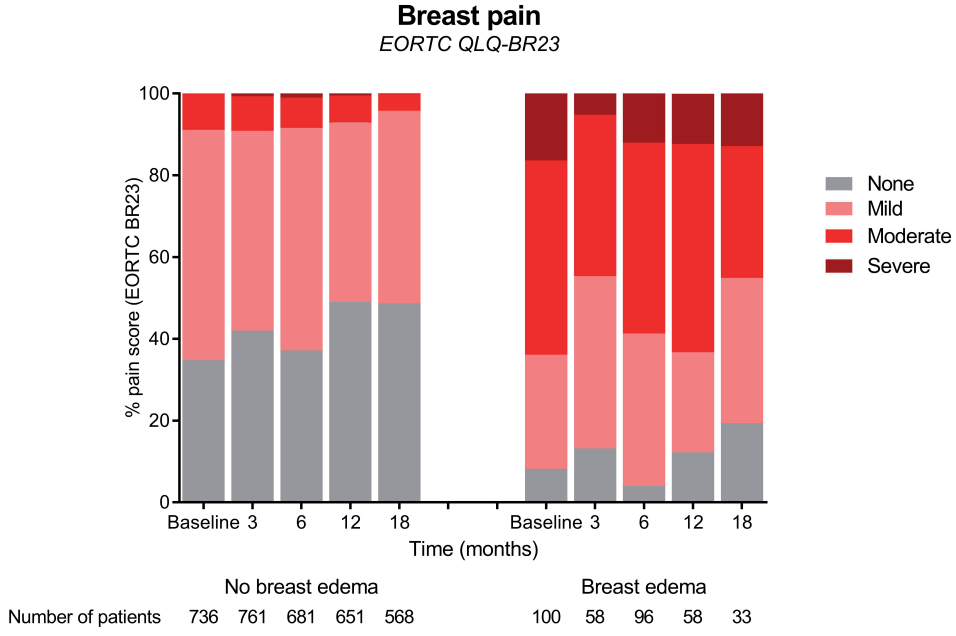

**Table 3. Proportions of women with breast edema after various types of treatments as part of breast-conserving therapy (n=836)**

| | | Breast edema at baseline | | Breast edema at 3 months | | Breast edema at 6 months | | Breast edema at 12 months | | Breast edema at 18 months | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Dichotomous variables* | | % | p[1] | % | p[1] | % | p[1] | % | p[1] | % | p[1] |
| **Neoadjuvant chemotherapy with immuno-therapy** | *Yes (n=88)* | 12.5 | | 5.1 | | 12.0 | | 11.4 | | 4.4 | |
| | *No (n=699)* | 10.9 | 0.65 | 7.2 | 0.48 | 12.3 | 0.94 | 8.0 | 0.33 | 5.7 | 0.72 |
| **Oncoplastic surgery** | *Yes (n=92)* | 20.0 | | 10.2 | | 12.2 | | 4.1 | | 5.3 | |
| | *No (n=396)* | 10.2 | 0.04 | 7.1 | 0.44 | 12.2 | 0.99 | 6.6 | 0.50 | 5.5 | 0.99 |
| **Sentinel node biopsy** | *Yes (n=705)* | 10.1 | | 5.7 | | 11.8 | | 8.2 | | 5.5 | |
| | *No (n=131)* | 11.1 | 0.40 | 6.3 | 0.45 | 15.5 | 0.26 | 8.0 | 0.95 | 5.6 | 0.95 |
| **Axillary lymph node dissection (ALND)** | *Yes (n=120)* | 25.8 | | 14.4 | | 22.0 | | 14.7 | | 10.7 | |
| | *No (n=716)* | 9.6 | <0.01 | 5.8 | <0.01 | 10.8 | <0.01 | 7.0 | <0.01 | 4.6 | 0.04 |
| **Radiotherapy** | *Local (n=656)* | N/A | | 5.8 | | 11.0 | | 7.1 | | 5.3 | |
| | *Loco-regional* (n=180)* | N/A | | 10.5 | 0.04 | 17.1 | 0.04 | 12.8 | 0.03 | 6.8 | 0.65 |
| **Local radiotherapy boost** | *Yes (n=286)* | N/A | | 4.6 | | 12.0 | | 7.7 | | 8.1 | |
| | *No (n=459)* | N/A | | 6.8 | 0.31 | 10.2 | 0.51 | 6.7 | 0.74 | 2.8 | 0.01 |
| **Adjuvant chemotherapy** | *Yes (n=232)* | N/A | | 5.7 | | 22.4 | | 14.8 | | 11.2 | |
| | *No (n=604)* | N/A | | 7.6 | 0.35 | 8.4 | <0.01 | 5.4 | <0.01 | 2.9 | <0.01 |
| **Adjuvant endocrine therapy** | *Yes (n=656)* | N/A | | 7.6 | | 14.8 | | 9.7 | | 6.1 | |
| | *No (n=180)* | N/A | | 6.7 | 0.58 | 10.4 | 0.08 | 7.0 | 0.19 | 5.0 | 0.59 |
| *Continuous variables* | | Median (IQR) | | p[2] | | | | | | | |
| **Age (in years)** | *Breast edema (n=207)* | 58 (16) | | 0.62 | | | | | | | |
| | *No breast edema (n=629)* | 58 (16) | | | | | | | | | |
| **Tumor size (in millimeter)** | *Breast edema* | 17 (14) | | <0.001 | | | | | | | |
| | *No breast edema* | 13 (10) | | | | | | | | | |

[1] p-value based on two-sided Chi-square test
[2] p-value based on Mann-Whitney U test
*includes radiotherapy on axillary and/or periclavicular lymph nodes
N/A: At baseline radiotherapy and adjuvant chemotherapy have not yet been initiated.

**Figure 2. Impact of breast edema on health-related quality of life domains following breast-conserving surgery and radiotherapy (unadjusted scores) with 95% confidence bands**

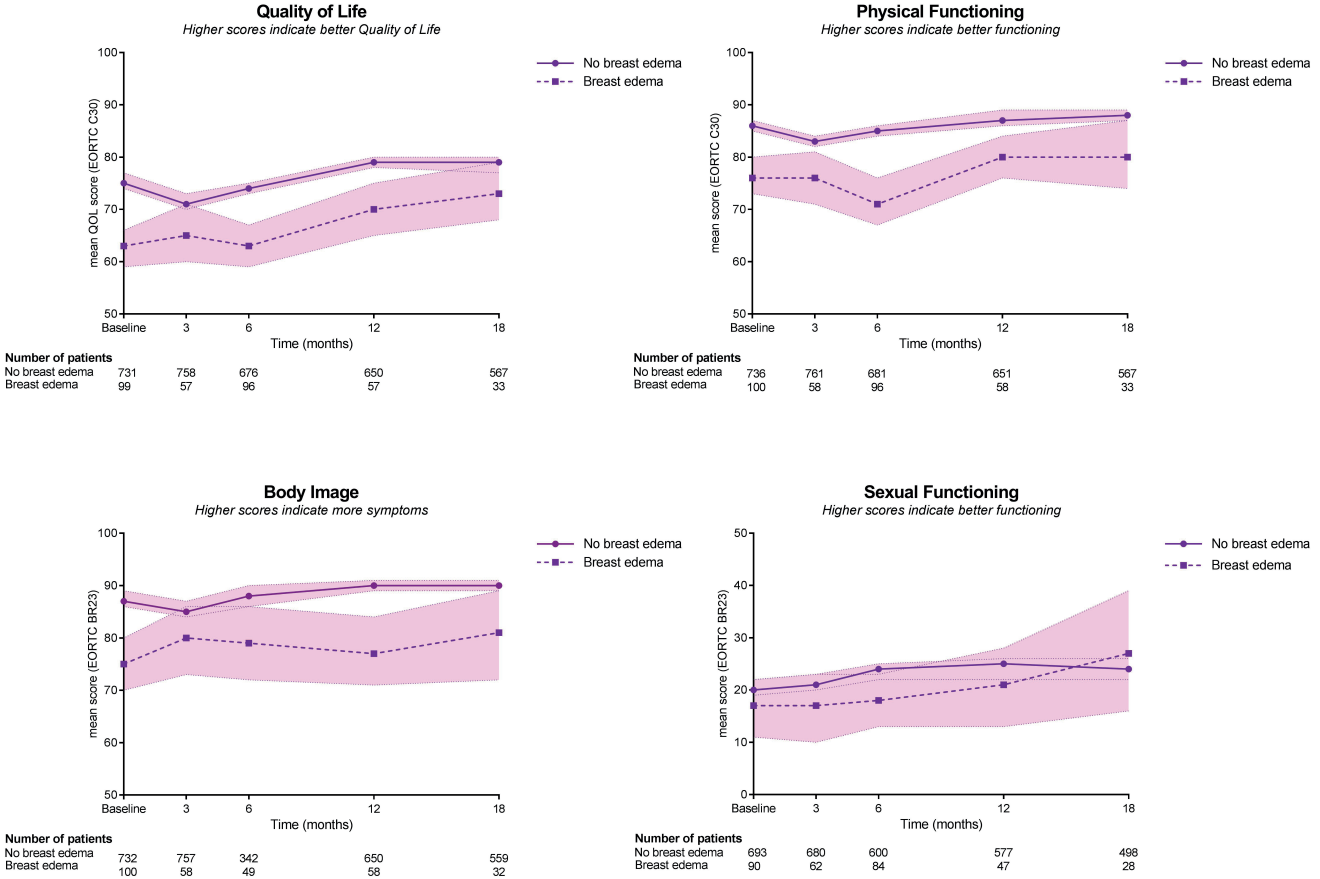

**Table 4. Results from mixed model analysis. Patient reported outcome score of patients with self-reported breast edema and patients without breast edema at different time-points (n=836)**

| | Group | Baseline | | | 3 months | | | 6 months | | | 12 months | | | 18 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Between-Group Difference | | | Between-Group Difference | | | Between-Group Difference | | | Between-Group Difference | | | Between-Group Difference | |
| | | Mean[1] | MD[2] | 95% CI | Mean[1] | MD | 95% CI | Mean[1] | MD | 95% CI | Mean[1] | MD | 95% CI | Mean[1] | MD | 95% CI |
| **Breast pain** | *No edema* | 25.3 | Ref. group | | 23.0 | Ref. group | | 25.0 | Ref. group | | 20.4 | Ref. group | | 19.6 | Ref. group | |
| | *Edema* | 52.2 | 26.9* | 21.5; 32.3 | 45.2 | 22.2* | 16.0; 28.2 | 51.9 | 26.9* | 22.5; 31.4 | 51.3 | 30.9* | 25.4; 36.3 | 42.9 | 23.2* | 16.3; 30.1 |
| **QoL** | *No edema* | 71.7 | Ref. group | | 69.4 | Ref. group | | 72.4 | Ref. group | | 76.3 | Ref. group | | 76.1 | Ref. group | |
| | *Edema* | 63.6 | 8.1* | 4.2; 12.1 | 68.2 | 1.2 | -3.2; 5.7 | 65.1 | 7.3* | 4.0; 10.5 | 74.6 | 1.7 | -2.3; 5.7 | 74.4 | 1.7 | -3.5; 6.8 |
| **Physical functioning** | *No edema* | 81.2 | Ref. group | | 79.7 | Ref. group | | 80.4 | Ref. group | | 83.1 | Ref. group | | 83.0 | Ref. group | |
| | *Edema* | 78.1 | 3.1* | 0.1; 6.0 | 81.3 | 1.6 | -4.8; 1.7 | 76.1 | 4.3* | 2.0; 6.7 | 81.9 | 1.2 | -1.8; 4.0 | 83.3 | 0.3 | -4.1; 3.5 |
| **Body image** | *No edema* | 83.4 | Ref. group | | 83.7 | Ref. group | | 84.6 | Ref. group | | 87.4 | Ref. group | | 87.0 | Ref. group | |
| | *Edema* | 73.8 | 9.6* | 6.1; 13.1 | 83.9 | 0.2 | -4.2; 3.7 | 78.1 | 6.5* | 3.6; 9.4 | 85.8 | 1.6 | -2.0; 5.0 | 83.7 | 3.3 | -1.3; 8.0 |
| **Sexual functioning** | *No edema* | 19.3 | Ref. group | | 22.3 | Ref. group | | 28.8 | Ref. group | | 36.5 | Ref. group | | 30.9 | Ref. group | |
| | *Edema* | 17.1 | 2.2 | -4.1; 8.5 | 20.3 | 1.9 | -5.7; 9.6 | 27.6 | 2.5 | -4.1; 6.3 | 30.5 | 2.7 | -0.7; 12.5 | 34.8 | 4.8 | -1.5; 11.0 |

Quality of Life (QoL), Physical functioning according to EORTC QLQ-C30; Body image, Sexual functioning and Breast pain according to EORTC QLQ BR23. Scores range from 0-100. Higher scores on QoL, physical functioning and Sexual functioning indicate better functioning. Higher scores on Breast pain indicate more pain.
Between-group effects were assessed using mixed models including the measurements obtained at baseline and at 3, 6, 12 and 18 months.
A random intercept per patient was included in the model.
Abbreviations: MD; mean difference, CI; confidence interval, QoL; quality of life.
[1]Mean scores adjusted for adjusted for age, axillary lymph node dissection, tumor size, local radiotherapy boost, loco-regional radiotherapy and/or adjuvant systemic treatment, depending on the sample size.
[2]Difference in adjusted mean scores between patients with no breast edema and breast edema at baseline, 3, 6, 12 and 18 months.

# DISCUSSION

To date, this is the largest study assessing breast edema, which was done prospectively and from the patients' perspective, by using PROs to diagnose breast edema and its impact on HR-QoL and breast pain. Within the first 18 months after breast-conserving surgery and radiotherapy, 25% of patients reported breast edema at some point in time. Prevalence of breast edema varied from 6 to 12%, with the highest risk at 6 months and the lowest at 18 months after the start of radiotherapy. Patients undergoing oncoplastic surgery, axillary lymph node dissection, local radiotherapy boost, loco-regional radiotherapy, adjuvant chemotherapy and patients with a larger tumor had a higher probability of developing breast edema. The presence of breast edema was independently associated with more breast pain at all time-intervals up to 18 months, and with poorer QoL, physical functioning and body image at baseline and 6 months.



Several other studies assessed the occurrence of breast edema after BCT, and showed a wide range from 10-90%.[10] In the absence of a golden standard for diagnosing and measuring breast edema, this range may be due to heterogeneity in methods for measuring and defining breast edema (e.g. inclusion of mild edema or only more prominent forms of breast swelling). In clinical oncology practice, breast edema is often measured using physician-reported measures, such as the Common Terminology Criteria of Adverse Events (CTCAE). However, interobserver agreement for CTCTAE to diagnose breast edema is low. As a result, breast edema often remains underdiagnosed and untreated in clinical practice. Therefore, we assessed breast edema from the patient's perspective.

Like us, two studies assessed patient-reported breast edema after BCS.[10] One study included 100 patients with early-stage, low risk breast cancer who were treated with adjuvant partial breast irradiation after refusing to undergo standard whole-breast irradiation after BCS. At five years after treatment, nine women (9%) reported breast edema.[16] A comparison with our population is not possible, since patients undergoing partial breast irradiation are not included in the UMBRELLA cohort, and we did not assess outcomes 5 years after treatment. The other study included 131 patients who received BCT between 2005 and 2010, of whom 75% reported breast edema at some point in time between 0 and 60 months following

BCT.[8] This high number may be due to the cross-sectional design. Differences in prevalence of breast edema are also explained by the use of different PRO-instruments and different breast edema definitions.

We identified 6 risk factors for breast edema following BCT, i.e. oncoplastic surgery, ALND, larger tumor size, local radiotherapy boost, loco-regional radiotherapy and adjuvant chemotherapy. Larger tumor size, local radiotherapy boost and adjuvant chemotherapy were also identified as risk factors in other studies, while the association of breast edema with ALND and loco-regional radiotherapy was not found by previous studies.[10,17,18] In contrast to some previous reports, sentinel node biopsy and adjuvant endocrine therapy did not increase the risk of breast edema in our study.[10,19,20] To our knowledge, we were the first to assess modern day treatment options such as oncoplastic surgery and neoadjuvant chemotherapy with/without immunotherapy. Oncoplastic surgery led to an increased risk of breast edema at baseline only (i.e. after surgery but before the start of radiotherapy). This may be explained by a temporary impairment of lymph drainage systems during the mobilization of larger volumes of tissue when applying oncoplastic breast-conserving surgery.

Lymphedema of the arm is associated with reduced HR-QoL and impaired function of the affected arm.[21,22] Results from the AMAROS trial showed that loco-regional radiotherapy leads to significantly less symptomatic lymphedema of the arm compared to ALND (11% vs. 23% after 5 years).[23] Therefore, to reduce arm morbidity in patients with limited nodal involvement, axillary lymph node irradiation (as part of loco-regional radiotherapy) is increasingly applied instead of routine ALND.[24] Our study shows that both loco-regional radiotherapy and ALND increase the risk of breast edema. This increased risk of breast edema may be an argument for patients with limited nodal involvement to refuse additional axillary lymph node irradiation or ALND. Therefore, physicians should discuss this information with patients when outweighing oncological benefits versus potential side effects of additional axillary treatment.

An important aim of our study was to assess the association between breast edema and HR-QoL, as data are lacking. Although results of our study are not surprising, this is the first study to systematically assess breast edema in relation to HR-QoL

over time in a large sample of modern-day patients. Thus our results provide more robust and in-depth scientific proof of the association between breast edema and impaired HR-QoL, providing physicians with clinically relevant numbers to share with their patients. Adriaenssens et al. cross-sectionally assessed the influence of breast edema of QoL using the same PRO-instrument as we did (i.e. EORTC QLQ-BR23) in 131 patients undergoing BCT.[8] Their data were collected cross-sectionally hampering conclusions about the temporal occurrence relation. Similar to our findings, patients with breast edema reported significantly worse body image and no statistically significant differences in sexual functioning. Degnim et al. also assessed the impact of breast edema on QoL in a group of 124 woman following non-mastectomy breast procedures between 2006 and 2009.[9] Within a median follow up period of 11 months, they did not find statistically significant differences in QoL between patients with and without breast edema, which may best be explained by their sample size. They used a different breast cancer specific PRO-instrument (FACT-B), hampering direct comparison with our results.



In our study, breast edema occurred more often at 18 months after a local radiotherapy boost. This elevated risk is relevant to take into consideration when deciding on the radiotherapy treatment plan, and should be discussed with the patient. This may be closely linked to breast fibrosis, a process where skin and underlying tissue become less elastic, which starts to develop later in time.[25,26] In the EORTC boost versus no boost trial, severe fibrosis at 20 years after BCT with boost was 5.2% (99%CI 3.9–6.4) compared to 1.8% (99%CI 1.1–2.5) in the no boost group.[27]

This study has several limitations. We used EORTC-BR23 question 51 to identify patients with breast edema ('swelling of the breast'). As a result, part of our data may also include other factors that could be labeled by patients as breast swelling such as hematoma or seroma. This may also be an explanation for the high incidence of breast swelling at baseline (before the start of radiotherapy), as seroma and hematoma are most often seen within the days to weeks following breast-conserving surgery. Unfortunately, to date no other PRO instruments exist to identify isolated patient-reported breast edema.[28]

Oncoplastic surgery was identified as a risk factor for breast edema. Collecting data on oncoplastic surgery was challenging, since not all operative reports described in detail which closure techniques were applied. Data was conclusive in 488 of 836 patients (58%) (i.e. whether or not oncoplastic surgery was applied), identifying 92 patients who underwent oncoplastic surgery to close larger surgical defects during breast-conserving surgery. Prospective studies assessing larger groups of patients treated with oncoplastic breast-conserving surgery are required to further study its association with breast edema. We encourage surgeons to include clear descriptions of the use of oncoplastic surgery in their operative reports to enable such studies.

Another limitation is that questionnaire return rates decreased over time; 87% at baseline, 74% at 3 months, 73% at 6 months, 69% at 12 months and 71% at 18 months. This may not be an issue when non-response is random, but could be problematic in case of differential non-response (i.e. result in under- or overestimation of breast edema prevalence when only patients with – or only those without – breast edema stop returning questionnaires).

This study identified several risk factors for breast edema that could change clinical decisions when outweighing risks and benefits of applying these treatment options (e.g. oncoplastic surgery, ALND, radiotherapy boost to the tumor bed and loco-regional radiotherapy). Our study also shows that breast edema is associated with reduced health-related QoL, and especially with more breast pain (at all assessed time-intervals from baseline to 18 months). To date, there are no evidence-based treatments for breast edema, thus these findings highlight the importance to start systematically evaluating and developing targeted interventions for breast edema to reduce its impact on the lives of patients and survivors of breast cancer.

# CONCLUSION

Breast edema occurs frequently after breast-conserving therapy, and is associated with more breast pain and reduced health-related QoL. Patients undergoing oncoplastic surgery, axillary lymph node dissection, radiotherapy boost to the tumor bed, loco-regional radiotherapy, adjuvant chemotherapy and patients with

larger tumors should be informed about their higher probability of developing breast edema. Risks and benefits of applying these treatment options should carefully be outweighed during shared-decision making between patient and physician.

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# Part 2

Innovations in patient-reported outcome (PRO) utilization

# Patients' and health care providers' opinions about benefits of a supportive health app during the treatment for breast cancer

*JMIR Cancer, 2016*

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D Bruinvels
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# ABSTRACT

## Background

Health apps are increasingly being used in clinical care and may hold huge theoretical potential. However, they are often implemented in clinical care before any research has been done to confirm actual benefits for patients, physicians and researchers.

## Objectives

This study aimed to explore experiences of patients and health care providers with the use of a supportive breast cancer app during the first 6 months following diagnosis, in terms of benefits for clinical practice and research purposes.

## Methods

Between June 2013 and April 2014, breast cancer patients of all ages were invited shortly after diagnosis to use a supportive breast cancer app (i.e. OWise breast cancer), and were all followed for 6 months. Patients were asked to use the app at their own convenience. In-depth interviews were conducted regularly with patients and their medical team (i.e. physicians and nurses) to evaluate their experiences.

## Results

Fifteen patients (aged 30-63 years) participated. The medical team consisted of seven physicians and three specialized breast cancer nurses. Twelve of the 15 patients used the app to obtain information on breast cancer and treatment. Eleven patients evaluated this information as useful. All 15 patients used the app to record consultations with practitioners, and 14 found this useful. Symptom registration was used by 8 patients, and was found useful by four. Overall, 14 out of 15 patients would recommend the app to other patients. The app, in particular the recording function, was rated as useful by 9 out of 10 medical professionals, and they reported that it did not increase consultation time. These 9 professionals would recommend the app to their patients.

## Conclusions

This evaluation of a supportive health app shows positive experiences among patients and their medical team. Based on experiences in this study, patients may need to be actively encouraged to regularly register symptoms within health apps to generate sufficient patient reported app data for use in clinical practice and scientific research.

# INTRODUCTION

Health apps are increasingly being used by physicians and patients in routine clinical care.[1] Lancet Oncology predicted that by 2018 approximately 1.7 billion smartphone and tablet users will have downloaded at least one health app.[2] These apps have the potential to be of benefit to patients, physicians, nurses and researchers. The US Food and Drug Administration (FDA) has noted that health apps can help patients "in the management of their health and wellness, promote healthy living and gain access to useful information whenever and wherever they need it".[2] Apple recently introduced ResearchKit, with the aim to combine patient data from various health apps and make them accessible to medical researchers.[3] This may further promote the use of health apps for research purposes.

In the field of breast cancer research, patient-reported outcomes (PROs) are becoming increasingly important to better understand and quantify symptoms, psychosocial well-being and side effects of treatment from a patient's perspective.[4,5] Mobile health apps may prove to be useful in the collection of PROs, as many patients already use their smartphones to collect and share personal information. However, it is still unknown to what extent health apps can be used to collect reliable PROs.



The use of supportive health apps may hold huge theoretical potential, but little research has been done about actual benefits prior to implementation in clinical care.[1,6-8] This information should be available before physicians and nurses advise their patients to use an app during their treatment.

This study aimed to explore first experiences with the use of a supportive breast cancer app during diagnosis and treatment, with the aim to better understand potential benefits in clinical practice. In addition, we aimed to evaluate to which extent self-reported app data could be used for research purposes. The aim was to evaluate the app on three levels, i.e. patient experience and satisfaction, physicians' and nurses' opinions, and scientific potential.

# METHODS

Between June 2013 and August 2013 (and between March 2014 and April 2014), breast cancer patients consecutively visiting the Department of Surgery of the University Medical Center Utrecht in the Netherlands were invited to use a supportive breast cancer app. All patients were invited to participate, with the exception of patients who were unable to read and understand the Dutch language, patients under the age of 18 years and patients who were considered too emotional to receive study information at the time of recruitment.

Shortly after diagnosis, the study was first introduced by a nurse (practitioner), and patients received written study information to read at home. If the patient was interested in participating, a meeting with the researcher was scheduled 1-3 days later for the informed consent procedure.

Patients were recruited within the first week after breast cancer diagnosis, which allowed them to start using the app prior to deciding on a final treatment plan. Each patient was followed for 6 months to evaluate their experiences with the app shortly after diagnosis but also during treatment and after treatment was initiated. Patients were asked to use their own mobile devices. However, if they were interested in participating but did not have a smartphone or tablet, the researcher offered an iPad, which they could borrow during study participation.

Out of the few available Dutch supportive breast cancer apps, we chose to evaluate the OWise breast cancer® app, version 1.0. This app was developed in 2013 by Px Healthcare, The Netherlands. We chose this app because it can be downloaded and used free of charge for iOS and Android platforms and includes the following functionalities[9]:

1. Patient repository for information (e.g. audio-recorded consultations, and imaging)
2. Physical and psychological symptom registration (i.e. pain, fatigue, mental mood, etc.)
3. Timeline of treatment trajectory and appointments
4. Personalized information about breast cancer and treatment according to Dutch breast cancer guidelines, tailored to tumor characteristics, age, and menopausal status

A researcher briefly demonstrated these functions, after which patients were invited to use the app at their own convenience. There was no minimum amount of time to be spent using the app. This approach was chosen to understand which parts of the app patients would use based on their own needs.

In-depth interviews were conducted using a pre-defined semi-structured interview guide *(appendix 1).* This interview guide was developed by our team of breast cancer physicians, specialized breast cancer nurses and clinical epidemiologists, and it was based on questions that were considered relevant from a clinical point-of-view. All interviews were conducted by one researcher (DYA) from the breast cancer research team of the University Medical Center Utrecht, who was not involved in the clinical care of the participants. Interviews with patients were conducted every two weeks in the first 3 months and monthly in the last 3 months, either face-to-face or by phone. Nurses and physicians were interviewed once shortly after they were first exposed to the app, and two times approximately 1 and 3 months after patients had used the app in their presence several times.



The interview guide was also designed to assess which app functions patients found most useful and for what reason. Questions for the medical team were designed to probe their opinions about the influence of the app on disease related knowledge and disease related behavior of patients during patients' visits. In addition, medical professionals' attitudes towards being recorded with the app were explored. The researcher interviewed each patient, physician and nurse separately at all times. After each interview a summary was transcribed and added to the participants' study file. Descriptive statistics were calculated using SPSS software (version 22) to summarize the data.

This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and was conducted according to the principles expressed in the Declaration of Helsinki. All patients gave written informed consent to participate in this study.

# RESULTS

## Overview

During the recruitment period, 40 patients visited our medical center consecutively, of which 21 (53%) were not approached for participation because the nurse felt the setting was inappropriate for discussing studies (e.g. too emotional) or because the patients were not interested in participating in any kind of research. A total of 19 patients received study information, after which 4 (21%) declined study participation. One patient declined because she would be treated in another hospital, two patients felt the interviews would take up too much time, and one patient was not interested in using the app.

## Patients' experiences

A total of 15 breast cancer patients with a median age of 51 years participated in this study. The youngest patient was 30 years of age, while the oldest patient was 63 years of age. On average, each patient was interviewed 8 times. Prior to entering the study, ten patients had frequently used apps on their mobile devices, while five were relatively inexperienced with the use of apps.

At baseline, patients were asked why they decided to participate in this study. The main reasons for participation were 1. an interest in this particular health app, 2. the hope of gaining benefit from using the app, 3. an interest in apps in general, and 4. an interest in participating in research to help future patients.

Three patients expressed more specific reasons:
One patient had received treatment for contralateral breast cancer in the past and was particularly interested in recording conversations with her medical team. During her previous treatment, she found it difficult to remember all the information provided by the various different physicians. Another patient had recently lost her husband to cancer and found it difficult – due to her current emotional mental state – to process and remember new information. She hoped that by having her treatment-related information and audio recordings all in one place, she would be more in control. The third patient was a full-time non-medical researcher and found it interesting to be on the other end of a study for a change. Prior to entering the study, 10 patients out of 15 (67%) had frequently used apps

on their mobile devices, while 5 (33%) were relatively inexperienced with the use of apps.

Personalized information on breast cancer and treatment as provided by the app was used by 12 out of 15 patients (80%). Out of the 12 patients who used this information, 11 patients (92%) found it useful (Table 1). All patients (n=15) used the audio recording function to record consultations with their nurses and physicians, and 14 (93%) of them found this to be useful. Overall, 14 out of 15 patients (93%) would recommend the app to other patients.

**Table 1. Patients' and health care providers' experiences with specific app functions**

| **Patients** | |
|---|---|
| **Age (jn years)** | |
| • 30-39 | 3 |
| • 40-49 | 2 |
| • 50-59 | 8 |
| • 60-65 | 2 |
| **Used information from the app** | 12/15 (80%) |
| • Found it useful | 11/12 (92%) |
| **Used audio recording function** | 15/15 (100%) |
| • Found it useful | 14/15 (93%) |
| **Used symptom registration function** | 8/15 (53%) |
| • Found it useful | 4/8 (50%) |
| **Would recommend app to other patients** | 14/15 (93%) |
| **Physicians and nurses** | |
| **Found it useful for patients to record consultation** | 9/10 (90%) |
| **Thought patients appeared to be better informed** | 2/10 (20%) |
| **Would recommend this app to their patients** | 9/10 (90%) |

The patient who would not recommend the app to others, reported that it did not add much to the information as provided by the medical team and on the Internet. She did not feel comfortable recording medical consultations and registering symptoms. Table 2 presents quotations regarding specific app functions as provided by patients.

**Table 2. Quotes from patients regarding specific app functions**

| App functions | Supportive quotations (n=14) | Non-supportive quotations (n=1) |
|---|---|---|
| **Information about breast cancer and treatment** (based on Dutch guidelines) | "A very useful overview of information, with links to all relevant websites in one place. I thought that was really helpful". | "To me the information in the app does not add much to the information that I can find on the internet or as provided by my doctors". |
| **Patient repository for information** (e.g. audio recorded consultations) | "I shared the audio with my parents who could not be present at the consult. It was comforting to know that they heard the information first hand from the surgeon instead of my own interpretation. At the same time, I heard important things during playback that I had missed during the initial consultation".<br><br>"I forgot important things the doctor said and it felt comforting to know that I could listen to the conversation again. From that moment on I recorded every consult".<br><br>"I regretted not recording several important consultations, because the ones I did record I listened to several times". | "I can imagine it being helpful to some patients, but I personally do not need to listen to a consult again. I would feel uncomfortable having to ask every doctor if it's okay to record the conversation". |
| **Symptom and feeling registration** | "I used the symptom registration function on a daily basis during the first month until 2 weeks after the surgery. It helped me a lot to see the graphical overview of my symptoms on a weekly basis. I stopped using it when I started to feel better and my symptoms did not fluctuate anymore''.<br><br>"The app gave me a familiar feeling in a difficult time of continuously changing faces and feelings, and registering my emotions in the app helped me to express feelings that I would have otherwise kept to myself". | "I'm a very grounded person. Breast cancer happened to me, but I do not want to think about it daily. I've never kept a diary in my life, so I have no desire to start one now". |
| **Timeline** | "In the timeline I registered all my appointments. Keeping an overview of ongoing treatments was very difficult with so many different doctors and appointments, but the app helped me to keep that overview, which made me feel in control". | "I already have a calendar for all my other personal appointments, so I do not need an app for this. I do not feel the need to separate personal appointments from hospital appointments. I'll just deal with it all at the same time". |

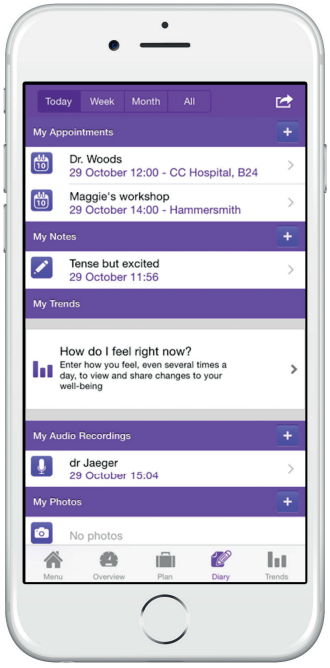



**Figure 1. Screenshot of the OWise app (day overview).**

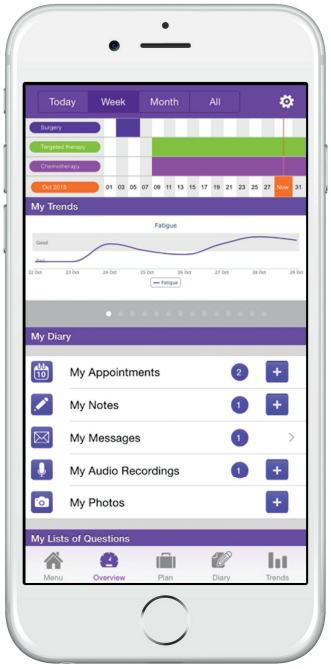



**Figure 2. Screenshot of the OWise app (week overview).**



## Physicians' and nurses' experiences

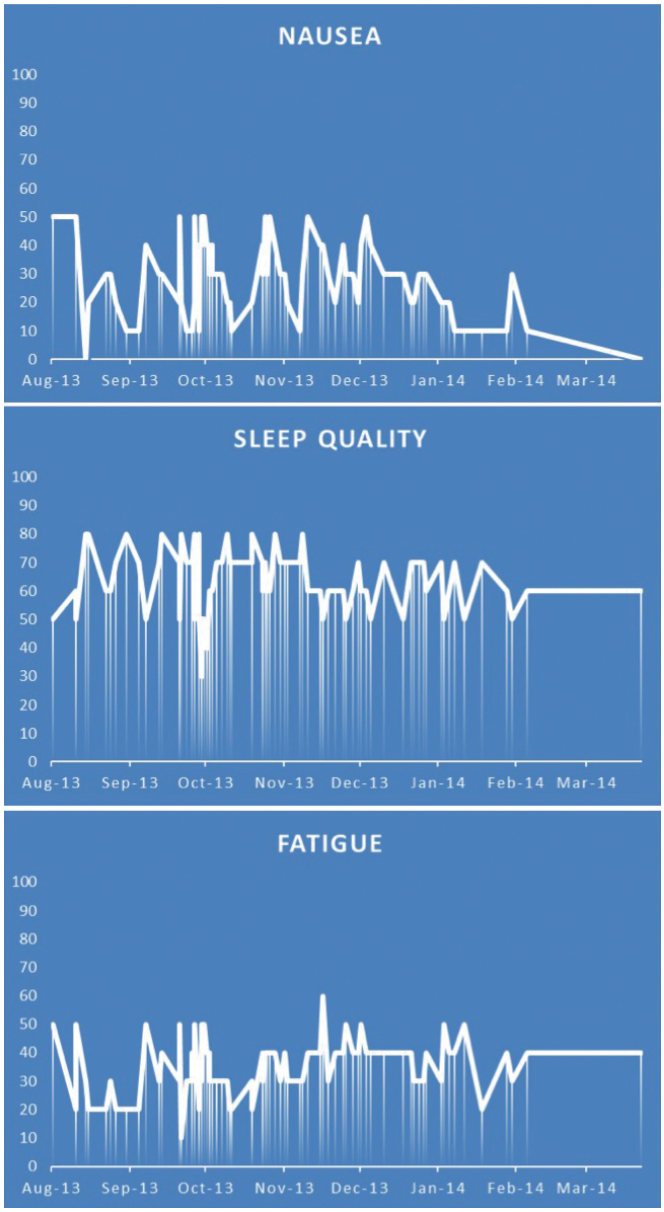
The medical breast cancer team consisted of two breast surgeons, a medical oncologist, a radiation oncologist, a plastic surgeon, a gynecologist, a clinical geneticist and three specialized breast cancer nurses. All ten team members were recorded by patients at least once, and they all reported that being recorded did not influence consultation time. Two physicians indicated that they chose their wording more carefully. These two physicians indicated that they felt uncomfortable while being recorded at first, but also that they got used to it over time. The audio recording function was rated as useful by nine health care professionals. Two physicians had the impression that patients were better informed as a result of using the app. Overall, nine out of ten medical professionals (90%) would recommend the app to their patients. The one physician who would not recommend the app to patients, believed the app did not add to the care and information as already provided by physicians and nurses (Figure 3).

**Figure 3.Quotes from health care providers about the app in clinical practice.**


## Scientific potential of patient reported app data

Eight out of 15 patients used the symptom registration function at least once during the first month after diagnosis. One patient used this function daily (923 data entries), four patients weekly (121-355 data entries), and three patients monthly (10-30 data entries). Seven patients never used this function. Four of the 8 patients (50%) who used this function found it useful. An example of symptoms registered by one patient is presented in Figure 4. This patient received neo-adjuvant chemotherapy during the first three months of her treatment.

**Figure 4.Example of a graphical overview of patient-reported outcomes as obtained from the OWise app's symptom registration function.**




The levels of nausea, sleep quality, and fatigue range from minimum (0) to maximum (100). A vertical line corresponds with the input of data by the patient. This patient received chemotherapy between August 2013 and December 2013. This data was provided by Px HealthCare with written permission from the patient.

# DISCUSSION

This study of a breast cancer support app shows positive experiences among patients and their medical team. The app functions patients found most useful were the option to record audio from consultations with their medical team, and the personalized information about disease and treatment. Physicians and nurses found the recording function most useful and would recommend the app to their patients.

Patients were asked to use the app at their own convenience, which made it possible to assess which functions of the app they wanted to use. This was based on their own needs in routine clinical practice. In this group of patients, the use of a symptom registration function varied from never to several times a day. With limited data entries in this small study group, we did not further explore the PROs that were generated from the app. We suggest that patients may need to be actively encouraged to regularly register their symptoms in the app. If this is done between hospital visits, results could then be shared during visits with their physicians and/or nurses. The medical team could then address symptoms that may have been left unnoticed otherwise, while researchers could evaluate these PROs in clinical studies when patients consent to the use of their data for research purposes.

The app in this study stores all audio recordings on the mobile device, but – in contrast to the standard recording function on mobile devices – only allows for playback within the app without the option to edit or share the file with others. As a result, audio files are not stored on external servers or in internet clouds, which serves as protection for patient data, but also protects the recorded physician/nurse against uncontrolled sharing and editing of their words.[10] This feature was appreciated by several members of our medical team and increased their willingness to be recorded. We recommend using apps that incorporate these kinds of conditions and restrictions, to allow audio recording in the consulting room with protection of all parties involved in the recording process.

In this study, we chose to collect data by frequent in-depth interviews in order to obtain a complete first impression on the aspects of the app that patients and the

medical team (dis)liked or found useful. The implication of this approach was that we could only include a small number of patients, which may limit generalizability of the results. The strengths of this study were that we included patients of all ages, with or without an interest in apps, but also included a multidisciplinary medical team, which allowed for an in-depth evaluation of the needs of a relatively wide range of patients and medical professionals.

## CONCLUSIONS

This qualitative evaluation of a supportive breast cancer app shows benefits for patients and their medical team, especially because of the option to make audio recordings of consultations and the availability of relevant information in the app. However, in this study group, the use of the feature to register symptoms varied between patients. We recommend that future studies aiming to use patient-reported app data for scientific research, encourage patients to regularly register their symptoms within these apps to generate sufficient data.



## ACKNOWLEDGEMENTS

The authors would like to thank Px HealthCare for providing 3 iPads on loan to 3 patients, who did not own a smartphone or tablet themselves, for use during this study and for providing study participants' data of PROs.

## CONFLICT OF INTEREST

David Bruinvels is medical director at Px HealthCare, the company that created and owns the OWise breast cancer app. He is currently not employed by Px Healthcare and is a minor share holder of Px Healthcare. The first and last author vouch for the integrity of this manuscript.

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# APPENDIX 1

## Semi-structured interview guide

**Appendix 1: Semi-structured interview guide**

All questions are used as guidance during interviews with patients. Questions are used to trigger response and follow-up questions are conceived spontaneously. After each answer follow-up questions are asked to understand why something was used/helpful, and why not.

**Questions for patients:**

- How often did you use the OWise app in the past 2 weeks/month? How often since the start of the study?
- Did you use the app to prepare for conversations with your doctors and nurses? Did you use information from the app?
- Did you record any conversations with your doctors or nurses? If so, have you listened to those recorded conversations again?
- Did you register symptoms/mood within the app?
- What is your overall opinion about the app? Does using the app help you in any way during this time of your life/treatment?
- Do you think the app is helpful when preparing for conversations with your doctors?
- Would you recommend the app to other patients?

**Question for doctors and nurses:**

- Do you think the app has an effect on your conversations with patients? Do you, or do they, behave differently?
- Do patients appear to be better informed?
- Do patients use the recording function during conversations with you? How did you feel about being recorded? Did you behave differently?
- Would you recommend this app to your patients?

# 7

# Quality of life and patient satisfaction after one-stage implant-based breast reconstruction with an acellular dermal matrix versus two-stage breast reconstruction (BRIOS): primary outcome of a randomised controlled trial

*Lancet Oncology, 2018*

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# ABSTRACT

## Background

There is increasing interest in the use of acellular dermal matrices (ADM) in implant-based breast reconstruction (IBBR). Suggested advantages are that ADMs facilitate one-stage IBBR and improve aesthetic outcomes. We compared immediate one-stage ADM-assisted IBBR with two-stage IBBR (current standard of care). Our previously reported secondary endpoint showed that one-stage ADM-assisted IBBR was associated with significantly more adverse outcomes. Here, we present the primary endpoint results aiming to assess whether one- stage IBBR with ADM provides higher patient-reported quality of life (QOL) compared with two-stage IBBR.

## Methods

This multicentre, open-label, randomised controlled trial (BRIOS study) was done in eight hospitals in the Netherlands. We recruited women aged older than 18 years with breast carcinoma or a genetic predisposition who intended to undergo skin-sparing mastectomy and immediate IBBR. Participants were randomly assigned to undergo one-stage IBBR with ADM (Strattice, LifeCell, Branchburg, NJ, USA) or two-stage IBBR. Randomisation was stratified per centre and indication for surgery (oncological or prophylactic) in blocks of ten participants. The primary endpoint was patient-reported QOL, as measured with the BREAST-Q (ie, health-related QOL scales and satisfaction scales), in the modified intention-to-treat population. The study follow-up is complete. This study is registered with the Netherlands Trial Register, number NTR5446.

## Findings

Between April 14, 2013, and May 29, 2015, we enrolled 142 women, of whom 60 were randomly assigned to receive one-stage ADM-assisted IBBR and 61 to receive two-stage IBBR. Of these, 48 women (17·0 months [SD 7·8]) in the one-stage group and 44 women (mean follow-up 17·2 months [SD 6·7] in the two-stage group completed the BREAST-Q at least 1 year after implant placement. We found no significant differences in patient-reported QOL domains, including physical wellbeing (one-stage 78·0 [14·1] vs two-stage 79·3 [12·2], p=0·60), psychosocial wellbeing (72·6 [17·3] vs 72·8 [19·6], p=0·95), and sexual wellbeing (58·0 [17·0] vs 57·1 [19·5], p=0·82), or in the patient- reported satisfaction domains: satisfaction with breasts (63·4 [15·8] vs 60·3 [15·4], p=0·35) and satisfaction with outcome (72·8 [19·1] vs 67·8 [16·3], p=0·19).

## Interpretation

Taken together with our previously published findings, one-stage IBBR with ADM does not yields superior results in terms of patient-reported QOL compared with two-stage IBBR. Risks for adverse outcomes were significantly higher in the one-stage ADM group. Use of ADM for one-stage IBBM should be considered on a case-by- case basis.

# INTRODUCTION

Worldwide, over a decade experience has been acquired with the use of acellular dermal matrices (ADM) in implant-based breast reconstruction (IBBR). However, the debate on the potential benefit of their use is still ongoing. Initially, the use of ADM was propagated mainly because it might facilitate one-stage IBBR. The ADM is used to augment the subpectoral pocket, allowing for direct placement of a larger-volume implant. Improvement of aesthetic results was suggested as an important additional advantage, due to a better definition of the inframammary fold (IMF), improved lower pole projection, and more coverage of the implant. Later on, it was suggested that ADM may also reduce the risk of capsular contracture.[1-3]

To date, data regarding these potential benefits are inconclusive.[2,4] Current evidence is limited, as most studies are of low quality with a high risk of selection bias.[1] Concerning the safety of ADM-assisted IBBR, reported outcomes vary widely, with complication rates ranging from 4 up to 50 percent.[1,5] Furthermore, there is limited data regarding patient satisfaction after ADM-assisted breast reconstruction. In addition, diverse patient-reported outcome measures (PROMs) are being used, varying from self-designed surveys to validated questionnaires.[1] With a general shift in healthcare towards patient-centeredness, patient-reported outcomes (PROs) have gained importance to assess health outcomes from the patients' perspective.[6] The BREAST-Q was developed to assess health-related quality of life (QoL) and patient satisfaction after breast surgery. It was introduced in 2009 and has been widely used to evaluate PROs after breast reconstruction, and it has been shown that BREAST-Q is able to detect small clinically meaningful differences between individual patients and groups.[7, 8]

The Breast Reconstruction In One Stage (BRIOS) study was initiated in 2012 to compare QoL after ADM-assisted IBBR with the outcomes after conventional two-stage expander/implant breast reconstruction. The BRIOS study was an open-label, phase IV, multicentre, randomised controlled trial conducted in the Netherlands. We hypothesized that patient-reported QoL and aesthetic satisfaction, as measured by the BREAST-Q, would be higher after ADM-assisted IBBR, due to improved aesthetic outcomes and a lower treatment burden.

Furthermore, we hypothesized that safety outcomes would be similar for the two procedures. In May 2015, the Dutch Health Care Inspectorate requested we performed a preliminary safety analysis due to concerns about safety of ADM use in IBBR.[9] We found that ADM-assisted IBBR was associated with significantly more adverse outcomes, which was a secondary outcome of this study. These early safety outcomes were reported previously.[9,10] In the present article, we report on patient-reported QoL (i.e., health-related QoL and Satisfaction), which was the primary endpoint of the BRIOS study, and physician-reported aesthetic outcome.

# METHODS

## Study design and participants

The Breast Reconstruction In One Stage (BRIOS) study was a prospective, multicentre randomised controlled trial. The objective of the study was to compare outcomes of one-stage implant-based breast reconstruction combined with ADM (Strattice, LifeCell, Branchburg, NJ, USA) (one-stage IBBR with ADM) with outcomes of conventional two-stage tissue expander/implant BR (two-stage IBBR). The primary endpoint of the BRIOS study was QoL assessed with the BREAST-Q at one year after placement of the definitive implant. For this study, quality of life as measured with BREAST-Q consisted of relevant scales from the health-related QoL domain (i.e., Physical Well-Being, Psychosocial Well-Being and Sexual Well-Being) and Satisfaction domain (i.e., Satisfaction with Breasts and Satisfaction with Outcome). In total, 8 hospitals in the Netherlands participated (VUMC, MUMC, UMCG, EMC, HAGA, AM, OMC and MMC), which were selected on the basis of having surgical experience with two-stage IBBR. The protocol was approved by the institutional review board at each study centre. All patients provided written informed consent. This study is registered at the Netherlands Trial Register, number NTR5446. The BRIOS study was performed in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice and the CONSORT statement.[11] The full study design, methodology, inclusion/exclusion criteria and surgical techniques were previously described.[9]

## Randomisation and masking

Patients were eligible to participate if they had confirmed breast cancer or a genetic predisposition (i.e., a BRCA1 or BRCA2 gene mutation), were aged 18 years or older and intended to undergo a skin-sparing mastectomy followed by IBBR. The randomisation schedule was generated with an online randomisation system (ALEA version 2.2) by the coordinating researcher (REGD), and was stratified by study centre and type of indication for surgery (i.e., oncological or prophylactic). Patients were randomised in fixed blocks of ten to achieve roughly balanced groups. The study was open label, and surgeons and patients were informed about the allocated treatment at least 3 days before surgery.

## Procedures

All patients underwent skin-sparing mastectomy, followed by either an immediate one-stage IBBR, in which a definite implant was placed in combination with a Strattice ADM (LifeCell, Branchburg, NJ, USA), or a two-stage IBBR, which involved immediate total submuscular placement of a tissue expander which was later exchanged for a definite implant.[9]



Patients who provided informed consent and participated in the study were invited by email or regular mail to complete the questionnaires (BREAST-Q and EQ-5D) before the initial surgery and one year after placement of the definite implant. The BREAST-Q is a validated questionnaire to evaluate patient-reported health-related QoL and satisfaction after breast reconstruction.[7] The BREAST-Q reconstruction module contains 14 independent scales representing both health-related QoL domains and Satisfaction domains. Domains pertaining to health-related QoL are: Psychosocial well-being, Sexual well-being and Physical well-being: chest and upper body. Satisfaction domains are Satisfaction with Breasts, visibility of the implant and feeling of rippling, Satisfaction with Outcome, Satisfaction with Nipples, Satisfaction with Care regarding information, surgeon, the medical team and office staff. For the primary outcome, we selected the 5 most relevant BREAST-Q scales to measure QoL related to the surgical outcome (i.e., Psychosocial well-being, Sexual well-being and Physical well-being: chest and upper body, Satisfaction with Breasts and Satisfaction with Outcome).

The EQ-5D and patient burden are used to assess the cost-effectiveness of both methods and will be published separately. After implementation of the protocol direct post-operative pain measurement proved not feasible, and it was decided for logistic reasons, to measure pain using the BREAST-Q Physical Well-being scale only. Specifically question 'O' of the BREAST-Q Physical Well-Being scale was used, assessing 'Aching feeling in your breast area?' on a 5-point scale, ranging from 1. None of the time, a little, some, most to 5. All of the time. In addition, demographic data were recorded.

Physician-reported aesthetic outcome was assessed from photographs using the Aesthetic Items Scale.[12] This is a standardized method, first described by Visser et al. and Brinkman et al.[13,14] Five standardized photographs (frontal, oblique and lateral) were made before and at one year after placement of the breast implant. The photos were evaluated independently by 5 experienced plastic surgeons. All photographs were compiled into a powerpoint presentation. They were shown in random order without giving any additional information (e.g., on pre-or postoperative status, reconstruction method used, or whether any complications had occurred or secondary revisions had been performed). To minimize bias, blank slides were shown between photographs and the random order of the photographs was different for each observer. The observers rated the aesthetic outcome on 5 items with a 5 point Likert-scale.[12] Surgeons were also asked to give an overall rating on a scale from 0 to 10 (for both breasts and for each breast separately). Twenty random photographs were shown twice to determine the intra-observer agreement.[9]

Additional procedures in patients with a two-stage reconstruction during their second operation were noted (i.e. secondary revision surgeries), consisting of scarification of the capsule, capsulotomy/capsulectomy, lipofilling, symmetrisation reduction mammoplasty/ augmentation, or a combination. Furthermore, all additional surgeries besides the initial surgery according to the protocol were scored. The procedures were divided into improvement of redundant tissue (dogear correction and scar revision), layer thickness (lipofilling), (position of) the implant (lowering of the IMF, new implant, contralateral symmetrisation reduction mammoplasty/ augmentation), contralateral preventive mastectomy or a combination.

## Outcomes

The primary outcome of the study was patient-reported QoL, measured with the BREAST-Q at one year after placement of the definite implant.[8] Secondary outcomes were the incidence of perioperative and postoperative complications (safety), physician-reported aesthetic outcomes (assessed by a panel of independent plastic surgeons, based on standardised photographs taken one year after surgery), pain, general quality of life (EQ-5D) and burden on the patients in terms of number of procedures and time invested. In this article we report on the primary outcome and the physician-reported aesthetic outcomes. Safety outcomes have been published previously.[9,10]

## Statistical analysis

The main hypothesis was that patients in the one-stage group compared with the two-stage group would report a higher quality of life at one year after placement of the definite prosthesis. Calculation of the sample size was based on the expected "Satisfaction with Breast" score assessed with BREAST-Q in the two-stage IBBR group. We expected a mean score of 60 points (SD 20) in the two-stage IBBR group and took a difference of 10 points between groups to be clinically relevant.[15] We estimated that a group size of 65 women in each group would provide 80% power to detect at least a 10-point difference with Student's *t* test ($\alpha$=0·05). Anticipating a dropout rate of 8%, we therefore aimed to enrol 70 women per group.

Data were analysed according to the treatment they were intended to receive (i.e., intention to treat analysis), regardless of which treatment they actually received. Descriptive statistics were used for demographic data and clinical outcomes. Differences between the groups were assessed for all BREAST-Q scales using Student's t-tests for continuous variables and chi-square tests for categorical variables. Linear regression analyses were used to assess differences between the two groups for all BREAST-Q scales. Analyses were corrected for the stratification variables (indication of surgery and centre of treatment).[16,17] An additional exploratory analysis was performed to correct for implant removal, due to the unexpected, high difference in implant removal rate between the groups. Differences in postoperative pain were assessed using a Fisher exact test for outcomes of the BREAST-Q Physical Well-Being scale, question 'O. Aching feeling in your breast area?'.

Regarding physician-reported aesthetic outcomes, average scores of the five observers were calculated and differences in aesthetic outcomes between the groups were analysed using linear regression analysis in which also the influence of the preoperative scores, implant removal and secondary revision surgery were assessed. Inter- and intra-observer agreement among the five surgeons were determined by calculation the intraclass correlation coefficients (ICCs). An ICC of >0.7 was considered to indicate a good reliability agreement.

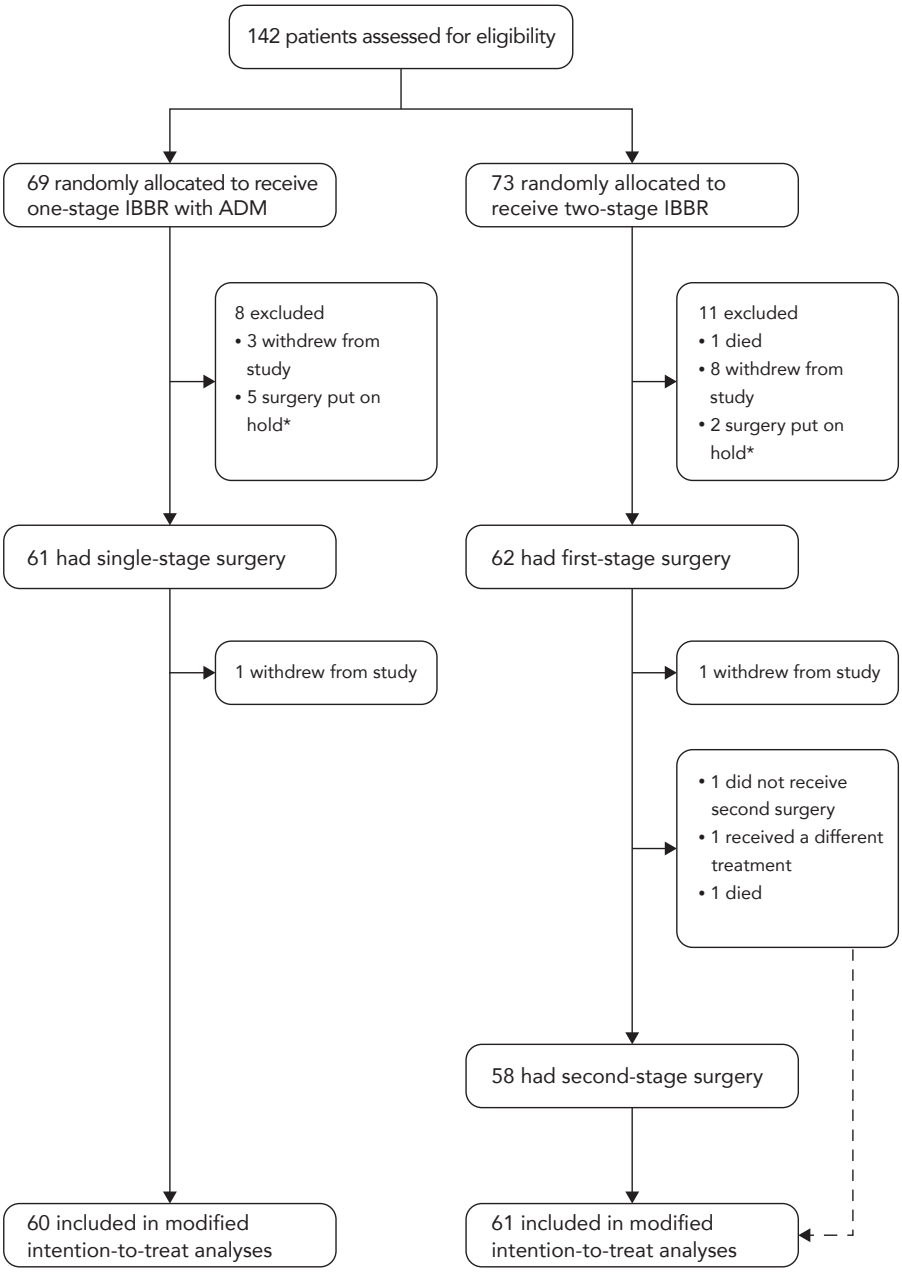
To explore correlations between the patient-reported "Satisfaction with Breasts" (BQ1) and the overall aesthetic outcome as scored by the plastic surgeons, the Pearson correlation coefficient was calculated. These analyses were not prespecified in the protocol. Statistical analyses were performed using SPSS (version 22) and STATA (/SE 14.1).

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

# RESULTS

Participants were recruited between April 14, 2013, and May 29, 2015. In total 142 eligible patients were randomly allocated to receive one-stage IBBR with ADM (n=69, 49%) and to receive two-stage IBBR (n=73, 51%) (Figure 1). In May 2015, the Dutch Health Care Inspectorate requested a preliminary safety analysis due to concerns about safety of the ADM.[9] The local ethics committee decided to suspend surgery for the patients who had not yet been operated. As a result, 7 (5%) patients were not operated due to preliminary study suspension. An additional 14 (10%) patients were not operated prior to study suspension due to refusal of further study participation (n=13, 9%) and due to death from disease as a result of severe progression of breast carcinoma including metastases (n=1, 1%).

**Figure 1. Trial profile**




IBBR = implant-based breast reconstruction. ADM = acellular dermal matrix. * The ethics committee put surgery on hold for these patients.

In total, 60 (42%) patients (92 reconstructions) were included in the one-stage IBBR group and 61 (43%) patients (91 reconstructions) in the two-stage group. Only one patient received two-stage IBBR instead of the allocated one-stage IBBR. This patient withdrew from study follow-up after the second surgery. The mean follow-up after placement of the One-stage IBBR was performed in 61 (43%) of 142 patients and two-stage IBBR in 63 (44%) patients. In both groups, one patient refused further participation, one patient went on to other treatment (two-stage) and one patient died due to metastatic breast cancer after receiving the first surgery (two-stage). In total, 60 (42%) patients (92 reconstructions) were included in the one-stage IBBR group and 61 (43%) patients (91 reconstructions) in the two-stage group. Only one patient received two-stage IBBR instead of the allocated one-stage IBBR. This patient withdrew from study follow-up after the second surgery. The mean follow-up after placement of the definite implant at time of completing the BREAST-Q was 17·0 ± 7·8 months in the one-stage group and 17·2 ± 6·7 in the two-stage group.

Baseline demographic characteristics after randomisation were similar in both groups (Table 1). For example, the mean age was 43·5 ± 11·6 and 47·4 ± 12·2 years, the treatment was prophylactic in 21 (35%) of 60 and 33 (37%) of 61 patients, and 32 (53%) and 30 (49%) of patients underwent bilateral reconstruction in the one-stage group and two-stage group respectively. Mainly skin-sparing mastectomies were performed and in a quarter of the procedures an incision was made at the inframammary fold. Adjuvant chemo- and radiotherapy were administered in 15 (25%) and 6 (10%) of 60 patients in the one-stage group and 18 (29%) and 9 (15%) of 61 patients in the two-stage group (Table 1).

Surgical complications and reoperations were extensively reported previously.[9] Implant removal occurred more frequently in the one-stage group (29%, n=17 patients; n=24 reconstructions) compared with the two-stage group (7%, n=4 patients; 4 reconstructions) (Table 2). The majority of patients in the one-stage group who had their implants removed (n=17; 24 reconstructions) subsequently underwent two-stage expander/implant reconstruction (n=13). In the two-stage group, patients who had their tissue expander removed underwent secondary reconstruction with a new expander (n=1), implant (n=1) or autologous flap (n=2) (Table 2). During the exchange of the tissue expander to the definite

implant, the following additional procedures were performed: Scarification of the capsule (2%, n=1), capsulo/capsulectomy (16%, n=10), lipofilling (8%, n=5), contralateral symmetrisation reduction mammoplasty/augmentation (15%, n=9), or a combination (7%, n=4). In the patient who was randomised to the one-stage group, but who received the two-stage reconstruction, scarification of the capsule and a capsulotomy was performed. Additional secondary revision surgeries were performed in 20·0% (n=12) of the patients in the one-stage group and 26% (n=16 patients) in the two-stage group. Improvement of redundant tissue was performed in 1% (n=1) of the patients in the one-stage group compared to 5% (n=3) in the two-stage group, improvement of layer thickness in 7% (n=4 one-stage) versus 2% (n=1 two-stage) and of the implant in 3% (n=2) in the one-stage compared to 12% (n=7) in the two-stage group. A combination was performed in 4 (7%, 7%) patients in both groups. A contralateral preventive mastectomy was performed in 1 (2%, 2%) patient in each group.

The pre-operative and post-operative BREAST-Q were completed by respectively 31 (52%) and 48 (80%) of 60 patients in the one-stage IBBR and 32 (52%) and 44 (72%) of 61 patients in the two-stage IBBR (Figure 1). The preoperative "Satisfaction with Breasts" was 75·8 ± 17·5 in the one-stage group and 70·9 ± 19·5 in the two-stage group. The postoperative "Satisfaction with Breasts" was respectively 63·4 ± 15·8 and 60·3 ± 15·4 (Table 4). There were no statistically significant differences in scores between the groups (Table 5). Also, none of the other BREAST-Q scales (i.e., "Satisfaction with Outcome", "Psychosocial well-being", "Sexual well-being" and "Physical well-being chest and upper body") showed differences between the two groups (Table 5). A secondary exploratory analysis where we adjusted for implant removal also did not result in statistically significant differences in BREAST-Q outcomes between the two groups.

Post-operative pain as reported within the BREAST-Q Physical Well-Being scale, question 'O. Aching feeling in your breast area?', did not differ between both groups (p=0.374).

**Table 1. Patient characteristics**

| | One-stage ADM-assisted IBBR (n=60; 92 reconstructions) | Two-stage IBBR (n=61; 91 reconstructions) |
|---|---|---|
| **Age (years)** | 43·5 ± 11·6 | 47·4 ± 12·2 |
| **Prophylactic mastectomy** | 35·0% (n=21) | 37·7% (n=33) |
| **Therapeutical mastectomy** | 65·0% (n=39) | 62·3% (n=38) |
| **Unilateral reconstruction** | | |
| Right | 25% (n=15) | 19·7% (n=12) |
| Left | 21·7% (n=13) | 31·1% (n=19) |
| **Bilateral reconstruction** | 53·3% (n=32) | 49·2% (n=30) |
| **Axillary lymph node dissection** | | |
| Right | 2·2% (n=2) | 1·1% (n=1) |
| Left | 4·3% (n=4) | 2·2% (n=2) |
| **Nipple-sparing mastectomy** | | |
| Right | 19·6% (n=18) | 15·4% (n=14) |
| Left | 18·5% (n=17) | 20·9% (n=19) |
| **Skin-sparing mastectomy** | | |
| Right | 31·5% (n=29) | 30·8% (n=28) |
| Left | 30·4% (n=28) | 33·0% (n=30) |
| **Incision** | | |
| IMF | | |
| Right | 12·0% (n=11) | 11·0% (n=10) |
| Left | 10·9% (n=10) | 15·4% (n=14) |
| No vertical component | | |
| Right | 30·4% (n=28) | 31·9% (n=29) |
| Left | 30·4% (n=28) | 30·8% (n=28) |
| Vertical/diagonal | | |
| Right | 7·6% (n=7) | 2·2% (n=2) |
| Left | 7·6% (n=7) | 6·6% (n=6) |
| Wise pattern | | |
| Right | 1·0% (n=1) | 1·1% (n=1) |
| Left | 0% (n=0) | 1·1% (n=1) |
| **Mastectomy weight (gram)** | | |
| Right | 384·3 ± 151·1 | 376·8 ± 149·8 |
| Left | 362·5 ± 132·5 | 357·0 ± 128·4 |
| **Implant volume (mL)** | | |
| Right | 384·7 ± 105·3 | 426·9 ± 127·2 |
| Left | 394·6 ± 95·5 | 406·4 ± 115·1 |
| **Adjuvant chemotherapy** | 25·0% (n=15) | 29·5% (n=18) |
| **Adjuvant radiotherapy*** | | |
| Right | 5·0% (n=3) | 4·9% (n=3) |
| Left | 5·0% (n=3) | 9·8% (n=6) |
| **Follow-up (months) at time of BREAST-Q** | 17·0 ± 7·8 (n=48) | 17·2 ± 6·7 (n=44) |

* For the primary outcome of the study, all breasts are taken into account for the evaluation of radiotherapy

Reported values are mean ± SD

**Table 2. Removal of implants and reoperations (per protocol population*)**

| | One-stage ADM-assisted IBBR group (n=59) | Two-stage IBBR group (n=62) |
|---|---|---|
| **Removal** | | |
| Any | 17 (29%) | 4 (7%) |
| Tissue expander | .. | 3 (5%) |
| Implant | 6 (10%) | 1 (2%) |
| ADM | 1 (2%) | .. |
| ADM and implant | 10 (17%) | .. |
| **Secondary reconstruction method after implant removal** | | |
| No reconstruction | 2 (3%) | 0 |
| New expander | .. | 1 (2%) |
| New implant | 0 | 1 (2%) |
| Expander or implant | 9 (15%) | 0 |
| Combined autologous and implant reconstruction | 1 (2%) | 0 |
| Autologous reconstruction | 4 (7%) | 2 (3%) |

* The effect of the surgical method on outcomes per patient were analyses per protocol, ie patients were analysed according to the reconstruction they eventually received. Only 1 patient was randomised to the one-stage group, but received the two-stage expander/implant based reconstruction. The patient-reported QoL was assessed according to intention to treat analysis.



**Table 3. Postoperative BREAST-Q and physician-reported aesthetic outcome (intention to treat population)**

| | One-stage ADM-assisted IBBR group (n=60) | Two-stage IBBR group (n=61) |
|---|---|---|
| **BREAST-Q** | | |
| Questionnaires completed | 48 (80%) | 44 (72%) |
| Uncomplicated course | 39 (65%) | 40 (66%) |
| Implant removal with new reconstruction | 7 (12%) | 4 (7%) |
| Implant removal without reconstruction | 2 (3%) | 0 |
| **Physician-reported aesthetic outcome** | | |
| Photographs available | 54 (90%) | 52 (85%) |
| Uncomplicated course | 41 (68%) | 50 (82%) |
| Implant removal with new reconstruction | 10 (17%) | 2 (3%) |
| Implant removal without reconstruction | 3 (5%) | .. |

Values are percentage (number of patients)

## Table 4. Preoperative and postoperative BREAST-Q scales

| | Preoperative | | Postoperative | | p value* |
|---|---|---|---|---|---|
| | One-stage ADM-assisted | Two-stage IBBR | One-stage ADM-assisted | Two-stage IBBR | |
| Available questionnaires, n | 32 (53%) of 60 | 31 (51%) of 61 | 48 (80%) of 60 | 44 (72%) of 61 | .. |
| Satisfaction with breasts | | | | | |
| Data available, n | 32 (53%) of 60 | 31 (51%) of 61 | 48 | 43 | .. |
| Mean (SD) | 75·8 (17·5) | 70·9 (19·5) | 63·4 (15·8) | 60·3 (15·4) | 0·35 |
| Visibility of rippling | | | | | |
| Data available, n | .. | .. | 44 | 40 | .. |
| Mean (SD) | .. | .. | 3·2 (1·0) | 2·9 (0·9) | 0·14 |
| Sensation of rippling | | | | | |
| Data available, n | .. | .. | 43 | 40 | .. |
| Mean (SD) | .. | .. | 3·1 (1·0) | 2·8 (0·9) | 0·26 |
| Satisfaction with outcome | | | | | |
| Data available, n | .. | .. | 48 | 43 | .. |
| Mean (SD) | .. | .. | 72·8 (19·1) | 67·8 (16·3) | 0·19 |
| Psychosocial wellbeing | | | | | |
| Data available, n | 32 (53%) of 60 | 31 (51%) of 61 | 48 | 44 | .. |
| Mean (SD) | 68·2 (11·8) | 68·4 (19·5) | 72·6 (17·3) | 72·8 (19·6) | 0·95 |
| Sexual wellbeing | | | | | |
| Data available, n | 32 (53%) of 60 | 28 (46%) of 61 | 47 | 39 | .. |
| Mean (SD) | 63·5 (14·4) | 63·5 (23·8) | 58·0 (17·0) | 57·1 (19·5) | 0·82 |
| Physical wellbeing: chest and upper body* | | | | | |
| Data available, n | 32 (53%) of 60 | 31 (51%) of 61 | 48 | 44 | .. |
| Mean (SD) | 78·4 (15·7) | 84·3 (11·2) | 78·0 (14·1) | 79·3 (12·2) | 0·60 |
| Median (IQR) | .. | .. | 77·0 (91·0–68·8) | 81·0 (85·0–71·8) | .. |
| Satisfaction with nipples | | | | | |
| Data available, n | .. | .. | 17 | 13 | .. |
| Mean (SD) | .. | .. | 73·3 (17·2) | 76·7 (20·7) | 0·63 |
| Satisfaction with care: information | | | | | |
| Data available, n | .. | .. | 48 | 44 | .. |
| Mean (SD) | .. | .. | 65·1 (15·5) | 69·5 (19·9) | 0·24 |
| Satisfaction with care: surgeon† | | | | | |
| Data available, n | .. | .. | 48 | 44 | .. |
| Mean (SD) | .. | .. | 84·1 (18·6) | 84·6 (21·7) | 0·63 |
| Median (IQR) | .. | .. | 91·0 (31–100) | 100·0 (25–100) | |
| Satisfaction with care: medical team† | | | | | |
| Data available, n | .. | .. | 48 | 44 | .. |
| Mean (SD) | .. | .. | 86·7 (22·0) | 82·8 (24·1) | 0·47 |
| Median (IQR) | .. | .. | 100 (0–100) | 100 (0–100) | |
| Satisfaction with care: office staff | | | | | |
| Data available, n | .. | .. | 48 | 44 | .. |
| Mean (SD) | .. | .. | 86·4 (18·8) | 84·7 (21·0) | 0·69 |

ADM=acellular dermal matrices. IBBR=implant-based breast reconstruction. *Difference between the postoperative BREAST-Q of the one-stage and two-stage IBBR. †Non-normal distribution.

Photographs were available for 54 (90%) of 60 patients in the one-stage group and 52 (85%) of 61 patients in the two-stage group. The mean pre-operative score for physician-reported aesthetic outcome was 8·4 ± 0·4 in the one-stage and 8·3 ± 0·8 in the two-stage group. The postoperative scores were lower in both groups, with a mean score of 6·2 ± 1·6 in the one-stage and 6·2 ± 0·9 in the two-stage group. There were no statistically significant differences between the two groups based on the physician-reported Aesthetic Item Scale, also when adjusting for the preoperative panel score, implant removal and secondary revision surgeries (Table 6). The intra-observer agreement was good in all observers with ICCS ≥ 0·843 (95% CI 0·461; 10). The inter-observer agreement for physician-reported aesthetic outcomes was moderate with ICC ranging from 0·518 (95% CI 0·355; 0·640) to 0·758 (0·704; 0·804).

An exploratory analysis was performed to assess the correlation between patient-reported outcomes of the BREAST-Q and physician-reported aesthetic scores at 12 months post surgery. This correlation was low, with a Pearson correlation of r= 0·343 (p=0·002) between the Satisfaction with Breasts and the mean overall physician-reported aesthetic score. Correlations between other scales and physician-reported aesthetic outcomes ranged from 0·065 to 0·448.



**Table 5. Regression analyses of differences between one-stage ADM-assisted IBBR and two-stage IBBR**

| | Difference* | p value | Adjusted analyses† | p value |
|---|---|---|---|---|
| Satisfaction with breasts (n=91) | 1·4 (–5·1 to 8·0) | 0·665 | 2·8 (–3·5 to 9·2) | 0·378 |
| Satisfaction with outcome (n=91) | 4·3 (–3·6 to 12·2) | 0·283 | 5·4 (–2·5 to 13·3) | 0·179 |
| Psychosocial wellbeing (n=92) | –1·9 (–9·8 to 5·9) | 0·622 | –0·6 (–8·3 to 7·2) | 0·887 |
| Sexual wellbeing (n=86) | –0·3 (–8·9 to 8·2) | 0·937 | 0·6 (–8·1 to 9·2) | 0·899 |
| Physical wellbeing (n=92) | –3·0 (–8·6 to 2·6) | 0·291 | –2·8 (–8·5 to 2·9) | 0·329 |

Data are the difference (95% CI) between the two groups. ADM=acellular dermal matrices. IBBR=implant-based breast reconstruction. *Analyses adjusted for stratification factors (indication and centre). †Secondary analyses regarding possible factor influencing patient-reported outcomes (off-protocol analyses); adjusted for indication, centre, and implant removal.

**Table 6. Preoperative and postoperative aesthetic scores based on photographs per group**

| | Preoperative | | Postoperative | | p value* |
|---|---|---|---|---|---|
| | One-stage ADM-assisted IBBR (n=56) | Two-stage IBBR (n=54) | One-stage ADM-assisted IBBR (n=54) | Two-stage IBBR (n=52) | |
| Shape (1–5) | 4·5 (0·5) | 4·5 (0·7) | 3·5 (0·9) | 3·2 (0·7) | 0·075 |
| Volume (1–5) | 4·5 (0·5) | 4·4 (0·7) | 3·9 (0·9) | 4·0 (0·6) | 0·867 |
| Symmetry (1–5) | 4·3 (0·7) | 4·3 (0·8) | 3·4 (1·0) | 3·1 (0·8) | 0·087 |
| Scars (1–5) | 4·9 (0·4) | 4·8 (0·5) | 3·3 (0·8) | 3·4 (0·7) | 0·362 |
| NAC (1–5)† | 4·9 (0·2) | 4·9 (0·3) | 3·8 (0·9) | 3·7 (0·8) | 0·721 |
| Total score (1–10) | 8·2 (0·8) | 8·2 (1·2) | 6·3 (1·5) | 6·2 (1·0) | 0·569 |
| Only side of reconstruction included in the study (1–10)‡ | 8·4 (0·4) | 8·3 (0·8) | 6·2 (1·6) | 6·2 (0·9) | 0·909 |

Data are mean (SD). ADM=acellular dermal matrices. IBBR=implant-based breast reconstruction. NAC=nipple areolar complex. *Difference between postoperative aesthetic score of one-stage and two-stage IBBR. †Not applicable if a skin sparing mastectomy without a nipple reconstruction was done or if patients had a history of skin sparing mastectomy. Data were only available from 56 participants for preoperative one-stage IBBR, from 52 for preoperative two-stage IBBR, from 37 for postoperative one-stage IBBR, and from 39 for postoperative two-stage IBBR. ‡Only left or right side if unilateral reconstruction was done.

# DISCUSSION

The first reports after the introduction of ADM in the field of breast reconstruction in 2005 were overwhelmingly promising. [18,19] It was suggested that the use of ADM is cost-effective, because it makes one-stage IBBR feasible, and leads to improved aesthetic results, by creating a more natural looking breast.[1, 3] However, evidence of these potential benefits remained inconclusive. We performed the multicentre randomized controlled Breast Reconstruction In One Stage (BRIOS) study to investigate these hypothesized benefits of ADM-assisted one stage IBBR relative to the conventional two-stage IBBR. In the present study, we found that patient-reported QoL as measured by the BREAST-Q (i.e., health-related QoL and Satisfaction) at least one year after placement of the definite breast implant did not differ between both groups, even after adjusting for implant removal. Assessment of the aesthetic outcome by experienced plastic surgeons did not reveal significant differences between both groups either. Hence, in the present trial we were not able to confirm the presumed advantages of one-stage IBBR with ADM over two-stage IBBR.

As breast reconstruction primarily aims to restore physical appearance and well-being, its value can only really be judged by the patient herself. The BREAST-Q

was developed in the context of the worldwide momentum to adopt patient-reported outcomes (PROs). The BREAST-Q is a comprehensive tool to evaluate QoL by assessing both health-related QoL and satisfaction, which has now been implemented into clinical care in many centres and used in studies to evaluate outcomes for breast surgery. Patient-reported Satisfaction with Breasts after breast reconstruction with implants in general varies between 55 and 70.[20,21] The values reported in our study lie within this range (63·4 in the one-stage group vs. 60·3 in the two-stage group).

In this study, high rates of surgical complications, reoperations and implant removal occurred in the one-stage group. A complicated course could negatively affect the patient's experience, QoL and satisfaction. Therefore, we performed additional secondary exploratory analyses. In these exploratory analyses, we adjusted the 12-month BREAST-Q scores for implant removal. Also after adjusting, there were no statistically significant differences in BREAST-Q scores between groups. For patients with an uncomplicated course, i.e., breast reconstruction without implant removal, the values remained almost equal compared to the entire group including patients with a complicated course (one-stage 64·4; two-stage 62·7).



The overall postoperative BREAST-Q scores were in general lower compared to the preoperative scores. Only postoperative Psychosocial Well-being scores were higher, indicating higher emotional health and self-esteem after breast reconstruction. Two studies previously reported on the use of the BREAST-Q to assess ADM-assisted IBBR and reported a high level of patient satisfaction.[22,23] Unfortunately, the authors did not use the recommended QScore Scoring Software to calculate official BREAST-Q scores, which hampers comparison to our results. The Mastectomy Reconstruction Outcomes Consortium (MROC) study is an example of a large prospective, observational cohort including all patients undergoing first-time breast reconstruction assessing PROs using several questionnaires including the BREAST-Q.[24] With the inclusion of large numbers of patients, their results may improve our understanding of which factors are most important for patient satisfaction after breast reconstruction. However, results after solely one-stage IBBR with ADM are not yet available from the MROC study population. Srinivasa et al. reported on the MROC study comparing one-stage (n= 99, 6·9%) and two-stage IBBR (n=1329, 93%), and found significantly more ADM use in the

one-stage group (93% vs. 52%). They also found comparable BREAST-Q scores in both groups (68·3 vs. 63·8), and their mean scores are similar to mean scores in our trial.[21] We chose to also assess patient-reported experience measures (PREMs) (i.e., BREAST-Q Satisfaction with Information, Satisfaction with Care, and Satisfaction with Surgeon). Despite higher complications after ADM use, these results did not show any differences between the groups, indicating that patients were equally satisfied with pre-operative communication and information about potential risks and benefits.[21]

Proponents of the use of ADMs in IBBR are mainly enthusiastic about the technique because it could supposedly allow for more natural aesthetic outcomes than two stage sub-muscular reconstructions. In our study, the aesthetic outcomes were also assessed by a panel of 5 experienced plastic surgeons. We could not establish improved cosmesis after ADM-assisted reconstruction. For the group of women, who underwent successful one-stage reconstruction with ADM (i.e., without reoperations), the post-operative physician-reported aesthetic score averaged 6·5 relative to 6.2 in the two-stage group. When adjusting for reoperations or implant removal, this difference in aesthetic scores between the groups was not statistically significant. Possibly differences in cosmesis between the two IBBR techniques were smaller than our detection limit (with the present sample size a difference ≥ 0·8 in aesthetic score could be detected). Minor non-statistically significant differences in shape (p=0·075) and symmetry (p=0·087) between the one- and two-stage IBBR were seen, both in favour of the one-stage group, which suggest that there might be some advantages in the aesthetic outcome as assessed by the health care professional with respect to breast volume and symmetry. Further research on this subject is required. Again, the overall mean post-operative aesthetic scores were considerably lower than pre-operative scores (6·2 vs. 8·2). One explanation might be that the reconstructed breast often does not match the natural breast.

Generally, it is assumed that cosmesis is an important factor in the satisfaction and quality of life of the patient. However, consistent with previous studies, the correlation between patient-reported satisfaction with breasts and physician-reported aesthetic score was quite low (r= 0·34), implicating that patients' satisfaction cannot be explained by the aesthetic outcome as observed by plastic surgeons.[12, 25, 26]

Although the previously suggested advantages of one-stage IBBR with ADM could not be verified with this study, we should be cautious to draw definite conclusions. This study is limited by a lower than anticipated response and inclusion rate in which n=48 (80.0%) patients in the one-stage group and n=44 (72.1%) patients in the two-stage group completed the BREAST-Q, instead of the anticipated 65 patients per group. With this number of respondents, the difference in BREAST-Q score must be greater than 9·5 to be able to detect a statistically significant difference. Hence, a smaller difference in patient satisfaction between the two groups may still be present, but whether such potentially smaller differences are clinically relevant remains uncertain. Up till now, there are no widely accepted clinically relevant differences, known as minimal important differences (MIDs). Pusic et al. recently indicated distribution-based MIDs for the BREAST-Q scales, with a difference of 4.0 points within groups for the Satisfaction with Breast and Sexual well-being domains and 3.6 points for the Psychosocial well-being domains.[27] Based on these differences, patients in the one-stage ADM group report clinically relevant, but statistically non-significant higher Satisfaction with Outcome (72·8 ± 19·1) compared to the two-stage group (67·8 ± 16·3), but lower Satisfaction with Information (one-stage 65·1 ± 15·5 vs. two-stage 69·5 ± 19·9).



The interpretation and clinical meaning of PROs are not yet fully determined, and future studies should focus on the interpretation of these relevant outcomes. While the BRIOS study was initiated at a time when there was much hype and expectations regarding the potential benefits of ADMs, the results should be interpreted in the light of what we know today. It is now thought that ADM-assisted breast reconstruction is a very delicate procedure, requiring a strict patient selection, and a very well trained and experienced surgical team.[28-30] One-stage breast reconstruction is inherently less forgiving than two-stage breast reconstruction, since implant volume cannot be adapted and more strain is placed on the mastectomy skin flap and the wound. While two-stage IBBR reconstruction can more readily be successfully performed, the one-stage technique requires an experienced team, which recognizes tacit risk factors, which at present cannot be quantified. As yet, it remains unclear whether the use of an ADM in one-stage breast reconstruction is an additional complicating factor, as no randomised studies have been performed to compare one stage IBBR with and without ADM. Moreover, we do yet not know which type of ADM should be preferred. While in

North America most ADMs are human derived, these are not approved in Europe. In the present study, we used Strattice, which is a porcine-derived ADM. It is unclear whether differences in performance exist between ADMs derived from animal and human origin.

To conclude, in the multicentre randomised BRIOS trial study one-stage implant-based breast reconstruction (IBBR) with an acellular dermal matrix (ADM) was not associated with higher health-related QoL or patient satisfaction compared to the conventional two-stage expander/implant based IBBR. Furthermore, both patient-reported and physician-reported aesthetic outcomes showed comparable results between the groups. With a higher risk on complications, the precise role of the ADM in implant-based breast reconstruction has yet to be proven, and its use should currently be considered critically on a case-by-case basis.

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8

# Introducing BREAST-Q computerized adaptive testing: brief and individualized patient-reported outcome assessment following reconstructive breast surgery

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# ABSTRACT

## Background

BREAST-Q is a widely used patient-reported outcome (PRO) instrument measuring health-related quality-of-life and patient satisfaction in breast surgery. Shorter assessment potentially increases patients' willingness to complete scales, but simply offering a short-form version leads to unacceptable loss in measurement precision. We aimed to develop a computerized adaptive test (CAT) to shorten BREAST-Q's Satisfaction with Breasts scale whilst maintaining reliability of measurement.

## Methods

We created a CAT, which repetitively administered questions from the pool of 16 questions, until pre-specified levels of reliability were reached (i.e., standard errors (SE) of 0.32-0.55). In a simulation study, we tested the CAT's feasibility for all potential Satisfaction scores. In a second study using actual patient data, 5000 breast reconstruction patients who had previously completed the full scale were randomly selected from a large database. Their full-scale Satisfaction scores were compared with their CAT-derived scores.

## Results

In both studies, by applying CAT, the Satisfaction with Breasts scale could be reduced to an average of 10 questions when using the minimum level of measurement precision for individual-patient measurement (SE 0.32), compared to 4 questions when using the minimum precision level for group-based research (SE 0.55). Score estimates were highly correlated between CAT assessment and the full scale (0.91-0.98 in simulation study, 0.89-0.98 in patient data study).

## Conclusions

Applying CAT to BREAST-Q's Satisfaction with Breasts scale facilitates reliable assessment with 38% to 75% fewer question than the full version. The novel BREAST-Q CAT version may decrease response burden and help overcome barriers to implementation in routine care.

# INTRODUCTION

Breast reconstruction rates have rapidly increased in the past decade, and the cosmetic outcome is now a common subject when discussing surgical options for breast cancer.[1,2] Patient-reported outcomes (PROs) have become essential to determine the success of breast reconstructions since their primary surgical goal is to improve body image and health-related quality of life (HR-QoL).[3,4] PROs are usually assessed using validated questionnaires, designed to quantify HR-QoL and other important outcomes from the patient's perspective.[3] PROs are used for research (e.g., which treatment works best) and for clinical care (e.g., how is this patient doing and should we change the course of treatment?).

When collected in routine clinical care, PROs may help clinicians and patients gain timely insight into patients' symptoms, preferences and progress; a process shown to improve patients' self-efficacy, HR-QoL, the patient-physician dialogue and even survival.[5-11] Sharing PRO scores from patients with similar preferences may help guide their decisions (e.g. breast-conserving surgery versus mastectomy with reconstruction), while evaluating PROs in specific subgroups could improve patient selection for the different surgical options (e.g., implant reconstruction versus autologous reconstructions in the setting of radiotherapy).[2]



In order to use PROs for these important purposes, the PRO-instruments need to be scientifically sound, able to detect changes over time, and should measure outcomes that matter to patients in the area of interest. Generic instruments, and even cancer-specific questionnaires, may thus not be sensitive enough to evaluate relevant surgical outcomes (e.g., cosmetic satisfaction, complications specific to the surgical area).[3,4]

With these limitations in mind, the BREAST-Q was developed to measure HR-QoL and patient satisfaction for patients undergoing breast surgery.[13] The BREAST-Q has shown to be valid, psychometrically robust and capable of detecting clinically meaningful changes over time.[12-15] Since its inception in 2009, the BREAST-Q has been widely used in surgical research and clinical trials, clinical practice, and quality improvement initiatives.[2,15-17] The BREAST-Q scale that measures patient satisfaction with breasts has become part of the ICHOM Standard Set for Breast cancer.[4]

The BREAST-Q consists of scales that can be used independently. Each scale is scored individually, and there is no total score for all scales combined. This allows investigators and clinicians to use only those scales that are relevant in a given study or clinical scenario (e.g., 'Physical well-being' during follow-up visits, 'Satisfaction with Breasts' after scars have healed). Despite this system of independently functioning scales, in certain clinical and research situations, there may be a need for even shorter assessments (e.g., to reduce the patient burden when many different questionnaires are being administered, or to facilitate quick assessment in a busy clinical setting). The need to reduce response burden may especially apply to oncology, where patients are often overwhelmed with complex information to process and many forms to complete.

Simply offering a 'short-form version', however, may lead to unacceptable loss of precision and an inability to measure smaller clinically relevant changes over time.[18,19] Computerized adaptive testing (CAT) is an innovative solution used to individualize and shorten (existing) questionnaires, whilst maintaining reliable estimates for scores[18-29] Instead of presenting all questions in a fixed order, CAT uses an algorithm to decide which question will be presented to the patient next. Based on each answer, the most informative and most appropriate question is then selected until a pre-specified level of measurement precision is reached. For some patients, this level could be reached after a few questions, while other patients need to complete all questions in a scale. As a result, CAT may not only shorten scale completion time, but may also prevent the presentation of questions that are less relevant to an individual patient.[18-30]

We aimed to develop a CAT for the BREAST-Q 'Satisfaction with Breasts' scale of the reconstruction module, and to assess its performance in terms of efficiency, precision, and comparability to the full scale.

# METHODS

## BREAST-Q and Rasch Measurement Theory

BREAST-Q was developed according to international guidelines for PRO instrument development[7,12,31,32], and its domains and questions were constructed with extensive input from patients. Rasch Measurement Theory (RMT) was used to guide scale development and refinement. In general, scales that fit the Rasch model have an ordering of questions in the same way that numbers increment along a ruler, with an equal distance between each increment (i.e., interval scaling). Furthermore, the ordering of questions follows a clinical hierarchy. Questions that correlate with, for instance, lowest HR-QoL are on the far left of the ruler, while questions that correlate with highest HR-QoL are located on the far right of the ruler. For example, only patients with the most symmetrical autologous reconstructions will likely confirm being satisfied or very satisfied when looking in the mirror without their clothes on (the question on the far right of the Satisfaction with Breasts 'ruler').

This approach to scale development has become popular in the past decade, as it enhances the ability to understand the clinical meaning of a patient's score, since the score for each scale can be interpreted as a location on the 'Rasch ruler'. This facilitates the interpretation of findings both on a group level (i.e., relevant for research) and on an individual level (i.e., relevant for measurement and follow-up in clinical care).

In comparison, PRO instruments developed using the more traditional Classical Testing Theory – which applies to the majority of PRO instruments available for breast cancer – are mainly valid for use in group- or population-based research. [21,22,25,27] Also, in the Classical Testing approach, statistical analyses are conducted at the scale level rather than question level, meaning that all questions must be delivered to all patients, often resulting in long scales. In contrast, Rasch analysis produces precise psychometric information about individual questions within a scale leading to greater flexibility in the manner in which the scale is administered, including the potential to administer scales using computerized adaptive testing. A more in-depth description of the Rasch model, Classical Testing Theory and psychometrics can be found in other sources.[21,22,25,27,31]

## Computerized adaptive testing

Computerized adaptive testing may be applied to scales that have been developed using Rasch analysis – such as the BREAST-Q. Each question is calibrated to a position on the Rasch ruler. As a result, the answer to each question helps determine a patient's position on that ruler. Instead of presenting all questions in a fixed order, CAT uses an algorithm to decide which question will be presented to the patient next. After each answered question, the CAT uses the current position on the ruler (i.e., Rasch-derived item location) to determine a provisional score. The CAT then selects the question that will provide the most additional information about this provisional score. Only when another question provides relevant additional information would that question be presented next. As a result, the assessment is tailored to each individual patient.[18-25] The CAT algorithm continues to administer questions until a pre-determined level of measurement precision (known as the stopping rule) has been reached. Once the stopping rule has been reached, the assessment is completed and the final score is calculated.

## The BREAST-Q CAT

For this study, we tested CAT feasibility for the 'Satisfaction with Breasts' scale, as this is one of the longer and most widely used BREAST-Q scales of the reconstruction module.[12,13,15] The fixed-order full scale consists of 16 questions. The question on the far left of the Rasch ruler evaluates 'How you look in the mirror clothed', while the question is the far right evaluates 'How you look in the mirror unclothed'.

Psychometric properties (e.g., where each question's response options are located along the ruler) were used to create a CAT for this scale. These properties were also used to determine the opening question of the CAT (usually a question that is located around the middle of a scale's Rasch ruler or around the scale's mean population score ).[19, 25-28]

After a patient responded to the opening question, the CAT algorithm first estimated the patient's provisional Satisfaction with Breasts score. This provisional Satisfaction score was calculated with a surrounding confidence interval, known as the standard error (SE). After each next question was answered, a new provisional Satisfaction score and SE were calculated. As each response added more

information on how satisfied the patient was with their reconstructed breast(s), the SE of the score estimate decreased. The CAT continued to administer questions until the SE fell below the pre-specified stopping rule, after which the assessment ceased, and a final score was calculated.

To assess the performance of the CAT in a variety of situations, stopping rules were set to 3 different standard errors (i.e., 0.32, 0.45 and 0.55). These SE values were chosen because they are equivalent to reliability values (i.e., Cronbach alpha) of 0.90, 0.80 and 0.70 respectively (reliability = 1- SE2). A reliability of 0.70 is generally seen as the minimum value for reliable group measurement, whereas the minimum for individual-level measurement is 0.90.[19,20,28]

We performed two studies with the CATs. During the first study, all possible values for the Satisfaction score on the Rasch ruler were simulated with intervals of 0.10. The CATs were created using R coding, and the simulations were conducted in R Studio using modified FireStar code. During the CAT process, each question was only administered once.

To compare scores retrieved by CAT with scores from the fixed-order full scale, we conducted a second study using actual patient data. Five thousand patients were randomly selected from a larger sample of more than 17,000 patients who had previously completed the 'Satisfaction with Breasts' scale. These data had previously been collected prospectively in an industry-sponsored post-marketing breast implant surveillance study. These women had all undergone implant-based breast reconstructions in the United States after a breast cancer diagnosis, were 22 years or older, and fluent in English. For these 5000 randomly selected patients, 'Satisfaction with Breasts' scores were initially calculated based on their full-scale responses and separately by using their responses to run the CAT. As a result, this second study emulates what would have happened if the CAT were used when the patient was completing the scale. Pearson correlation coefficient was calculated to assess comparability between scores.

# RESULTS

Psychometric properties retrieved by Rasch analysis of the original BREAST-Q field test data confirmed suitability for CAT. More details about these properties have been described elsewhere.[12-14] The question that provided the most information at the population mean for the 'Satisfaction with Breasts' scale of BREAST-Q's Reconstruction module was 'How equal in size your breasts are to each other?'. Therefore, this question was chosen as the opening question of the CAT for all patients.

With CAT, the 'Satisfaction with Breasts' scale could be reduced to an average of 10 questions when the minimum level of measurement precision for individual-level measurement was chosen (SE 0.32). This provided a reduction of 37.5% in questions as compared to the full 16-item scale, with a correlation of 0.98. The scale was reduced to an average of 4 questions when using the minimum acceptable level for group-based research (SE 0.55), providing a reduction of 75%, with a correlation between the final scores of 0.91.

**Table 1. Summary of CAT studies for BREAST-Q 'Satisfaction with Breasts' scale**

| | Stopping rule (SE theta) | Number of questions used (mean) | Reliability (Cronbach's alpha) | Correlation full scale score with CAT score |
|---|---|---|---|---|
| **Study 1** | | | | |
| | 0.55 | 4 | 0.7 | 0.91 |
| | 0.45 | 7 | 0.8 | 0.94 |
| | 0.32 | 10 | 0.9 | 0.98 |
| **Study 2** | | | | |
| | 0.55 | 4 | 0.7 | 0.89 |
| | 0.45 | 7 | 0.8 | 0.93 |
| | 0.32 | 10 | 0.9 | 0.98 |

**Study 1:** All possible values for the 'Satisfaction with Breasts' score were simulated with intervals of 0.10.
**Study 2:** Comparison between full-scale responses from 5000 actual patients vs. CAT-derived scores when scores were treated as if they had been collected adaptively
NB: full scale consists of 16 questions

In a second step, the CATs were applied to the existing full-scale responses of the random sample of breast reconstruction patients (n=5000) as if their responses had been collected adaptively. These results were equal to the simulation study, showing that CAT-derived Satisfaction scores from actual patients were also only marginally different from the scores based on full-scale data (Pearson's correlation 0.89-0.97). Results from both studies are summarized Table 1. Details of individual question parameters used in these simulations are available from the corresponding author.

# DISCUSSION

This study shows that applying CAT to BREAST-Q's Satisfaction with Breasts scale of the reconstruction module shortens the scale substantially (38-75%) whilst maintaining reliable outcomes.

Although the reduction in the number of questions is appealing, we do not recommend using BREAST-Q CAT for every situation. There will still be situations where the highest level of measurement precision is required. For example, when robust PRO measurement is to be obtained, such as in certain Randomized Controlled Trials or perhaps also to inform certain value-based healthcare systems. There may also be clinical scenarios where clinicians will be interested in seeing responses to particular questions that the CAT may decide to skip. It is also important to note that BREAST-Q CAT can only be applied when the scale is being administered on a computer (or smartphone/tablet).

In recent years there has been a proliferation of studies using CAT to improve the efficiency of PRO instruments that were also developed using similar psychometrics methods (i.e., RMT, Item Response Theory). The global Patient-Reported Outcome Measurement Information System (PROMIS) initiative has produced a large number of item banks to measure broad aspects of patient-reported health and QoL. Our results concur with their results, and those of other CAT investigations, which all demonstrate the effectiveness of CAT as a tool to reduce the length of PRO assessments whilst maintaining reliability of measurement. Overall, CAT assessments appear to take less time than fixed-form full versions of the same PRO-instruments.[18-30]

=An important strength of this study is that we performed two different kinds of studies to evaluate the CAT - a first simulation to test CAT feasibility for all potential Satisfaction with Breasts scores, and a second study to test the CAT using actual patient data. Our findings gave us insight into the expected reduction in questions for the CAT in a real-life situation. Both studies gave similar results.

An important limitation of this study is that we simulated CAT responses derived from a previously collected sample. Therefore, we were unable to collect information on completion time for the BREAST-Q CAT in a true administration environment. Such Information could be relevant to determine whether fewer questions in a scale will also reduce actual completion time. As the questions of the fixed-form BREAST-Q and the CAT are presented in the same format, we expect the percentage of time saved during CAT administration to be roughly equal to the scale reduction percentage due to CAT.[33]

There is a trade-off between assessment length and precision. Although the ratio between the two is optimized using the CAT algorithm, decisions regarding stopping rules are contextual and thus should be decided upon by researchers/ clinicians. Scores from the fixed-form full version and the CAT version of the Satisfaction with Breasts scale are directly comparable. As such, we recommend that investigators who are new to PRO assessment and/or BREAST-Q first orientate themselves using the more straightforward fixed-form version of the BREAST-Q. Once familiar, we recommend progression to the BREAST-Q CAT to maximize the efficiency of each assessment. Information needed to create CAT versions of the Satisfaction with Breast scale is available from the corresponding author.

This study was performed using only one BREAST-Q scale from the reconstruction module. Psychometric properties from the other scales confirm suitability for CAT. However, CAT adds less benefit to shorter scales, due to the limited information available from a smaller pool of questions. Adaptive assessments may therefore be less relevant for some of the other BREAST-Q scales (e.g. 10-item psychosocial well-being scale, and the 6-item sexual well-being), which are already quite brief.

Recent studies have demonstrated the clinical benefit – even an association with longer survival – of symptom monitoring using PROs during routine cancer

treatment.[9-11] The enhanced efficiency of the BREAST-Q CAT could serve to further break down barriers to using and implementing PROs in breast surgery, potentially improving clinical care and providing answers to important questions that can only be answered by patients themselves.[2,16,17]

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9

# Summary

in English and in Dutch

# INNOVATIONS IN PATIENT-CENTERED BREAST CANCER RESEARCH

Although breast cancer prognosis has improved in the past decades, treatment still severely impacts patients' quality of life, emotional and sexual functioning. Many new experimental interventions rapidly arise aiming to improve breast cancer care. Randomized controlled trials are required to identify which of these interventions are (most) effective, with the least side effects and best quality of life (QoL). To evaluate these side effects and QoL, patient-reported outcomes (PROs) are needed. RCTs are the gold standard to show effectiveness of treatments, but are often beset by recruitment issues, disappointment bias and limited generalizability. PROs are gaining popularity, but the questionnaires used to collect PROs are often long. Therefore, novel ways to conduct efficient randomized studies are needed, and novel ways to efficiently collect PROs are needed as well. The focus of this thesis was to explore and evaluate potential solutions for these challenges.

Part 1 of this thesis was dedicated to implementation and evaluation of the cohort multiple randomized controlled trial design (cmRCT). A novel pragmatic trial design thought to increase efficiency and generalizability of trial results (the design is explained in more detail in Chapter 2 and 3). We first introduced the staged-informed consent procedure for cmRCT (Chapter 2), which consists of several stages, including asking broad informed consent for randomization. This avoids that patients are randomized without their prior consent, and informs patients that they may serve as controls without further notice when not selected for an intervention after giving broad informed consent. Only those randomized to the intervention arm will sign a second informed consent to undergo the intervention being offered. By applying staged-informed consent, cmRCT studies adhere to ethical guidelines and ethical concerns may be avoided. This staged-informed consent was applied when setting up the UMBRELLA cohort for patients with (in situ) breast cancer (Chapter 3). The UMBRELLA cohort showed that it is logistically and ethically feasible to implement cmRCT into a clinical breast cancer setting, resulting in high patient participation. Trial results of the first cohort RCT are to be expected in 2019. In Chapter 4 we presented results from a survey study, where we assessed patients' understanding of the cmRCT design. This study was

conducted among participants in three ongoing cmRCT cohorts with embedded trials in the field of breast cancer, bone metastases and colorectal cancer. Patients' understanding of randomization and broad consent was adequate shortly after enrollment, and also after being selected for an intervention, but more frequent reminders are necessary to also keep those who were not approached for interventions well informed and aware of broad consent throughout cohort participation. Part 1 concluded with an example of what may be done with UMBRELLA data, by presenting results from an observational study conducted with clinical and patient-reported outcomes (Chapter 5). This study assessed prevalence, determinants and the effect on QoL of breast edema in patients treated with breast-conserving therapy. Study results suggest that breast edema is an underestimated clinical problem, triggered by commonly applied treatment options including axillary lymph node dissection, loco-regional radiotherapy, local radiotherapy boost, oncoplastic surgery, adjuvant chemotherapy, and is independently associated with impaired quality of life and more breast pain. These results may be used to improve and develop interventions to reduce the impact of breast edema on patients' lives, as evidence-based treatment does not exist for breast edema. UMBRELLA provides an ideal framework for future trials to test interventions aiming to reduce breast edema.

In part 2, methods to improve patient-centered outcome utilization were assessed. We first explored potential advantages of using a supportive breast cancer app in clinical practice by assessing patients' and health care providers' opinions about benefits of this app in routine care (Chapter 6). Both patients and health care providers appreciated the app during follow-up, especially the option to record audio from clinical consultations with the medical team, but collecting PROs with this app proved to be technically challenging. In order to generate sufficient amounts of usable data, patients need to be actively engaged by their medical team to register PRO data within the app. Nonetheless, health-app are a promising development with the potential to capture PROs anywhere, anytime. Chapter 7 showed results of the BRIOS trial – the first RCT where the patient-reported outcome instrument BREAST-Q served as the primary outcome. This pragmatic RCT followed a classic design, and assessed health related quality of life and cosmetic satisfaction after a novel one-stage implant-based breast reconstruction technique using an acellular dermal matrix (ADM), compared to

the standard of care two-stage procedure using tissue expanders followed by a definitive breast implant later in time. There were no differences observed in QoL and Satisfaction with Breasts between the two breast reconstruction methods, but significantly more adverse outcomes were observed in the ADM-assisted one-stage group. Although BREAST-Q is already widely used, further improvements to reduce patient burden and survey fatigue were desired. This thesis concluded by shortening and individualizing the BREAST-Q by applying computerized adaptive testing (CAT). With CAT, instead of answering all questions in a static order, an algorithm selects the next questions from the pool of all available questions, until a preset level of measurement precision had been reached. For some patients this dramatically shortens the assessment, while others still have to complete all questions before an estimate of their outcomes will be reached. In general, BREAST-Q CAT resulted in 38% to 75% fewer questions than the full version. This is an important step forward to further increasing uptake of BREAST-Q both in research and in clinical practice.

# INNOVATIES OP HET GEBIED VAN PATIËNT-GERICHT BORSTKANKER ONDERZOEK

## Borstkanker

Borstkanker is een veelvoorkomende aandoening met ingrijpende gevolgen. In Nederland krijgt 1 op de 8 vrouwen tijdens hun leven te maken met borstkanker.[1,2] Er zijn de afgelopen decennia veel ontwikkelingen geweest om de behandeling van borstkanker te verbeteren. In Nederland is de 10-jaars overleving sterk verbeterd van 61% in 1981 naar 79% vandaag de dag.[3] De grootst behaalde winst is dat tumoren in een vroeger stadium ontdekt worden door borstkankerscreening, en daarnaast zijn behandelopties sterk verbeterd, waardoor borstkankerbehandeling vaker curatief kan zijn.[4] Tegenwoordig vormen borstsparende operaties gevolgd door bestraling van de gehele borst de standaardbehandeling voor de meeste vormen van borstkanker, waardoor een volledige borstamputatie nu slechts in de minderheid van de gevallen nodig is.[5] Bestraling is preciezer geworden met minder schade aan omliggend gezond weefsel, en chemotherapeutische middelen grijpen gerichter aan op kankercellen met minder bijwerkingen. Door het toepassen van plastisch chirurgische technieken (genaamd oncoplastische chirurgie) en het geven van chemotherapie voorafgaand aan de operatie, kunnen ook vrouwen met grote tumoren steeds vaker veilig borstsparend geopereerd worden met goede cosmetische resultaten.[6,7]

Ondanks deze belangrijke verbeteringen, leiden ook de huidige behandelingen tot bijwerkingen die een behoorlijke impact kunnen hebben op de kwaliteit van leven en het cosmetische resultaat na borstkankerbehandeling. Na chemotherapie ervaart tot 90% van de patiënten cognitieve beperkingen, en een chronisch pijnlijke gezwollen armen na een okselkliertoilet is veelvoorkomend (23% vijf jaar na behandeling).[8-10] Er kan dus nog veel vooruitgang worden geboekt om het leven van patiënten na borstkankerbehandeling zo optimaal mogelijk te maken.

## Uitdagingen op het gebied van borstkanker onderzoek

Veel van de grote verbeteringen zijn ontdekt in onderzoeken waaraan grote groepen patiënten hebben deelgenomen. Bij dit soort onderzoeken kan worden onderzocht of de nieuwe behandeling effectiever is dan de – op dat moment geldende – standaardbehandeling. Om dat zo objectief mogelijk te kunnen doen,

wordt er middels loting bepaald welke van de twee behandelingen een patiënt toegewezen krijgt. Doordat het lot bepaalt wie welke behandeling krijgt, zijn de groepen voorafgaand aan de start van de behandeling in opzet gelijk. Als er na het starten van de behandelingen verschillen worden gevonden, dan berusten deze verschillen daadwerkelijk op het effect van de nieuwe behandeling. Om die reden zijn dergelijke lotingsstudies (ook wel Randomized Controlled Trials, of in het kort RCTs genoemd) de gouden standaard om te bepalen welke behandeling het meest effectief is.

Er zijn veel verschillende experimentele behandelopties voor borstkanker in ontwikkeling, op uiteenlopende gebieden zoals chirurgie, radiotherapie, chemotherapie, ondersteunende apps, lifestyle beïnvloedende interventies, etc. Ook binnen het UMC Utrecht zijn er veel nieuwe behandelopties, zoals nieuwe manieren van bestralen waarbij eenmalig een hoge dosis straling op de tumor wordt gegeven voorafgaand aan de operatie (in plaats van meerdere weken bestraling na de operatie), of een nieuw bestralingsapparaat waarmee de tumor real-time gevolgd kan worden door tegelijkertijd een MRI-scan te maken zodat zo min mogelijk gezond weefsel mee bestraald wordt.[11,12] Al deze veelbelovende behandelingen moeten eerst goed onderzocht worden in lotingsstudies, zodat alleen bewezen effectieve behandelingen uiteindelijk standaardzorg voor grote groepen patiënten zullen worden. Doordat er steeds meer – en steeds sneller – experimentele behandelopties ontwikkeld worden is het uitdagend om al deze opties in aparte lotingsstudies te evalueren. Het is ook lastig om uitkomsten van verschillende lotingstudies met elkaar te vergelijken door verschillen in uitkomstmaten en verschillen in momenten waarop deze uitkomsten gemeten worden. Door dergelijke uitdagingen wordt evaluatie in lotingsstudies soms overgeslagen. Dit kan ertoe leiden dat nieuwe, effectievere behandelingen de patiënt nooit bereiken, maar ook dat ineffectieve behandelingen juist wel aangeboden worden aan patiënten als goede evaluatie niet heeft plaatsgevonden.

Bij zulke lotingsstudies wordt eerst gekeken welke patiënten in aanmerking komen voor de behandeling op basis van deelnamecriteria voor het onderzoek. Als een patiënt in aanmerking komt, worden zowel de nieuwe, experimentele behandeling als de standaard behandeling goed uitgelegd. Als een patiënt geïnteresseerd is in het ondergaan van de experimentele behandeling, wordt er geloot. Patiënten

die toezeggen deel te nemen aan een lotingsstudie, doen dit omdat ze interesse in de experimentele behandeling hebben. Als ze dan loten voor de standaard behandeling, zijn veel patiënten teleurgesteld dat ze de nieuwe behandeling niet kunnen ondergaan, hoewel ze weten dat de experimentele behandeling ook ineffectief of zelfs slechter kan blijken te zijn. Patiënten krijgen dan de standaard behandeling, maar willen vaak uit teleurstelling niet meer deelnemen als controle patiënt in zulke onderzoeken, of ondergaan via omwegen alsnog de experimentele behandeling. Hierdoor wordt het methodologisch lastig voor onderzoekers om op een betrouwbare manier te concluderen welke behandeling effectiever is. Ook als patiënten wel deel blijven nemen aan de lotingsstudie als controle patiënt, kan hun teleurstelling de resultaten beïnvloeden.[13] Als ze bijvoorbeeld hadden geloot voor een operatie middels de chirurgische robot zouden ze kleine littekentjes hebben, terwijl de standaardbehandeling grotere littekens geeft. Als er vervolgens gevraagd wordt hoe tevreden ze over de littekens zijn, kunnen de littekens door teleurstelling opeens heel groot en vervelend lijken, terwijl dit geen probleem zou zijn geweest als het alternatief van de kleine littekens niet bekend was geweest. Binnen het kankeronderzoek, wordt 40% van de lotingstudies nooit afgemaakt, omdat patiënten uit het onderzoek stappen of omdat er onvoldoende mensen deel willen nemen.[14]

Een ander probleem is dat bij dit soort onderzoeken vooral aan patiënten met de meest gunstige kenmerken gevraagd wordt om deel te nemen, bijv. jonge, relatief gezonde vrouwen. Als een behandeling in deze groep effectief blijkt te zijn, wordt de behandeling na zo'n onderzoek vervolgens vaak ook aangeboden aan alle andere patiënten, zoals oude patiënten met veel andere bijkomende ziekten[15], terwijl helemaal niet bekend is of de gunstige effecten ook gelden voor bijvoorbeeld deze ouderen. En ook als oudere patiënten wel mee mogen doen, vragen artsen deze patiëntengroep vaak niet om deel te nemen, uit zorgen dat het teveel voor hen zal zijn. Dit beperkt de generaliseerbaarheid van onderzoeken, aangezien gevonden effecten in het onderzoek alleen generaliseerbaarheid zijn naar mensen met dezelfde karakteristieken als de deelnemers aan het onderzoek. Door al deze uitdagingen in lotingstudies, komen effectieve behandelingen te laat bij de patiënt terecht. Nieuwe manieren om lotingsstudies te verrichten zijn daarom hard nodig.

## Nieuwe onderzoeksmethoden

Het cohort multiple randomized controlled trial (cmRCT) design is een nieuwe methode om lotingsstudies te verrichten. Deze nieuwe onderzoeksmethode is ontwikkeld om de eerder genoemde uitdagingen tegen te gaan.[16] Het cmRCT design werkt als volgt: Patiënten wordt gevraagd of ze deel willen nemen aan een cohort onderzoek, waarbij gedurende langere tijd behandelinformatie, patiëntkarakteristieken (bijv. leeftijd) en informatie over kwaliteit van leven en functioneren verzameld zal worden. Voor elke te onderzoeken experimentele behandeling, wordt eerst aan de hand van inclusiecriteria gekeken welke patiënten potentieel in aanmerking komen. Deze patiënten vormen een subcohort van geschikte patiënten. Vanuit dit subcohort worden patiënten op basis van loting uitgenodigd om de experimentele behandeling te ondergaan. Patiënten die geloot hebben voor de experimentele behandeling, worden hierover geïnformeerd en gevraagd of ze deze experimentele behandeling willen ondergaan. Patiënten die geloot hebben voor de controle groep, krijgen zoals initieel al het plan was gewoon de standaardbehandeling, en worden niet opnieuw benaderd. Uitkomsten van patiënten die de experimentele behandeling aangeboden kregen, worden vergeleken met uitkomsten van controle patiënten die de standaardbehandeling ondergingen. Een belangrijk verschil met gewone RCTs is dus dat controle patiënten niet geïnformeerd worden over experimentele behandelingen waarvoor zij niet in aanmerking komen, nadat ze door het lot niet geselecteerd zijn. Een ander verschil is dat patiënten binnen dit onderzoek tegelijkertijd aan meerdere RCTs tegelijkertijd mee kunnen doen, en voor meerdere experimentele behandelingen in aanmerking kunnen komen, waardoor het makkelijker moet worden om meerdere nieuwe behandelingen tegelijkertijd in lotingsstudies te onderzoeken.



## Patiënt-gerapporteerde uitkomsten

Patiënt-gerapporteerde uitkomsten, beter bekend als patient-reported outcomes (PROs), zijn speciaal ontwikkelde instrumenten – meestal vragenlijsten – om uitkomsten zoals bijv. kwaliteit van leven, fysiek en emotioneel functioneren, en cosmetische tevredenheid, vanuit het perspectief van de patiënt te kwantificeren.[17,18] Waar voorheen door artsen ingeschat moest worden wat de kwaliteit van leven van patiënten was, kan dat nu op betrouwbare wijze door de patiënt zelf gerapporteerd worden.

PROs worden veel gebruikt voor onderzoeksdoeleinden, maar het vergelijken van dergelijke onderzoeken is vaak lastig vanwege verschillen tussen studies in de momenten waarop PROs verzameld worden, maar ook verschillen in het type vragenlijst dat gebruikt werd. Een internationale organisatie, genaamd ICHOM (International Consortium for Health Outcomes Measurement), heeft een standaard selectie voorgesteld van vragenlijsten en meetmomenten om overal ter wereld exact op dezelfde manier borstkankeruitkomsten te meten middels kwalitatief hoogwaardige vragenlijsten.[19] De vragenlijsten in de standaard selectie voor borstkanker zijn de kanker-specifieke EORTC QLQ-C30 vragenlijst voor algemene kwaliteit van leven[20], de borstkanker-specifieke EORTC BR23 voor borstkanker-gerelateerde symptomen[21], en de BREAST-Q voor kwaliteit van leven en cosmetische tevredenheid na borstkanker-gerelateerde chirurgie.[22] Deze standaardselectie van ICHOM kan ertoe leiden dat PROs vaker uitgevraagd zullen worden tijdens routine ziekenhuiszorg en vaker gebruikt zullen worden tijdens onderzoeken. Het afnemen van PROs, en deze gevonden waarden bespreken met patiënten tijdens hun behandeling, leidt tot betere communicatie tussen patiënt en arts, betere kwaliteit van leven voor patiënten, en zelfs tot een betere overleving aangezien symptomen vroeger gemeld worden aan artsen zodat er sneller gehandeld kan worden.[2] Het enige nadeel van PROs is dat ze vaak erg lang zijn, en dit belastend voor patiënten kan zijn. Kortere vragenlijsten zijn vaak minder gevoelig om goed te meten wat een patiënt ervaart, dus nieuwe manieren om vragenlijsten efficiënter af te kunnen nemen zijn nodig.

Samenvattend, het nieuwe cmRCT design lijkt een veelbelovende stap voorwaarts om op efficiënte wijze de effectiviteit van experimentele behandelingen te evalueren in lotingsstudies, zodat alleen superieure behandelingen toegepast worden met de minste bijwerkingen. Om dit te kunnen verwezenlijken is het belangrijk om patiënten actiever en beter te betrekken bij het verbeteren van de zorg. Hierbij kunnen patiënt-gerapporteerde uitkomsten een belangrijke rol spelen, aangezien op deze wijze de ervaringen van grote groepen patiënten verzameld kan worden, zodat van elke patiënt geleerd kan worden. Hiervoor zou het cmRCT van grote waarde kunnen zijn, zeker als patiënt-gerapporteerde uitkomsten op makkelijke en korte wijze uitgevraagd kunnen worden tijdens onderzoeken. In dit proefschrift werden beide onderwerpen onderzocht.

## Bevindingen proefschrift

In het eerste deel van dit proefschrift stond cmRCT centraal. In hoofdstuk 2 werd de staged-informed consent procedure gepresenteerd. Middels deze methode wordt eerst toestemming aan alle patiënten gevraagd of ze in aanmerking willen komen voor lotingsstudies, door akkoord te gaan met loting gedurende de periode dat ze deelnemen aan het cmRCT cohort (ook wel geduid als broad informed consent). Daarbij geven patiënten ook toestemming om als controle patiënt te fungeren, indien ze niet loten voor de nieuwe behandeloptie. Enkel de patenten die loten voor een nieuwe behandeling, zullen hiervoor benaderd worden en een 2e keer informed consent moeten tekenen om de aangeboden behandeling daadwerkelijk te ondergaan. Op deze wijze zorgt het staged-informed consent ervoor dat alle patiënten goed geïnformeerd het cohort in stappen, en dat ethische richtlijnen rondom informed consent gevolgd worden, waardoor ethische bezwaren rondom cmRCT gereduceerd worden.

Deze staged-informed consent procedure werd gevolgd bij de ontwikkeling en implementatie van het UMBRELLA cohort – het eerste cmRCT cohort voor patiënten met borstkanker. Het UMBRELLA cohort (hoofdstuk 3) toont dat het logistiek en ethisch mogelijk is om cmRCT in te voeren in een borstkanker kliniek, waaraan grote hoeveelheden patiënten deelnemen (>85% van de benaderde patiënten). Resultaten van de eerste lotingsstudie binnen het UMBRELLA cohort worden verwacht in 2019.

In hoofdstuk 4 hebben we onderzocht hoe goed patiënten het cmRCT en de staged-informed consent procedure begrijpen. Bijna 600 patiënten die participeerden in de 3 cmRCT cohorten in het UMC Utrecht (darmkanker, botuitzaaiingen en borstkanker), en in de RCTs binnen deze cohorten, namen deel aan deze vragenlijstenstudie. Patiënten bleken zowel het design als broad consent goed te begrijpen kort na de informed consent procedure, en ook nadat ze benaderd werden voor een nieuwe behandeloptie in een lotingsstudie. Patiënten konden zich minder goed herinneren of ze wel of niet broad consent hadden gegeven als ze tussendoor niet benaderd waren voor een nieuwe behandeloptie. Dit toont daarom dat alle cohort patiënten er frequenter aan herinnerd moeten worden dat ze deelnemen aan een cohort studie waarbij lotingsstudies verricht kunnen worden. Tot slot toont hoofdstuk 5 wat er onder andere mogelijk is met gegevens

uit het UMBRELLA cohort. In dit hoofdstuk is onderzocht hoe vaak lymfeoedeem – een pijnlijke zwelling – van de borst voorkomt, wat risicofactoren hiervoor zijn, en of lymfeoedeem van de borst een effect heeft op kwaliteit van leven. Deze studie toont dat lymfeoedeem van de borst een onderschat probleem is, wat veroorzaakt wordt door vaak toegepaste borstkankerbehandelingen, en dat het hebben van borstoedeem geassocieerd is met een slechtere kwaliteit van leven en meer pijn van de borst. Er zijn op dit moment geen goede behandelopties voor oedeem van de borst. Het UMBRELLA cohort kan in de toekomst goed benut worden om nieuwe behandelopties voor lymfeoedeem van de borst te evalueren.

In deel 2 van het proefschrift stonden nieuwe manieren centraal om patiënt-gerapporteerde uitkomsten (PROs) te verzamelen en verbeteren. In hoofdstuk 6 werd onderzocht wat de meningen van artsen, verpleegkundigen en patiënten waren omtrent een nieuwe ondersteunende borstkanker app (OWise). Zowel patiënten als hun behandelaars waren enthousiast over het gebruik van de app, met name de functie om gesprekken met artsen op te nemen. Helaas konden PROs minder goed verzameld worden met deze app, en waren deze data nog niet goed bruikbaar voor onderzoek in deze vroege versie van de app. Desondanks, bezitten apps wel de potentie om makkelijk PROs te verzamelen op elk gewenst moment van de dag.

In hoofdstuk 7 werden resultaten getoond van de eerste lotingsstudie waarbij de BREAST-Q – kwaliteit van leven en cosmetische tevredenheid vragenlijst – gebruikt werd om de einduitkomsten van deze studie te meten. Deze lotingsstudie onderzocht of een directe borstreconstructie middels een borstimplantaat met een acellulaire dermale matrix (ADM) zou leidden tot betere kwaliteit van leven en betere cosmetische tevredenheid dan de standaardbehandeling die in 2 stappen uitgevoerd wordt (i.e. eerst een tissue expander onder de huid om deze gedurende enkele maanden op te rekken, waarna in 2$^{e}$ instantie een definitief borstimplantaat geplaats wordt). Er werden geen verschillen gevonden in patiënt-gerapporteerde kwaliteit van leven en cosmetische tevredenheid tussen de twee groepen, maar de nieuwe ADM methode leidde wel tot veel meer complicaties, waardoor voorzichtigheid geboden moet worden bij het aanbieden van deze behandeling.

Deel 2 van het proefschrift eindigde met een studie (hoofdstuk 8) waarbij gekeken werd naar mogelijkheden om de BREAST-Q in te korten middels een computerized adaptive test (CAT). In plaats van het invullen van de vragenlijst van vraag 1 t/m vraag 16, bepaalde de CAT middels een algoritme welke vragen gesteld werden, en in welke volgorde. Deze CAT zorgde ervoor dat alleen die vragen voor een individuele patiënt geselecteerd werden die de beste inschatting van tevredenheid van deze patiënt zouden tonen. Na elke beantwoorde vraag, werd een tijdelijke tevredenheidsscore bepaald, waarna het algoritme een vraag koos die verdere fine-tuning van de tevredenheidsscore van deze patiënt kon bieden. Bijvoorbeeld, als een patiënt aangeeft zeer tevreden te zijn met haar borsten als ze naakt in de spiegel kijkt, dan werd een vraag of ze tevreden was met kleding aan overgeslagen. Zodra een vooraf ingesteld niveau van meetbetrouwbaarheid bereikt was, zorgde de CAT ervoor dat er geen vragen meer gesteld werden en een eindscore berekend werd. In dit onderzoek hebben we uitkomsten van 5000 patiënten die de volledige BREAST-Q 'Tevredenheid met Borsten' vragenlijst invulden, vergeleken met uitkomsten als we CAT toepasten op hun antwoorden. Gemiddeld leidde BREAST-Q CAT tot een reductie van 38% tot 75%, in het aantal vragen ten opzichte van de volledige vragenlijst, om een inschatting met vergelijkbare meetbetrouwbaarheid van patiënten scores te verkrijgen. BREAST-Q CAT is een belangrijke stap voorwaarts en kan ertoe leiden dat meer patiënten BREAST-Q zullen invullen tijdens klinische zorg alsmede tijdens onderzoek, zodat van een grotere groep patiënten geleerd kan worden.

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10

# General discussion and future perspectives

# GENERAL DISCUSSION

In this thesis, many aspects of innovations in patient-centered breast cancer research have been addressed. In the next parts, we will zoom in on two aspects of this thesis, i.e. validity of cmRCT, and perspectives on the scientific use of PROs.

## Validity of cmRCT

This thesis showed that it is ethically and logistically feasible to implement a cmRCT cohort into a hospital-based breast cancer setting, and to conduct clinically relevant observational studies with cohort data.[1,2] Nonetheless, cmRCT cohorts are primarily set up with the intention to perform multiple randomized controlled trials (RCTs). In our hospital, four embedded trials are currently ongoing in the colorectal cancer cohort (i.e. BOOST and SPONGE trial), bone metastases cohort (i.e. VERTICAL trial) and breast cancer cohort (i.e. UMBRELLA FIT trial) with published results to be expected in 2019.[3-6] In the current literature, only one completed cmRCT-based trial is available [7,8] and preliminary results from one ongoing trial have recently been published (which will be discussed later on in this discussion).[9] As such, the advantages of cmRCT (e.g. increased efficiency, less disappointment bias) are mainly hypothetical, and potential validity issues have also been raised.[9,10] Future studies from fully completed cmRCT-based trials need to confirm how such trials perform in real-life.

## Patient selection in cmRCT

As originally proposed by Relton et al., when an intervention is ready for testing within a cmRCT cohort, in- and exclusion selection criteria are applied to the full cohort, and a subcohort of eligible patients is defined. From this subcohort, patients are randomly selected for the experimental intervention.[11] This random selection allows for obtaining the highest level of evidence for effectiveness of interventions.[12] However, for selection to be unbiased, all eligible patients must have equal probabilities of being selected, and trial arms should be interchangeable.

The original cmRCT approach by Relton et al. proposes that all eligible patients who were not selected for the intervention serve as controls.[11] This was considered to be important from an informed consent point of view. Relton et al explain

that randomization "is generally conceived as 'random allocation of all' and as something that is 'done' to all patients, and thus requires their prior consent". They argue, however, that when randomization is considered as 'random selection of some' then "nothing is 'done' to all patients and prior consent of all patients is not required".[11]

This way of defining unselected patients as controls was applied in the first fully completed cmRCT-based trial (i.e. DEPSY trial) conducted by Viksveen et al.[7,8] In this cohort RCT, a subcohort of eligible patients was first defined within the full cohort (n=4277), resulting in 566 patients eligible for the intervention. From this subcohort, 185 patients were randomly selected to undergo the intervention. The remaining 381 unselected patients automatically served as controls. As expected, this did not lead to baseline imbalance, as the basic principle of randomization was respected (i.e. allocation based on chance). However, by defining all unselected patients as controls, this can result in baseline imbalance in some scenarios.[9,13] For example, if the subcohort of eligible patients consists of 10% elderly patients, researchers may want to apply stratified random selection to ensure that 30% of those offered the intervention are elderly patients. This is not uncommon in standard RCTs. However, in standard RCTs, patients are randomized to an intervention and a control arm, and stratified randomization is applied to both arms. This means that both arms will be enriched in equal proportions (resulting in 30% elderly in both arms). In the cmRCT method as applied by Relton and Viksveen, where all unselected patients serve as controls, only the intervention arm would be enriched, as nothing can be actively done to the control arm. First, a subcohort of eligible patients would be identified based on inclusion criteria. For example, 1000 eligible patients, of which 100 patients are elderly. Suppose that sample size calculations have shown that 100 patients are needed in each arm. If 30% elderly are desired, this would result in 30 randomly selected elderly patients and 70 randomly selected other patients in the intervention arm. The control sample would then consist of the unselected 900 patients, of which 70 elderly and 830 other patients. The percentage of elderly in the control arm would then be 8% (70/900) versus 30% (30/100) in the intervention arm. This then results in baseline imbalance, and is therefore not a scenario that would be desired.

This approach can lead to biased results, which can easily be prevented by randomly selecting from two different eligible sub-cohorts, a young one and an older one, in the desired ratio. Another solution would be to do a stratified randomized cmRCT-based trial instead of 'random selection of some', with strata including 30:30 for the older group and 70:70 for the younger group. This would at the same time prevent that a large number of patients is unnecessarily included in a study. In the approach of Relton and Viksveen, instead of 100 control patients needed according to sample size calculations, 900 control patients would be included, after which the entire subcohort of eligible people has been 'used'. If, at a later moment in time, expansion of the study is deemed necessary due to, for example, problems with statistical power, no more eligible patients will be available in the subcohort to be offered the intervention. This then leads to validity issues as Reeves et al encountered.[9]

Reeves et al reported preliminary results from an ongoing cmRCT-based trial embedded within the CLASSIC cohort.[9] The CLASSIC cohort contains elderly patients with chronic conditions in the UK. Within the CLASSIC cohort, a behavior change intervention is being tested, called the PROTECTS trial.[9,15] Patients in the intervention arm receive 20 minutes of health coaching during a phone call. While conducting this cmRCT-based trial, the investigators encountered issues with statistical power and sample size. They had determined their sample size, with an expected attrition rate of 25%, based on previous pragmatic RCTs, resulting in 252 required patients per arm. They randomly selected 252 patients for the intervention, and the remaining 1054 served as control group. Eventually, only 40% accepted the intervention. As a result, the PROTECTS trial was underpowered to detect a statistical difference between the two groups. Aiming to increase power, they then offered the intervention to another random sample of 252 patients. Because their cohort itself had not increased in size, they selected the top-up intervention sample from the 1054 patients that were initially labeled as controls (i.e. all unselected patients). Due to this decision, patients who were initially allocated to the control group, were offered the intervention during the top-up, after which these patients formally crossed-over from the control to the intervention arm. This introduced bias by changing the make-up of the initial ITT control group. These patients formally served as controls for the first six months, and served as intervention group for the remainder of their trial participation.

Furthermore, patients selected from the top-up sample differed from the initial intervention sample in terms of timing when starting with the intervention, and timing of endpoint collection. This makes it difficult to interpret any changes in mean differences between the trialed groups, as changes could be due to time effects, usual care treatment effect from the first 6 months but also intervention-related effects from the time thereafter.

These issues may primarily affect cohorts that do not increase in size. In such cohorts, the subcohort of eligible patients from which random sampling will be applied, also will not expand. Thus sample size calculations and acceptance rates of interventions are even more important in non-expanding cohorts, as increasing the sample size later in time may be more difficult without affecting validity.

In our hospital, we apply cmRCT to cohorts that continuously expand in size, with new patients entering the cohorts on a daily basis. Therefore it is easier to recalculate and adapt the sample size when acceptance of the intervention appears to be lower than expected. The before mentioned issues can also be avoided by randomizing consecutive patients to the control and intervention arm, instead of using all unselected patients as controls. This is what we are doing in the three ongoing cmRCT cohorts at our hospital.[3-6] The remaining unselected patients can still be randomized later on in the study if necessary to increase power.

As discussed in the beginning of this paragraph, by applying classic randomization in cmRCT, prior informed consent is required for the entire cohort, as all patients in the control and intervention arm have been subjected to randomization. For this we created the staged-informed consent procedure (as presented in Chapter 2), during which we ask broad informed consent for future randomization and for serving as controls without further notice. Since patients entering any kind of prospective cohort study, including cmRCT cohorts, always have to provide informed consent upon enrollment, also asking broad informed consent for randomization seems like a small extra step. Furthermore, in UMBRELLA, approximately 85% of patients agree to broad consent for randomization[2], which shows that this added question does not dramatically impact recruitment.

## Statistical analysis of cmRCT

The primary analysis for most RCTs – including cmRCT-based trials – is an intention-to-treat (ITT) analysis. This entails that all participants will be analyzed according to the treatment arms they were randomly allocated to, irrespective of the actual treatment received after randomization.[14] In general, ITT avoids biased effect measures, which could occur when removing those from the analysis who withdrew, declined the intervention or who received the treatment from the opposite trial arm after randomization (i.e. cross-over).

In classic pragmatic RCTs, patients hear about the intervention prior to randomization. If they do not agree to trial participation, they will not be randomized, and will not be part of the trial or the analyses. In a cmRCT-based trial, patients are randomized before being offered the intervention, which means that as part of ITT those declining the intervention will also be analyzed as part of the intervention arm. Therefore, in cmRCT, the intervention arm consists of a mixture of patients who accept the intervention and patients who decline (i.e. non-consenters). This is an important difference to classic RCTs, which needs to be taken into account when determining sample size for cmRCT-based trial. In cmRCT, we actually estimate the effect of merely offering the intervention, independent of whether the patient accepts it. The effect of this will be lower than the actual effect of the intervention itself, especially if acceptance rates for this intervention are low.[11]

In the preparations of the previously mentioned depression trial by Viksveen et al, the authors did not account for potential dilution in their sample size calculation.[8] In their trial only 40% of patients who were offered the intervention accepted. If acceptance rates of the intervention are low, additional statistical analyses may be helpful to still get an estimation of the actual effect of the intervention. ITT analysis showed a statistically significant small effect size (d=0.30). To account for the diluted effect, the investigators applied complier average causal effect (CACE) analysis, a form of instrumental variable analysis.[16] It is a method for adjusting for non-consent, by inflating the ITT effect by the proportion of patients who complied with the intervention. This provides an estimate of the effect that may be expected when all patients who are offered the intervention would accept it.[17] After applying CACE analysis, a moderate effect size (d=0.57) was found in favor of the intervention.

CACE analysis should be applied with caution, as not all assumptions for CACE may always be met for cmRCT trials. The three assumptions for CACE are: 1. Randomization was successful, 2. Those who decline the intervention receive the same treatment as controls, 3. Being offered the intervention (as opposed to receiving the intervention) does not affect your outcome.[16] In particular, this third assumption will not hold up for every type of intervention. For example, being offered an exercise intervention may result in patients increasing their physical activity levels also after declining the intervention. The explanation that physical activity could improve their quality of life may trigger non-consenters to increase their physical activity levels as well. Therefore, cmRCT-based trials are less ideal when intervention acceptance rates are expected to be low, or when non-consenters can be expected to change their behavior after declining the intervention.

## Multiple RCTs in cmRCT

A unique and key feature of cmRCT cohorts is their ability to allow for multiple embedded trials. The idea of running multiple cohort based RCTs, in which patients may participate simultaneously, sounds appealing to reduce recruitment time and increase efficient use of the cohort population.[11] However, since the recent inception of the design, no one has yet completed multiple cmRCT-based trials with overlapping sub-cohorts. In our hospital, two simultaneous cohort RCTs are currently running in the colorectal cohort (i.e. the rectal BOOST and SPONGE trial), which will be described in more detail later in this section.

With the increase in interventions becoming available for the same condition, the need for efficient trial designs, where patients can participate in multiple trials, or serve as controls for multiple interventions, is clear. However, it is of utmost importance to demonstrate that running multiple trials in a cohort, with (a part of the) patients participating in more than one trial, leads to valid results.

Participation in simultaneous trials is allowed if the interventions being tested do not interfere/interact with one another.[10,17] Interference happens when one intervention affects how well the other intervention works, and therefore directly affects trial outcomes. However, it is challenging to consider all potential interactions beforehand, and some unmeasured interactions may still be present. Therefore, when designing trials for cmRCT cohorts, it is important to know which

other trials are ongoing, and what these trials are evaluating and measuring. Researchers need to decide whether it is possible to allow patients from ongoing or other future trials to participate simultaneously in different trials.

Groenwold and Van Smeden performed a simulation study, and found that two of four simulated scenarios ensured complete independence of trials.[10] As was to be expected, trial results were independent when patients were only allowed to participate in one trial at a time (scenario 1), and when patients were allowed to participate in multiple trials irrespective of whether they were serving in the control or intervention arm of the other trial (scenario 2).

Regarding scenario 1, where patients are only allowed to participate in one trial, the authors state that there are no practical advantages of the cmRCT, and patients can no longer participate in other trials in this scenario, which could lead to ethical considerations. It is true that in this situation the cmRCT has no practical advantage with respect to efficiency of running multiple trials at the same time. However, ethics do not have to be a problem, as long as patients are informed at cohort enrollment that (unknowingly) participating in one trial could make them ineligible for other trials. Moreover, this is not different from participation in classic RCTs, where participation in other trials is most of the time highly undesirable. In UMBRELLA – and the other cmRCT cohorts in our hospital – it is explained during informed consent that this situation of temporary ineligibility could occur of which they will then not be notified.

Independent simulated trial results were also found in scenario 2, where patients were allowed to participate in multiple trials, irrespective of whether they were serving in the control or intervention arm of the other trial.[10] This had no implications for trial results when outcomes between the two trials had zero correlation (i.e. do not interfere). For this scenario to work, researchers would have to think carefully about the outcomes to select in such trials. Furthermore, the more unalike the two interventions are (e.g. radiotherapy on the breast vs health-app intervention for emotional support), the more easily interpretable results and potential interactions will be. Another potential challenge of competing in multiple trials, is that prognosis of patients may no longer be comparable between trial arms, due to effects of interventions from the other trial, which could induce biased effect

estimates. If receiving the intervention in trial A influences prognosis, while also serving as control in trial B, than results for trial B will be affected as well. One way to prevent this is by applying stratified randomization, as this allows for a better understanding of potential interaction between interventions.

In the colorectal cmRCT cohort in our hospital, participants of the BOOST trial (i.e. pre-operative radiotherapy boost on the rectum) are eligible to participate in the other cohort-based SPONGE trial (i.e. intraoperative surgical sponge to keep small intestines out of the surgical field).[5] Patients who have undergone the rectal boost have a higher risk of adverse events when undergoing the SPONGE intervention. Stratifying patients in the SPONGE trial based on their rectal boost status, allows for balancing out the number of patients between study arms who received the rectal boost, and more easily identifies potential interactions.

Groenwold and Van Smeden simulated two other scenarios where patients could participate in multiple trials, and these both showed dependency between trial results. In one scenario, patients receiving the intervention in trial A cannot participate in trial B, while controls in trial A can only receive control treatment in trial B. In another scenario, patients receiving the intervention in trial A can only serve as controls in trial B, while controls from trial A can receive the intervention or serve as controls in trial B. Both scenarios, by definition, will provide biased results. Probabilities of being selected for the intervention are not equal for all patients, and both study arms are not interchangeable in these trials, thus these scenarios do not represent random allocation. However, it is not unthinkable that researchers who do not fully understand the concept of randomization may apply these methods in real-life within their cmRCT cohorts. This highlights the importance of always assessing, when designing cmRCT-based trials, whether the assumptions of randomization will be met (i.e. equal probability of being selected, and interchangeable study arms).

## Outcome collection

In cmRCT, outcomes are being collected in a standardized way for the entire cohort. When planning trials, it is pivotal to carefully plan the timing of rolling out of the intervention in relation to the endpoint measurements that are fixed in time. If this is not done beforehand, this will result in logistical and validity issues, as Reeves

et al encountered in their trial. They had difficulty rolling out their intervention, after which endpoints were not always collected at the correct moment in time. In contrast, in the physical activity intervention in our breast cancer cohort, patients with low physical activity levels are identified 12 or 18 months after enrollment, after which the researchers carefully plan ahead to ensure the intervention is ready to be received shortly after approaching the patient. If measures need to be more tailored to the actual start/end date of the intervention, or extra measures are required, than there are two options in cmRCT:

1. Only collect extra measures for the intervention group (this provides extra information for the intervention group but these measures cannot be compared to controls and therefore cannot serve as endpoints), 2. Collect extra measures for the entire cohort (after which the extra measures may serve as endpoints and can be compared between both study arms). This second option requires explaining to all cohort patients why extra measurements are being collected, which may be difficult to explain without introducing disappointment bias in the trial or without knowingly withholding information.

## Some considerations when designing cmRCT

First, non-acceptance of the intervention (by those randomly selected to be offered the intervention) will occur in every trial. Due to the ITT analysis in cohort RCTs, this will lead to dilution, which should thus always be taken into account when determining the sample size.[9,16,17] Therefore, it is essential to think about expected acceptance rates of the intervention prior to starting the trial. Estimated acceptance rates can be hypothesized either based on previously performed classic RCTs or from running a smaller pilot cmRCT-based trial prior to starting the full trial.[9] In UMBRELLA we first ask broad consent for future randomization to interventions.[1,2] This filters out patients who are unwilling to accept randomization and interventions in general. Relton et al. also proposed asking patients upon enrollment into the cohort what type of hypothetical interventions they would be willing to accept, which could be used to determine inclusion criteria of trials and thus help to define sampling pools for certain interventions.[11] Most importantly, the intervention itself will determine the acceptance rate. Therefore, highly desired interventions are more likely to provide high acceptance rates, and interventions that, for example, require multiple extra hospital visits, or are expected to have more side-effects, will probably be less popular.

Second, it is important to know whether cohorts continue to increase in size as this may affect whether required sample sizes for cmRCT trials will be met. If the cohort size is non-expandable, then this may limit options to include more patients when acceptance rates for interventions are lower than expected. Non-expanding cohorts can also have consequences when performing multiple cohort based RCTs simultaneously, as this may not always be feasible if the sampling pool becomes too small to provide participants for both trials. Therefore, we recommend only randomizing the amount of patients needed in the cohort based RCT, instead of labeling all unselected patients as controls, as this reduces unnecessary loss of eligible patients available for top-up sampling or participation in other trials.

Third, irrespective of selecting patients based on 'random selection of some' or 'random selection of all', principles of randomization should be followed closely to eliminate bias in cmRCT-based trials. Randomization is only successful if selection is fully based on chance, with equal probability of being selected, and study arms are interchangeable.

And finally, when selecting endpoints for trials, timing of outcome collection in relation to the intervention is important to determine before starting the trial. Since outcome collection is done according to a fixed and standardized schedule for all cohort patients, timing of when to start the intervention and when to measure its effect is pivotal. If not closely matched, outcomes will not measure the effect at the desired time interval. This may also affect outcome comparability between patients, if there is heterogeneity between start of the intervention and when endpoints were collected. Therefore, syncing intervention initiation and endpoint collection uniformly for all trial participants is pivotal when designing cmRCT-based trials.

# FUTURE PERSPECTIVES FOR PATIENT-REPORTED OUTCOMES

Part 2 of this thesis addressed the use of patient-reported outcomes (PROs) as research endpoints (e.g. the first RCT with BREAST-Q as primary endpoint), new methods of PRO collection (e.g. Health-app) and ways to improve collection of PROs (e.g. shorter and individualized assessment of BREAST-Q by applying computerized adaptive testing).

Historically, PROs were developed for research purposes, and were collected on paper. To determine their scores, complex manual calculations or statistical software were required, which made it impossible to quickly obtain scores in clinical practice. Nowadays, patients may fill out questionnaires on mobile devices in the waiting room, with calculation being done automatically, after which their scores are available real-time for the clinician to assess. The use of PROs both in clinical oncology and cancer research continues to increase, as the value of PROs is now more widely acknowledged.[18-21] According to the US National Academy of Medicine "PROs are an essential element of person-centered, high quality care for patients with cancer"[22], and provide the best way to quantify patients' well-being.

In research, PROs have shown clinically relevant differences between treatments that hard endpoints cannot pick up (e.g. superiority of long-term cosmetic satisfaction in autologous breast reconstructions compared to implant-based reconstructions).[19] In clinical care, implementation of PROs has shown to improve the patient-physician dialogue, HR-QoL and even survival.[18-20] Studies have shown that clinicians often underestimate the impact of symptoms on patients' lives, and toxicity reporting – which was traditionally assessed by clinicians – can be done more reliable by patients.[23-28] In Memorial Sloan Kettering Cancer Center, an online symptom-reporting tool was evaluated in 286 cancer patients, which showed improved compliance to chemotherapy, with 83% reporting their symptoms on a monthly base from home during a mean follow-up of 34 weeks.[29, 30]

PROs are now also becoming the focus of value-based health care. Cost of cancer care continues to increase, and reducing the amount of resources allocated to treatments that are inferior, or have more side effects, becomes increasingly important.[31] Therefore, RCTs are required to select the most effective treatments with the best patient-reported outcomes. In the US, the health care system is currently being reformed, and value-based payment has been proposed where reimbursement will be adjusted based on PROs.[32] Outcomes between hospitals will be compared, after which those who underperform – after adjusting for hospital case-mix – may receive less payment from insurance companies whereas those with above average scores may receive bonus payout.[32,33] If such important decisions will (partly) be based on PROs, it is of utmost importance that the selected PRO-instruments are valid and reliable. Also, response rates for PRO-instruments need to be high and collected in a sample representative of the population of interest. If for example, only patients with the very best or the worst outcomes return questionnaires, then estimates will be biased and will not reflect average outcomes. This is often evaluated in research to understand generalizability of study results, and should also be evaluated if PROs are to be used for health-care reimbursement. To incorporate PROs in routine care, research or value-based health care systems, collection of PROs should be done at the most appropriate moment during follow-up and the correct PRO-instrument should be selected the for the appropriate indication.

The International Consortium for Health Outcomes Measurement (ICHOM) has created condition specific standard sets (e.g. breast cancer) for health outcome measurement aiming to standardize which PRO measures to use, and at what time points.[34] ICHOM's work promotes international homogeneous data collection and better comparability between studies, and may also be used by policy makers when designing value-based health care systems.

An important shortcoming of ICHOM's standard sets is that they do not provide instructions about which PRO-instruments are superior for individual patient assessment and which instruments for group-level research purposes. This is important, as not all instruments provide both options. PRO-instruments developed using classic psychometrics (i.e. classical testing theory), such as the widely used questionnaires from European Organisation for Research and Treatment of Cancer

(EORTC), are only validated to measure changes on a group-level. When used for individual patient measurement in clinical care, such PRO-instruments may not be not sensitive enough to detect smaller changes that may be clinically relevant during follow-up.[35-37] ICHOM also does not explain for which populations the PRO-instruments in their standard set are validated, which is important to promote proper use. For example, EORTC QLQ-C30 is validated for all cancer patients, EORTC BR23 is validated for breast cancer patients, and BREAST-Q is validated for breast cancer patients undergoing surgery. Using instruments in populations for which they have not been validated cannot guarantee outcome validity. Furthermore, some research questions cannot be answered when questions in the instrument are either too broad or too specific. For example, autologous and implant-based reconstructions shows no difference in perceptions of body image when asking broad questions about whether or not patients are "dissatisfied" with their body (i.e. EORTC BR23).[37,38] However, more targeted questions such as how satisfied patients are with the size, softness, symmetry and feel to touch of their reconstructed breast (i.e. BREAST-Q), do show clear differences between implant-based and autologous breast reconstructions.[37,38] In contrast, when interested in overall quality of life in these groups of patients, EORTC QLQ-C30 will be superior. This shows the importance of selecting the correct instrument depending on the questions that need to be answered. This becomes even more important if healthcare providers will receive (part of) their imbursement based on PROs, in which case the most sensitive instruments will be required.[32] If this is not done correctly, treatments will seem ineffective while it is actually the PRO-instrument that is ineffective in picking up the change.

Therefore, now that ICHOM[34] has established what needs to be measured and when, and now that clinicians understand the benefits of incorporating PROs into their practices, the next step is to ensure that the correct instruments are being used for the correct purposes. Clinicians and policy makers should get acquainted with the methodology behind the PROs they are (interested in) using. Goals between these stakeholders may differ, thus required instruments may also differ. Simply picking the instrument that is 'most widely used in the literature' or created by 'a group of respected clinicians/researchers' is not sufficient. In a time of evidence-based medicine, where we only want to offer the most effective treatment to each subgroup of patients, the same should be desired for PRO-instruments.

In cmRCT cohorts, PROs are ideal to collect as they cover a wide range of generic and disease specific outcomes. This allows for a wide range of potential endpoints (e.g. quality of life, physical activity, satisfaction with breasts), and thus a wide range of embedded trials (e.g. new radiotherapy technique, supervised training programs, new breast reconstruction techniques). Therefore, when setting up a cmRCT cohort an important first step is to decide what should be measured. The second step is getting familiar with the available validated PRO-instruments out there, for which the ICHOM standard sets may be valuable. The third step is to select the PRO-instruments that best suit the goals of the cohort and its expected embedded trials. Generic PRO-instruments will cover broad domains relevant for all cohort patients (e.g. overall physical functioning, overall quality of life), and allow for comparing different cohort populations, while disease specific instruments allow for answering more specific questions. For example, participants in all three cohorts in our hospital complete EORTC-QLQ C30, validated for all cancer types, allowing for overall comparisons between these three populations. This will not be possible when only measuring QoL with, for example, a breast cancer specific instrument such as BREAST-Q. Thus, cmRCT cohorts should measure a mixture of generic and more specific PRO-instruments, to increase their potential of capturing relevant outcomes and comparisons between different populations.

Barriers to implementing PROs in routine care were the lack of structured frameworks that combine PRO data collection with PRO feedback to patients, and conducting studies that resemble real-life experiences.[28] By providing all patients visiting the hospital with the option to participate in cmRCT cohorts, where routine care data and relevant PROs are being collected and fed back to patients, the desired situation where properly evaluated, effective treatments are easily implemented into clinical practice may be closer than ever before.

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11

# List of publications

# LIST OF PUBLICATIONS

(chronological order)

## In Press:

1. 'Introducing BREAST-Q Computerized Adaptive Testing – short and individualized patient- reported outcome assessment following reconstructive breast surgery',
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# Curriculum Vitae

# CURRICULUM VITAE

I was born in the Netherlands, on March 15th 1985, to ambitious Surinamese parents. I grew up in the Amsterdam region with two younger brothers and a large, loving family. My admiration for reconstructive surgery inspired me to become a doctor. I started medical school at the University of Amsterdam (UvA) / Academic Medical Center (AMC) in 2004, and was introduced to scientific research during my third year as a medical student after reaching out to plastic surgeons of the AMC. For several years, I studied venous malformations of the legs under the supervision of Professor Chantal van der Horst and Dr. Charlène Oduber. The process of answering a scientific question based on a clinical problem fascinated me and from that moment on I was hooked on research.

During internships at Jackson Memorial Hospital (Miami, 2008) and Mount Sinai Hospital (New York, 2011) I was introduced to breast reconstructions in breast cancer patients. Seeing what a successful reconstruction meant to a patient both physically and emotionally, and the creativity and skills it took from plastic surgeons, made me want to be involved in this field. After obtaining my MD degree in 2011, I worked as a resident at the department of Surgery (ANIOS) at the Red Cross Hospital & Dutch Burn Center in Beverwijk (supervisor Dr. Huib Cense). There, I simultaneously conducted a retrospective cohort study on breast reconstructions & radiotherapy with plastic surgeon Dr. Paris Melis.

All these experiences resulted in a PhD fellowship in the field of breast cancer, radiotherapy and clinical epidemiology at the UMC Utrecht. During this time, I was simultaneously trained as a clinical epidemiologist in the MSc Epidemiology Postgraduate program of the University of Utrecht. In 2015, I reached out to Professor Andrea Pusic aiming to shorten the patient-reported outcome instrument that she and her team had previously created (i.e. BREAST-Q). This led to research fellowships at Memorial Sloan Kettering Cancer Center (New York, 2015-2016) and at Harvard University (Boston, 2018), and the creation of the dynamic short version of BREAST-Q.

After returning to Amsterdam in 2016, I started Plastic and Reconstructive surgery residency, of which the first two years were completed at the General Surgery department at Flevoziekenhuis (under supervision of Dr. Paul Verbeek and Dr. Klaas In 't Hof). I recently started my third year of residency at the department of Plastic, Reconstructive and Hand surgery at Amsterdam University Medical Center (location VUmc – under supervision of Dr. Hay Winters). Currently, I am also a board member of the scientific committee of the Dutch Society for Plastic Surgeons (WK-NVPC), board member of the scientific committee of the Dutch Breast Implant Registry (DBIR) and member of the patient feedback taskforce of the NABON Breast Cancer Audit (NBCA).

My motto has always been "Hard work is the price we must all pay for success" (Vince Lombardi Jr.). To me, especially when it comes to realizing your dreams, hard work is always worth it! However, when I am not working, I enjoy singing, composing music, dancing, spending quality time with Quinten, friends and family, full-bodied white wines and exploring the world. It puts a smile on my face, each and every day, knowing that all the hard work paid off, and I am living the life that I always dreamed of.

12

# Acknowledgements

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Although I am never shy for words, this section is the most difficult to write. It's bittersweet, as this officially marks the end of my PhD. In the past 5 years, I've met amazing people, travelled the world to share our study results and experienced personal growth as a person, researcher and doctor in ways I would have never reached without completing this adventurous PhD fellowship. However, I am soooooo ready to put a bow on this project and start watching the final season of House of Cards (and if I'm honest...reruns of Temptation Island).

First and foremost, I want to thank all the patients who participated in our studies mainly to help gain knowledge for future patients. I am proud of what we've achieved with the UMBRELLA cohort. I remember the very beginning, trying to come up with the cohort name and sketching potential cohort logos, giving lectures together with Lenny Verkooijen aiming to convince doctors that this cohort would be worth it. Now, five years later, over 2500 patients are actively participating in UMBRELLA!

I owe a huge thank you to my PhD supervisors:

**Professor Lenny Verkooijen:** Thanks for offering me this wonderful opportunity. You are one of the most inspiring and intelligent people I know. Thanks for all the years of working and laughing together, teaching me your perfect writing skills, our weekly meetings where 10% was dedicated to research and 90% to gossip, our Texas road trip and all that I've learned from you.

**Professor Carla van Gils:** Thanks for always being supportive, empowering and in a great mood. Your mind is so sharp and you were capable of detecting errors and details that no one else could. You are a gifted epidemiologist, with the kindest and most patient personality. Thanks for always being interested in exploring my ideas and teaching me how to think like an epidemiologist.

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I also want to thank my two "paranymphs", who created similar cmRCT cohorts as part of their PhD's, and who stood by my side in Utrecht and at many conferences where they referred to us as "the three musketeers":

**Maarten Burbach and Joanne van der Velden:** I vividly remember the first time we met, on the first day of my PhD. Maarten was his most enthusiastic self when he welcomed me to the team and showed me my desk, while Joanne first thoroughly observed me to determine what to think of me. The three of us couldn't have been further apart in terms of personalities (red vs blue vs yellow), cultural backgrounds and our styles of working. Nevertheless, we were an amazing team and became like family. Having the two of you next to me, on the day of my PhD-defense, is the perfect way to end this journey that the three of us embarked upon. I look forward to many more years of friendship, conferences, fancy dinners and cocktails.

**Madelijn Gregorowitsch:** Maarten Burbach introduced me to you, and from that moment our energy has been a synergy. We have pushed each other to greater heights in our research than we would have been able to scale on our own. You took over the UMBRELLA cohort when I went to New York, and you have made it much better than I ever could have. Now, you are showing Andrea Pusic in Boston what you are made of, and I'm sure your talent will impress her as well. Fortunately our connection is not restricted to research and I am very grateful for all you have done for me. Hopefully someday soon we'll finally get a YES from JCO (after our many previous attempts), and a YES for your residency in plastic surgery (so we can perform surgeries together)!

**My mentor – Dr. Paris Melis:** Your support meant the world to me. You were always brutally honest, encouraging and always excited about everything I did. You were the best mentor a young student could have asked for. On many occasions I wish that you were still here, to give me well-needed advice during residency or in the OR, or simply to laugh and chat about life. You are gone, but certainly not forgotten.

**My family & inner circle:**
The amazing women in my life: my late grandmothers, my mother, my cousins Shar & Sham, "tante" Shir, Nada, Nienke, Sor and Cheryl. You all have shown me unconditional love and support. You taught me how to think without labels and limitations, and helped me to evolve into the person I am today. The amazing men in my life who have been my biggest fans, and who taught me how to fight for what I believe in: my late grandfathers, my father, my brothers and Quinten (i.e. the hidden ghost-writer of this thesis, who had to double check all my work, and had to be patient and supportive when I was working during our many exotic holidays over the past 12.5 years). It has not always been easy living with me, as I have missed many birthdays, holidays and life events due to my focus on plastic surgery and research. I am – and always will be – truly grateful for all the love and support I have received from all of you, even when I did not always deserve it.

**Others:**
I would also like to thank everyone else who motivated me to get involved in research, and all those who supported me throughout the years. This list includes friends from the past and present, high school teachers, colleagues, researchers and doctors that I've met throughout the years, and so many more. It is impossible to acknowledge each and every one individually, but please know that I am grateful and aware of your contributions.

This thesis marks the end of an important part of my life, but also marks the beginning of a new one: combining clinical work with my own research projects, and being able to spend more time with my inner circle. I am excited to see what the future holds.

I will continue living my life in search of magical moments, and in appreciation of all the wonderful experiences I've had in the past. The "big" achievements in life are wonderful, but these moments are rare. True happiness should be found in the little everyday moments, as I have truly come to find. Please keep on reminding me of this philosophy when I tend to forgot, and remind me to be present in your lives and to stay present in my own life as well.

*"Life is not measured by the amount of breaths we take, but by the moments that take our breath away"* ***Maya Angelou***